

**IMPACT OF EMOTIONAL HEALTH ON PREGNANCY RATES FOLLOWING ASSISTED CONCEPTION**

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**Abbreviations**

|  |  |  |  |
| --- | --- | --- | --- |
| ACTH | Adrenocortico trophic hormone | IDS | Infertility Distress Scale |
| ART | Assisted Reproductive Technology | IVF | In vitro Fertilisation |
| BDI | Beck’s Depression Inventory | IQ | Infertility Questionnaire |
| BMI | Body Mass Index | IRS | Infertility Reaction Scale |
| CART | Concerns during Assisted Reproduction Technology | ISES | Infertility Self-Efficacy Scale |
| CASI | Cognitive Appraisal Scale for Infertility | LH | Leutinising Hormone |
| CCR | Cumulative Conception Rate | LOT | Life Orientation Test |
| CES-D | Center for Epidemiological Studies-Depression | NICE | National Institute of Health and Clinical Excellence |
| COMPI | Copenhagen Multi-centre Psychosocial Infertility | NK | Natural Killer |
| CQ | Cognition Questionnaire | PANAS | Positive and Negative Affect Schedule |
| CRH | Corticotrophin Releasing Hormone | PCOS | Polycystic Ovarian Syndrome |
| CSIC | Coping Scale for Infertile Couples | PGWB | Psychological General Well-being |
| DACL | Depression Adjective Check-List | POMS | Profile of Mood States |
| DRK | Daily Record Keeping | PSS | Perceived Stress Scale |
| EM-INFERT | Emotional Health in Infertility Questionnaire | SAS | Zung Self-Rating Anxiety Scale |
| FAS | Fertility Adjustment Scale | SDS | Zung Self-Rating Depression Scale |
| FERTIQOL | Fertility Quality of LIfe | SF-36 | 36 item Short Form Health Survey |
| FPI | Fertility Problem Inventory | STAI | State-Trait Anxiety Inventory |
| FSH | Follicle Stimulating Hormone | TNF | Tumour Necrosis Factor |
| GnRH | Gonadotrophin Releasing Hormone | UCL | Utrechtse Coping Lijst |
| HADS | Hospital Anxiety & Depression Scale | UK | United Kingdom |
| HFEA | Human Fertilisation & Embryology Authority | VAS | Visual Analogue Scale |
| HPA | Hypothalamo Pituitary Axis | WOC | Ways of Coping |
| HPG | Hypothalamo Pituitary Gonadal Axis | WHO | World Health Organisation |
| ICSI | Intracytoplasmic Sperm Injection |  |  |

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**Abstract**

Infertility can be stressful and hence it is important to know whether this stress can affect the success of *in vitro* fertilisation (IVF).

Several studies have suggested a link between stress and reproduction. A systematic literature review concluded that the available evidence is inconclusive due to methodological limitations. It highlighted the need for a prospective well-designed study to examine the impact of emotional health on IVF outcome.

Fertility specific tools were critically analysed in order to choose an appropriate instrument for the study. A prospective study was designed to evaluate the emotional health and distress prior to treatment. The questionnaires used were Emotional health in infertility (EM-INFERT) and Fertility problem inventory (FPI). The primary objective was to correlate the emotional health scores to the pregnancy rates.

414 IVF patients were divided into three tertiles as per their EM-INFERT scores: poor emotional health (n=140), average emotional health (n=139) and high emotional health (n=135). Clinical pregnancy in patients with low emotional health was statistically similar to patients with high emotional health.The emotional health scores did not predict the success of IVF.

Further analysis explored the impact of IVF on the emotional health of infertile couples. The luteal phase was more distressing than the ovarian stimulation phase. Men had better emotional health than women throughout the treatment

but both partners had a significant drop in their emotional health after a negative result. The fertility-related distress can be affected by the duration and cause of infertility.

This study confirms that emotional health does not influence success of IVF but it identified patients who are at risk of significant distress during IVF. Addressing this, could make their journey a better experience and reduce dropout rates. The results of this study can help to design psychological interventions tailored to the individual needs of these patients.

**Chapter 1: Infertility and emotional health**

|  |
| --- |
| Overview  1.1 Infertility definition & prevalence  1.2 Causes of infertility  1.3 Treatment of infertility  1.4 Psychology of infertility  1.5 Effect of stress on reproduction  1.6 Rationale for the study |

* 1. **Infertility definition and prevalence**:

Infertility has become a growing problem for many couples over the last few years. In the UK, currently, one in seven heterosexual couples is diagnosed with infertility(1). Infertility is defined as inability to conceive, despite having regular unprotected intercourse. Existing clinical definitions of infertility vary with regards to the duration during which the couple have tried to conceive. World Health Organization (WHO) defines infertility as failure to achieve clinical pregnancy after 12 months of unprotected intercourse (2). Demographers, however define infertility as the inability of a non-contracepting, sexually active woman to have a live birth (3). The main difference between the two definitions is with regards to duration of infertility. Clinically infertility is defined as lack of conception over one or two years, while demographers estimate infertility over longer duration of 5-7 years (4). For the purpose of the current study, we use the NICE definition which is in line with UK practice. NICE defines infertility when a woman has not conceived after 1 year of unprotected vaginal sexual intercourse, in the absence of any known cause of infertility(1).

As there is no uniformity in defining infertility, prevalence rates vary within and between the populations (5). A recent WHO report estimated that 48.5 million couples worldwide were infertile in the year 2010 based on 5 year duration of infertility in women between the ages of 20 and 44 years (6) . This estimate was much lower than that of Boivin *et al* (2007), who estimated that 72.4 million women were infertile in 2007. This is due to the fact that the authors used data from published studies that used 12 or 24 months as the time taken to conceive for the definition of infertility. Evers (2002) hypothesises that the prevalence of infertility is likely to be increasing as more women are delaying having children until an age when natural female fertility is declining(7). A WHO report in 2011 described infertility as the fifth highest serious global disability (8). Approximately 25% of couples trying to conceive will get pregnant within a reproductive cycle, 60% in the first six months, 84% in the first year and 92% by the second year(1) .

* 1. **Causes of infertility**:

The main causes of infertility in the UK are ovulatory disorders (25%), tubal damage (20%), male factor (30%), uterine or peritoneal disorders (10%), and unexplained (25%) with no identified male or female cause (9). In about 40% of cases disorders are found in both partners that lead to infertility.

**Table 1.1: Factors affecting fertility(10)**

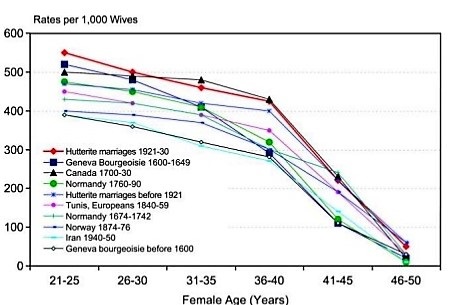
|  |  |
| --- | --- |
| 1. Female: | Age |
|  | Anovulation |
|  | Fallopian tube abnormalities |
|  | Endometriosis |
|  | Uterine abnormalities |
|  |  |
| 2. Male: | Sperm dysfunction |
|  | Previous vasectomy |
|  |  |
| 3. Psychosexual problems: | Vaginismus |
|  | Erectile dysfunction |
|  | Premature ejaculation |
|  |  |
| 4. Lifestyle: | Body mass index |
|  | Smoking |
|  | Alcohol consumption |
|  |  |
| 5. Unexplained infertility: |  |

Certain genetic conditions, environmental and social factors also can contribute to infertility. Infertility is classified as primary when there has been no pregnancy and secondary when there is failure to conceive following a previous pregnancy.

* + 1. **Female factors**

The single most important female factor is age, as fertility declines from the age of about 32 years. When the female age is 25 and under the cumulative conception rate (CCR) is 60% at six months and 85% at a year. When the female age goes upto 35 years, the CCR is reduced to 60% at a year and 85% at two years(11).

**Figure 1.1: Marital Fertility Rate by 5 Year age groups**



Menken and Larsen proposed that although the level of marital fertility varied among different populations, the pattern of age related decline in fertility was similar as illustrated in Figure 1.1 (12).

Another major cause of female infertility is ovulatory disturbance. Anovulation (the failure to ovulate) is usually characterised by amenorrhoea, (an absence of menstrual periods for six months or more). Ovulation may also be infrequent, resulting in oligomenorrhoea, (menstruation occurring with gaps of between six weeks and six months). The most common cause of anovulation is polycystic ovarian syndrome (PCOS). Other causes of amenorrhoea include hypogonadotrophic hypogonadism , hypopituatrism, weight and exercise related amenorrhoea, hyperprolactinaemia, premature ovarian failure and congenital abnormalities.

A third cause of female infertility is fallopian tube disease including blockage, and damage caused by pelvic inflammatory disease. Other female causes include endometriosis; uterine abnormalities such as sub-mucosal fibroids and congenital malformations, and the presence of adhesions misaligning the pelvic anatomical structures.

**1.2.2. Male factors**

The numbers and quality of sperm vary from time to time in the same person, and from person to person without fertility potential being affected(11). The World Health Organisation (WHO) (2010) parameters for ‘normal’ sperm are a count of 15 million or more per millilitre (ml) of ejaculate, a progressive motility rate of 32% or more within 60 minutes of ejaculation, and a normal morphology of 4% or more . Of those men presenting with male factor infertility almost 50% will have no identifiable cause(13). The causes of male infertility include trauma, infection, a history of mumps orchitis or testicular torsion, a history of cryptorchidism (undescended testes), chemotherapy and radiotherapy, environmental toxins for example lead, mercury, pesticides, and glycol ethers; drugs, for example, sulphasalazine (used in the treatment of inflammatory bowel disease), congenital abnormalities, antisperm antibodies and chromosomal abnormalities, for example, Klinefelter’s syndrome(11)

**1.2.3 Psychosexual problems**

Major psychosexual problems resulting in a failure to have intercourse account for less than 5% of infertility(11). Problems may include vaginismus, erectile dysfunction and premature ejaculation. More commonly problems arise as a consequence of the emotional pressure associated with infertility and trying to conceive, for example timing intercourse with ovulation and a loss of spontaneity(14).

**1.2.4 Lifestyle factors**

These include obesity, a very low body mass index (BMI), smoking, and excessive alcohol intake. Obesity in women is associated with a reduction in fertility, increased miscarriage rates and ongoing problems in pregnancy such as gestational diabetes and hypertension(15). In men obesity may be associated with hypogonadotrophic hypogonadism(16). Women with a very low BMI can have anovulation and amenorrhea(11). Smoking reduces fertility because of the toxic effects of metabolites on oocytes, sperm and embryos(17, 18). Long-term excessive alcohol intake is associated with poor testicular and sexual function in men, ovulatory disturbance in women, and general health problems in both men and women(11)

**1.2.5 Unexplained infertility**

Unexplained infertility is defined as the failure to conceive after a year in the absence of any abnormalities(11). Approximately 40%-65% of these couples will conceive spontaneously within three years. Thus, the duration of infertility and the woman’s age determine whether treatment should be offered or not. Beyond three years the chances of conceiving without treatment decline sharply.

**1.3 Treatment of infertility**

Treatment of infertility can be divided into medical treatment, surgical treatment and assisted conception (1).

Medical treatment of infertility involves use of ovulation inducing drugs like clomiphene citrate, letrozole and gonadotrophins. This is mainly indicated in female anovulatory infertility and male infertility with hypogonadotrophic hypogonadism.

Surgical treatment of infertility in women involves tubal microsurgery, tubal cannulation and uterine surgery for tubal obstruction and uterine adhesions. In males obstructive azoospermia can be surgically corrected by unblocking the epididymis, treatment of varicocele.

Assisted Conception: Over the past three decades assisted reproductive technology has revolutionised the treatment of infertility. Initially developed for tubal and male factor infertility, this has gradually become widely recognised as an effective method of treatment for most causes of infertility and after failure of other modalities.

**1.3.1 In vitro fertilisation (IVF):**

Twenty five to thirty percent of infertile couples are usually referred for IVF once other methods of treatment have failed (19). IVFprocedureinvolves surgical removal of oocytes (eggs) from the ovaries from a woman’s ovaries, fertilisation of oocytes in the laboratory and transferring the embryo back into the uterus. Since the birth of the first IVF baby in 1978, it is estimated that over 5 million babies have been born worldwide using this technique (20). The changing demographic and socioeconomic trends have resulted in increasing proportion of women seeking pregnancy at a later age resulting in an increased demand for fertility treatment over the years. Infertile couples are being increasingly drawn to IVF due to the high pregnancy rate per treatment cycle (21), compared with other therapies. However, it is a time consuming and challenging procedure which can also be a source of intense emotional strain due to high expectations of the couples undergoing treatment.

**1.3.2 Stages of IVF cycle:**

**Suppression of natural menstrual cycle:** This is done by daily injections for around two weeks to suppress the natural menstrual cycle. This step of down regulation is adopted in long protocols for IVF treatment. On the other hand, in short protocols, this stage is absent and treatment commences on day 3 of the menstrual cycle.

**Ovarian hyperstimulation:** This involves daily injection with follicle stimulating hormone (FSH). It is preceded by a baseline ultrasound scan of the uterus and ovaries and baseline hormone tests. This process will increase the number of eggs produced by the ovaries as compared to the natural menstrual cycle. It usually lasts for about 12-14 days depending on the response of the ovaries.

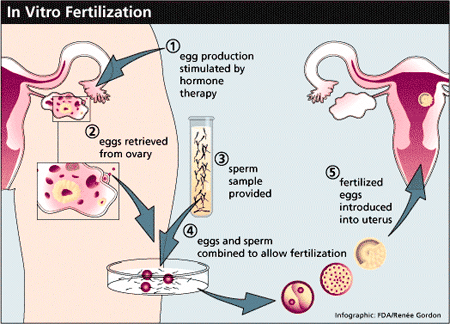
**Follicle tracking:** This is done by ultrasound scan and blood tests throughout the period of ovarian hyperstimulation. When the follicles have grown to meet the set criteria, human chorionic gonadotrophin injection is given 36 hours prior to oocyte retrieval to induce final maturation of oocytes.

**Oocyte retrieval:** This procedure is done under sedation. It involves a surgical technique of transvaginally aspirating the eggs with ultrasound guidance.

**Fertilisation of the eggs:** The eggs that are retrieved are then fertilised in the conventional way by culturing them *in vitro* in the laboratory or by injecting a single sperm into the egg by a process known as intracytoplasmic sperm injection (ICSI). The fertilised embryos are then cultured for 2-5 days depending on the number and quality of embryos.

**Embryo transfer:** The best quality embryo is selected from the available cohort and transferred into the uterus from day 2 to day 5 of the luteal phase.According to the NICE guidelines, elective single embryo transfer is offered to everyone. When there have been previous failed cycles or in cases where the woman’s age is over 37 years, up to two embryos can be transferred depending on the patient’s wishes.

**Figure 1.2: Stages of IVF cycle**

[](https://www.google.co.uk/url?sa=i&rct=j&q=&esrc=s&source=images&cd=&cad=rja&uact=8&ved=0ahUKEwiWja6pyJjVAhUEWBQKHfGHBGUQjRwIBw&url=https://babiesdesigned.wordpress.com/in-vitro-fertilization/&psig=AFQjCNFbnhXVB0tMeBK1pZGoANnUWWdceg&ust=1500664130127579)

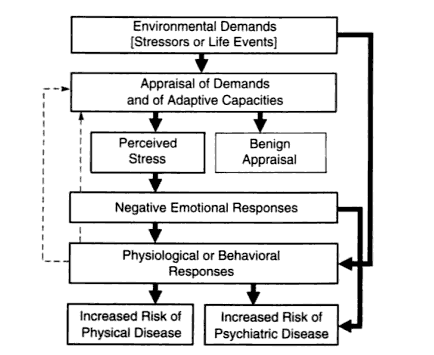
**1.3.3 Success and prognostic factors:** The success of IVF treatment depends mainly on the woman’s age. For the year 2010, the estimated live birth rates per treatment cycles ranged from 32.2% for women aged under 35 to 13.6% for women aged between 40–42 (22). The main factors that are used to predict the success rates are women’s age, duration of infertility, number of oocytes retrieved all of which reflect the ovarian function (1) .

* 1. **Impact of infertility on emotional health**

Infertility has been described by researchers as a ‘socially constructed reality’ rather than just medical impairment(23). Failure to achieve the desired social role of parenthood causes considerable psychological distress to couples. Infertility in women has been ranked the fifth highest serious global disability(8). The inability to have children has been shown to elicit feelings of low self-esteem, isolation, loss of control and depression (24). This can cause a significant disruption in people’s lives, leading to stress.

The term stress has been defined in various ways. Hans Selye defined stress as a real or perceived disturbance to an individual’s psychological wellbeing (25). He further divided stress into eustress and distress. Eustress is a positive form of stress that is deemed helpful and gives one the feeling of fulfilment in a challenging situation. Distress, however, is an aversive negative state that occurs when coping and adaptation processes fail to return a person to physiological and/or psychological homeostasis. The occurrence of eustress or distress is determined by an imbalance between the stressor, personal expectations, and resources available to cope with the stress. The transition of adaptive state of eustress into maladaptive state of distress depends on the duration and intensity of the stressor(25).

Cohen *et al* (26) conceptualised the relationship between stress and illness and discussed various approaches to measure stress. They put forward a model showing the integration of environmental, psychological and biological approaches to stress measurement. They proposed that individuals, when confronted with environmental demands, evaluate whether they have sufficient ability to cope with it. They may perceive themselves to be stressed if they find that the coping resouces are inadequate. The resulting negative emotional state then triggers physiological or behavioral responses which can threaten physical and emotional well-being (Figure 1.3). The model also illustrates that environmental demands can also directly risk illness in an individual just from the process of coping without perceived stress or negative emotions.

**Figure 1.3: Cohen’s model of stress based on integration of environmental, psychological and biological approaches**

Reproduced from ‘Measuring Stress’; book by Cohen, Kessler and Gordon

Two theoretical models have been identified that describe the psychological and emotional effects of infertility: a life crisis model, and a biopsychosocial model (27) .

The life crisis model described by Menning (28) views infertile couples as essentially having good mental health, but suggests they are exposed to a major negative event in the inability to achieve parenthood, which prevents them from fulfilling personal and societal expectations and goals. The crisis provokes a grieving reaction similar to that described by Kubler Ross (29), i.e. denial, anger, bargaining, depression and acceptance; the loss being the potential child and the parenting role. The strength and duration of the reaction depend on personality, coping style and motives for wanting children (30) but increases stress and anxiety, and reduces coping skills. This acute crisis of infertility can become a chronic stress condition if long-standing needing long-term intervention (31).

The biopsychosocial model of infertility (27) extends beyond the life crisis model. Biological, psychological and social phenomena interact and the effects are seen in the wider context of individuals, their relationships with partners, family and friends and society at large. The model suggests that infertility results in existential, physical, emotional and relationship stressors. Existential stressors include the effects of infertility on identity, self-image and self-esteem. Physical stressors are related to investigation and treatment which may involve undergoing painful procedures of an intimate nature, particularly for women. Emotional stressors are wide ranging, resulting in anger, depression and guilt to varying degrees. Relationship stressors relate to partner, family, friends and society. The model visualises infertility as a process with different stages, with the moderators of stress being social network support and coping.

There have been several studies which have investigated the emotional impact of infertility. These can be divided into qualitative and quantitative studies. Qualitative studies have predominantly presented infertility as a devastating experience especially for women. Some of the themes that emerged included feelings of loss of control, defectiveness, reduced competence, marital stress, feeling of alienation from the fertile world, social stigma, stressful nature of the treatment and strained relationship with health care providers (32). In a study by Freeman *et al* , 48% of the participants described infertility as their worst life experience(32). Shock and denial are widely reported by both men and women in the early stages of infertility (33). Women incorporate a self-identity as ‘infertile’ which becomes central to how they see themselves (34, 35). For some this continues even after they become pregnant (36). Self-esteem is reduced with feelings of defectiveness, incompetence and failure(36) . Women’s careers are put on hold to pursue treatment (34)and a sense of loss of control over their lives is frequently experienced (35), with feelings of powerlessness (37).

Women have described their emotional responses as grieving for the child that has never been(28). They describe feeling angry, intensely frustrated, and often anxious. Anger can be directed at themselves, their partners, friends and family, professionals involved in their care, or society at large. Men, on the other hand, tend more often to view infertility as disappointing, but not devastating. Their distress is often a response to their partner’s state and their own inability to solve the problem, rather than due to the infertility per se(35). Men and women both have considerable disruptions to their lives (38) due to a recurring monthly cycle of hope, anxiety and disappointment, when they are trying themselves to conceive, and while undergoing treatment(37). Substantial guilt about how past sexual behaviour and lifestyles may have affected fertility also can be experienced (28).

Personal relationships may become strained, with partners, family and friends(39), though there is also evidence of better relationships with partners(14). Sexual relationships can be strained because of the demand to time intercourse with ovulation and a perception that sex has become clinical and entirely about conception rather than an expression of love and intimacy(14). Relationships with pregnant friends or family members, or those with children often cause distress and emotional pain. Hence couples usually distance themselves for self-protection resulting in social isolation (37) . Blenner *et al* examined couple concordance in relation to couples being at different stages of the infertility process, and particularly not being in agreement about when to stop unsuccessful treatment. A lack of concordance is associated with an increased perception of distress (30, 40)

The findings from qualitative studies, however, have not generally been confirmed by quantitative research. Various studies have attempted to quantify the psychological effects of infertility. The different types of measures that have been used to measure the psychological effects are state and trait anxiety, depression, marital adjustment, marital satisfaction, sexual satisfaction, self-esteem, coping strategies, social support, well-being and quality of life.

Downey *et al* reported that infertile women believed they were highly distressed, although scores on standardised measures showed no differences from published population norms(41). Levels of state anxiety have generally been found to be elevated in infertile women compared with published population norms for the State Trait Anxiety Inventory (STAI) (42, 43). Raised levels of trait anxiety for men and women have been associated with poorer emotional responses to unsuccessful treatment (44). The only study identified that used a nationally representative sample confirmed an association between ‘sub-fecundity’ and generalised anxiety disorder(45).

Some studies reported raised levels of depression in infertile couples (46, 47) whereas others have failed to confirm this(41-43). Studies measuring marital adjustment and marital/sexual satisfaction have also been inconclusive. Marital adjustment has been defined as the accommodation of a husband and wife to each other at a given time (48). The majority of studies have found no significant differences in marital adjustment between the infertile and either published population norms or controls(49-51). On the other hand, some have found marital adjustment to be higher in infertile couples than in population norms (52, 53). Some studies have detected reduced sexual satisfaction for women during and after treatment (54), although others have failed to do so(55). Studies assessing self-esteem as an indicator of psychosocial wellbeing have also been split between those where no differences between the infertile and population norms have been found (55, 56), and those where a reduction in self-esteem in the infertile has been observed (52, 57).

It has been suggested that this lack of consistency in quantitative studies is due to failure to capture the emotional distress experienced by the infertile couples. This could be due to methodological flaws with regards to timing of measurement of distress, small sample sizes, poor sampling methods, lack of suitable controls and the use of general measures of psychological distress rather than measures specifically designed to measure distress of infertility. The difference between quantitative and quantitative studies could also be due to over exaggeration of the experiences of infertile women in qualitative studies.

**1.5 Impact of stress on reproduction**: Prolonged infertility can lead to chronic stress which has devastating effect on people’s lives. But stress is also known to cause or prolong infertility (58).

Prolonged stress can affect a range of physiological, hormonal and behavioural processes which affects physiological reproductive functioning. The various pathophysiological mechanisms by which stress can affect reproduction are as follows:

i. Acute stress activates the sympathetic adrenomedullary system (SAM) via the hypothalamus. This releases catecholamines norepinephrine in the brain and epinephrine in the adrenal medulla which can induce vasoconstriction in the uterus and ovaries, reducing their blood supply(59).

ii. Stress activated catecholamines can also affect fertility by interfering with the transport of gametes through the fallopian tube(59). The catecholamine secretion can be measured by salivary amylase. Lynch *et al* showed in her study that patients with increased salivary amylase have a 2 fold increased risk of infertility as compared to the ones with normal levels(60)

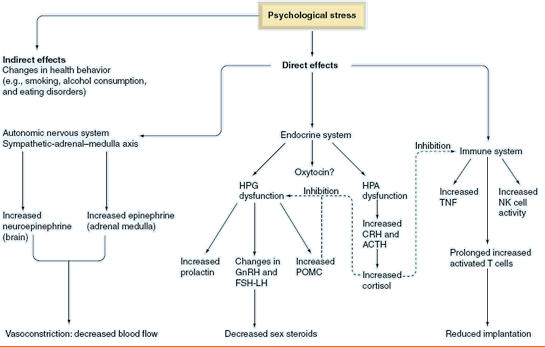
iii. When stress becomes long standing is activates the hypothalamo-pituitary (HPA) axis (61) which leads to increased secretion of prolactin and cortisol (Figure 1.3). Both these can effect on ovarian function by reducing GnRH drive(62). Wasser *et al* (1993) compared stress scores in four groups of infertile women with varying anatomical and hormonal profiles and concluded that some types of infertility may be stress-related through its effects on the HPA axis(63).

iv. Chronic stress is significantly associated with a high proportion of activated T cells in the peripheral blood which reduces embryo implantation (64)

v. Stress has also been implicated in decreased uterine receptivity through an ovarian-independent pathway(65). Kondoh *et al* in study transferred blastocysts from donor mice into the uterine lumen of ovariectomized mice following supplementation with estradiol and progesterone. The implantation was significantly reduced in the stressed recipient mice as compared to the controls. He proposed that stress altered uterine gene expression through an ovarian-independent pathway, resulting in decreased uterine receptivity.

vi. Stress is also known to alter the sperm quality(66). Harrison *et al* noted that semen quality was lower during IVF treatment than at other times leading to the assumption that stress during IVF may be responsible for this(67). Stoleru *et al* also noted that psychological factors were significant predictors of infertility in men(68).

vii. Indirect effects of stress: Indirect effects of stress are mediated by changes in health behavior which are detrimental to reproduction like smoking, alcohol and eating disorders.

**Figure 1.4 Effects of stress on reproduction**

**Source: Expert Review of Obstet Gynaecol 2008, Expert Reviews Ltd**

ACTH: Adrenocorticotropic hormone

GnRH: Gonadotrophin releasing hormone

FSH: Follicle stimulating hormone

LH: Luteinising hormone

NK: Natural Killer

The figure above shows various ways by which stress may affect physiological reproductive functioning in women. These include disturbances in gonadotrophin secretion, elevation of prolactin levels, local effects of catecholamines on the uterus and on the functioning of the fallopian tubes, disturbances to implantation as a result of immunological processes, and effects on behaviour such as drug or alcohol abuse and reduction in sexual activity (69, 70). However the evidence for stress being a factor in the aetiology of infertility, or for the prolongation of infertility, appears inconclusive. Demyttenaere *et al*, in their study of conception rates in normally fertile women having donor insemination, found significant correlations between baseline levels of trait anxiety as measured by the STAI and the number of treatment cycles needed to achieve a pregnancy (71). They also found that women who became pregnant but miscarried were initially more anxious. Lapane *et al* , in a population based study, have suggested that women with a history of depressive symptoms are almost twice as likely as those without depressive symptoms to report infertility(72). A number of studies have also suggested that increased stress levels may have detrimental effects on sperm quality (67, 73, 74).

A number of studies have focused on women or couples undergoing assisted reproduction, and in particular IVF, to assess whether treatment outcomes are affected by increased stress levels.

**1.7 Rationale for the study:** In the above sections we haveseen that stress can be both a cause and consequence of infertility. Moreover, infertile women who seek treatment find the experience even more stressful than infertility itself. Stress levels in women undergoing IVF have been measured using various parameters like anxiety, depression, mood, and positive and negative affect. Studies have reported higher anxiety (75, 76) and depression (77, 78) in patients undergoing IVF as compared to the control group. Verhaak *et al*.(79) observed that most women’s anxiety and general distress increased during the course of IVF treatment cycle. HPA activation due to stress can cause premature release of LH and luteinisation of the follicle, which can potentially damage the oocyte and also affect implantation in IVF cycles(80). If increased stress levels are known to prevent conception, then the question that needs answering is: does increased stress levels due to infertility and IVF reduce the chances of successful outcome?

The emotional burden of infertility and its treatment is being increasingly recognised as a significant priority as an increasing number of people undergo IVF and a significant proportion of them are not successful with the treatment. The evidence from existing literature seems to suggest higher levels of anxiety and depression in IVF patients, but the effect this has on the conception rates is inconclusive. Some studies reported significantly increased anxiety in patients who did not conceive with IVF as compared to the pregnant group(78, 81) , while others did not observe this (82). Similar inconsistences were also observed with regards to the effect of depression on conception rates after IVF(83, 84).

Two meta-analyses that have been published also show inconsistent results. The first meta-analysis by Boivin *et al* (85)which included 14 relevant studies did not find a relationship between distress and IVF outcome. The other meta-analysis by Matthiesen and colleagues was more comprehensive in that it examined stress, anxiety and depression individually and found a small but significant association between stress and reduced pregnancy chances after IVF (86)

A number of studies have looked at treatment persistence and reasons for early discontinuation of treatment. Early discontinuation in this context relates to a decision made by the couple, rather than advice given by professionals. In a study from Sweden, where three IVF cycles are state funded(87), it was found that 242 of the 450 couples not achieving a pregnancy stopped treatment before completing their three funded cycles. Amongst these couples the most common reason (26%) for discontinuing was psychological strain. This is supported in other studies (88-90). Strauss *et al* found that interpersonal problems and levels of psychological strain were predictive of which women would discontinue treatment early despite having not achieved a pregnancy, and that both men and women in couples who stopped treatment early reported more problems and conflict in their relationships than those who continued treatment. If couples are discontinuing treatment early because of psychological strain, then this could be indirectly affecting outcome.

Cousineau and Domar in their study showed that psychological interventions in couples undergoing IVF appeared to reduce anxiety, depression and increase pregnancy rates (91). A study by Domar *et al* reported increased pregnancy rates after a mind-body intervention programme to reduce stress during IVF was introduced (92). In a randomized trial, psychological distress and natural-killer-cell activity, both reduced significantly in women who received a five-session mind/body intervention resulting in higher pregnancy rates of 38% in the intervention group as compared to 13.5% in the controls (93). A recent meta-analysis suggested that psychosocial interventions for couples undergoing infertility treatment could be effective in reducing psychological distress and in improving pregnancy rates(94). These results do raise the possibility of a significant link between distress reduction and IVF outcome.

As increasing number of couples seek IVF treatment, it is important to know if psychological distress that is experienced during IVF is detrimental to the outcome. So far the studies have been inconclusive due to the differences in the variables used to assess stress, measurement tools and timing of stress assessment . In our next chapter we systematically review the evidence correlating emotional distress and IVF outcome.

**Chapter 2: A systematic review of the literature**

|  |
| --- |
| Overview  2.1 Background  2.2 Aims & Objectives  2.3 Methods  2.4 Results  2.5 Discussion of literature review  2.6 Conclusion of literature review |

**2.1 Background**

We have seen in the previous chapter that patients having IVF treatment often go through a roller coaster of emotions as they pass through various stages in their treatment process. There have been several studies linking psychological distress and reduced chances of pregnancy after IVF (95-98), but these results are inconsistent. The three meta-analyses that were performed in this topic also vary in their conclusions (85, 86, 99). Ebbesen *et al* examined the effect of depression on pregnancy outcome after IVF, while Boivin *et al* analysed the impact of pre-treatment anxiety and depression on IVF outcome. While the former study found a modest impact of depression on the success of IVF, while the latter found no such association. The third meta-analysis was done by Matthiesen *et al* and it was a bit more comprehensive. It examined stress, anxiety and depression and found significant link between stress and distress and decreased pregnancy rates after IVF. This lack of consensus in the meta-analyses can be explained by the fact that there were different inclusion criteria for each of the study and the diverse stress parameters were examined.

**2.2 Aims and Objectives**: To elucidate the connection between emotional distress and reproductive outcome, we conducted a systematic review of the available literature exploring the influence of emotional distress on the clinical pregnancy after IVF treatment focusing on various stress parameters individually. The aim of this review was to critically analyse the evidence exploring the association between stress and conception rates. The psychological distress that occurs before start of the IVF cycle avoids the confounding effects of treatment and procedure related stress. Pre-treatment distress has been the most common reason given by women who drop out of IVF treatment(90).The objective of this literature review was to correlate pre-treatment emotional distress to clinical pregnancy rate after IVF cycle.

**2.3 Methods:**

An extensive literature search was done of all the electronic databases. This search was applied to PubMed (1980-2013), ISI Web of Science (1985-2013), Biosis Citation Index (1969-2013), Medline (1950-2013), Psych INFO (1985-2013) and Applied Social Science Index & Abstracts (1987-2013). The search terms used were *anxiety, emotion\*, psychological stress, depressive disorder, depression, and distress AND in vitro fertilisation*, *IVF*, *intracytoplasmic sperm injection,* *ICSI*, *assisted conception, assisted reproduct\*.* MeSH terms were used in PubMed. Reference lists and bibliography of relevant papers were also hand searched for additional citations.

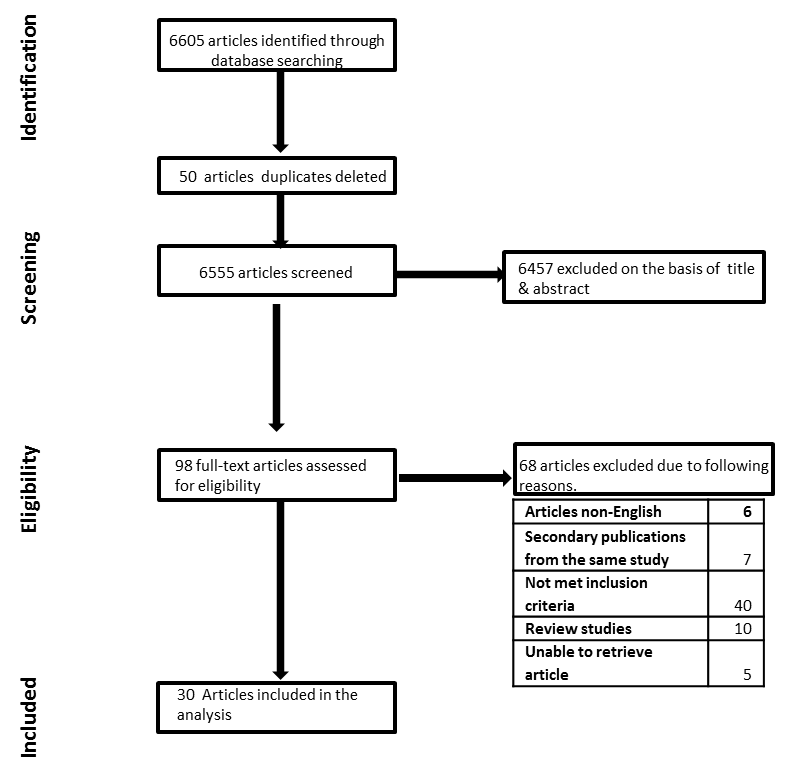
**2.3.1 Eligibility criteria**:

Prospective studies measuring psychological distress in patients undergoing IVF at the start of ovarian stimulation were included. The outcome of treatment was assessed in the form of clinical pregnancy after a single cycle of IVF or ICSI. Clinical pregnancy was defined as the diagnosis of intrauterine viable pregnancy confirmed by ultrasound examination. All studies that included donor gametes, frozen embryo replacement and artificial insemination were excluded. Non- English articles were also excluded from the review.

**2.3.2 Data collection process:**

A total of 6605 articles were extracted using the above search strategy. Of these 148 studies appeared meaningful. After excluding duplicates (n=50), abstracts and full texts of 98 studies were scrutinised as per the selection criteria. 30 studies were included in the review that fulfilled the inclusion criteria.

**Figure 2.1: Flow diagram of study selection**

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**2.3.3 Psychological Variables**

**Anxiety**: Anxiety is the psychological state associated with feelings of worry, nervousness, fear and concern (100). It is a normal reaction to stress and has been used extensively to measure and monitor stress. The two types of anxiety that are measured are state and trait anxiety. State anxiety is a temporary change in a person's emotional state characterized by feelings of tension and apprehension in response to an external stressor. It is a transitory phase and changes according to the particular situation. Trait anxiety refers to a general level of stress that is characteristic of an individual, attributed to their personality. It varies according to how individuals have conditioned themselves to respond to and manage stressful situations.

**Depression**: Depression is characterized by persistent low mood and a negative view of self (101). When persistent, it can compromise day to day functioning of an individual. Depression can inhibit reproductive function by abnormal regulation of luteinising hormone.

**Stress**: Stress refers to an individual’s reaction when faced with challenges beyond their coping abilities(25). When stress is prolonged or not resolved through coping or adaptation, it can have an adverse effect on an individual’s physical and emotional well-being.

**Fertility specific problems**: Infertility is a stressful experience that is capable of causing disruption in personal life and impacts social relationships with others. Generic questionnaires referring to anxiety and depression may not be able to capture specific issues relating to infertility. Fertility specific instruments can measure multidimensional infertility related stress which is a better indicator of emotional distress experienced by couples having IVF.

**Biochemical markers of stress**: In addition to behavioural features, stress can also be measured using hormonal markers. Serum prolactin is a known stress marker and hyperprolactinemia can interfere with gonadotrophin secretion and disrupt ovarian function. Stress also causes increase in secretion of cortisol and catecholamines by activating the hypothalamic-pituitary axis.

**2.3.4 Calculating effect sizes**

The effect sizes were calculated for each study which reflected the strength of association between distress scores and clinical pregnancy.A negative effect size indicates a negative association between psychological distress and clinical pregnancy after assisted conception.Effect sizes were calculated from mean scores and standard deviation of pregnant and non-pregnant groups. In some studies, effect size correlation could not be calculated due to insufficient data. Meta-analysis was not conducted due to severe heterogeneity between the studies.

* 1. **Results:**

**2.4.1 Study characteristics**: All 30 studies included in the review were prospective cohort studies. Four articles were abstracts published from conferences. The studies were evaluated in terms of selection of participants, measures of distress used, the instruments used to measure them and comparability of groups on outcome to ensure they fit the inclusion criteria but no specific scale was used. The studies included a total of 5683 patients. All participants were referred for IVF or ICSI treatment. The outcome of the treatment was determined by diagnosis of clinical pregnancy at the end of one treatment cycle. Psychological distress was measured using generic and fertility specific instruments. Five studies also assessed biochemical markers of stress. The mean stress scores were compared between pregnant and non-pregnant groups. The study characteristics are summarised in Table I, and the instruments are listed in Tables II, III & IV. All studies stated clinical pregnancy as their main outcome. Some also summarised biological end points such as the numbers of oocytes retrieved and fertilised (102, 103). A few presented live birth rates (104).

**Table 2.1. Characteristics of studies included in the review n=30**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Conclusion | 1. Women with a high Zung depression score, high active coping, high avoidance, and a high expression of emotion have lower pregnancy rates. 2. High anticipatory state anxiety levels and high anticipatory prolactin & cortisol concentrations have lower pregnancy rates.3. Women with high prolactin concentrations seem to have more oocytes but lower fertilisation rates | 1. Early Follicular phase: Conceiving (C) group had higher state anxiety and depression than the non-conceiving (NC) group but trait anxiety remained same. 2. Oocyte retrieval: C had higher anxiety and depression. Increased prolactin and cortisol in both groups. 3. Embryo transfer. Both groups were lower in all parameters. 4. Pregnancy test: Both groups were higher in all parameters. C showed negative correlations between the psychological measures and both hormones while NC showed no correlation | No indication was obtained of the possible prognostic value of psychosocial factors in predicting the chances of IVF success. | Pre-treatment distress had no significant association to clinical pregnancy. Women who did not conceive had more stress during treatment as shown by the DRK scores. Biological variable in these patients were also found to be related to stress. The direction of causality between stress and IVF outcome remains speculative. | 1. Prolactin, Cortisol & State anxiety all increased during stimulated IVF  2. There was a trend toward lower state and trait anxiety in pregnant women but the scores were not statistically significant. |
| Outcome of IVF | 10 pregnancies, 2 miscarriages | 23 pregnancies, 19 failed oocyte retrievals, 9 failed embryo transfers | 18 Clinical pregnancies. 30 patients did not reach the stage of embryo transfer | 17 pregnancies | 21 pregnancies |
| Parameters measured | State Anxiety Depression Coping | State & Trait Anxiety Depression Prolactin Cortisol | State Anxiety Depression Uncertainty Specific anxiety Fear of failure Practical issues | Marital satisfaction Anxiety Social desirability Coping Adjustment to infertility Childbearing focus Stress score | State & trait anxiety  Serum prolactin & Cortisol |
| Timing of measurement | Day 4-5 of cycle | Day 3-4 of cycle | Prior to IVF  3 weeks post Egg recovery | >1.8months before treatment | Day 2-4 of cycle |
| Outcome measure used | STAI,  Zung Depression,  UCL (Dutch version of westbrook coping scale)  Prolactin ,Cortisol | Personal Background Questionnaire  Depression Adjective Check list,  STAI,  Prolactin & Cortisol | IVF attitude scale  STAI  Hopkins-Symptoms-Checklist | Marital Adjustment Scale, STAI, Social desirability Scale, Miller Behavioural Style Scale, Infertility Questionnaire, Childbearing focus, Daily record keeping sheet | STAI,  Prolactin & Cortisol |
| Participants | 40 consecutive patients from infertility clinic | 113 married couples with no previous completed pregnancy and had unexplained or tubal infertility. | 126 women with first time IIVF. | 40 women with first time IVF. | Part1: Controls =24,  Unstimulated IVF=25,  Stimulated IVF=26.  Part 2: 95 patients having stimulated IVF |
| Study | Demyttenaere (1992) (69) | Merari (1992)(78) | Visser (1994)(76) | Boivin & Takefman (1995)(105) | Harlow (1996) (75) |
| No. | 1. | 2. | 3. | 4. | 5. |

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| --- | --- | --- | --- | --- | --- |
| Conclusion | 1. The non-pregnant group reported increased expression of negative emotions.  2. Increased depressive score was associated with lower pregnancy rates in female cause of infertility, whereas in male infertility, increased depressive symptomatology was associated with higher pregnancy rate. | State anxiety, trait anxiety, and depression were significantly lower in pregnant women than non-pregnant women. | 1. Significant relationship between baseline psychological factors and probability to become pregnant after IVF/ICSI.  2. State anxiety had a slightly stronger correlation to treatment outcome than depression | 1. Adrenaline/Cr ratio before treatment was positively associated with the scores of questionnaires on depression and state anxiety before treatment.  2. Scores on the BDI, State anxiety & Adrenaline/Cr ratio were significantly higher in the non-pregnant group versus the pregnant group at pre-treatment(*P* <0.05) | 1.At pre-treatment, the women who became pregnant showed lower levels of depression than those who did not.  2.Higher levels of depression in the non-pregnant women were due to a higher score on cognitive aspects of depression |
| Outcome of IVF | 23 pregnancies | 47 pregnancies | Not reported | Not reported | 59 women pregnant |
| Parameters measured | Depression  Coping | State & Trait anxiety, Depression | State & Trait Anxiety  Depression | State & Trait Anxiety  Depression  Urinary catecholamines & cortisol | State anxiety  Mood and marital satisfaction |
| Timing of measurement | Day 3 of cycle | Not specified | Days10-20 of the cycle preceding the stimulation cycle | Before treatment(T1) | 3 to 12 days before the start of their first treatment cycle |
| Outcome measures used | Zung depression,  UCL | STAI,BDI | STAI and BDI | STAI and BDI  Nocturnal urine test | STAI,BDI,POMS |
| Participants | 98 consecutive patients with primary infertility | 138 IVF patients 77 fertile controls | 237 patients having first time IVF. | 118 patients having first time IVF | 207 patients having first time IVF |
| Study | Demyttenaere (1998) (77) | Kee (2000)(106) | Smeenk (2001-a) (95) | Smeenk (2001-b) (107) | Verhaak (2001) (84) |
| No. | 6. | 7. | 8. | 9. | 10. |

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| --- | --- | --- | --- | --- | --- |
| Conclusion | Baseline (acute and chronic) stress affected biologic end points (i.e., number of oocytes retrieved and fertilized), as well as pregnancy, live birth delivery, birth weight, and multiple gestations. | Neither stress nor anxiety, measured at start of the cycle, appeared to be predictive of the IVF cycle results | Women with episodic anxiety,(high state anxiety before IVF cycle both times) were less likely to become pregnant after the second IVF/ICSI. | For women who were moderately concerned about missing work, the odds ratio was 2.83 for not achieving a pregnancy and those who were extremely concerned about finances had a very high risk (odds ratio 11.62) of not achieving a successful live birth  . | Trait anxiety, optimism and coping were all significant indicators of a single latent construct which was a better predictor of biological response to treatment than were any of them individually. |
| Outcome of IVF | 48 pregnancies & 30 live births | 21.6% pregnancy rate | 15 pregnancies | 48 pregnancies & 30 live births | 13 pregnancies |
| Parameters measured | Positive and Negative affect Anxiety, Depression Infertility-related stress Perceived stress | State and Trait anxiety  Stress | Episodic, Acute and Trait anxiety | Procedural concern  Missing work concern  Concerns regarding successful result and finances | Dispositional optimism  Trait anxiety  Escapist coping  Peak oestradiol |
| Timing of measurement | First clinic visit (baseline)  During treatment (procedural) | At initiation of the cycle | Before and after first IVF cycle | Baseline during initial clinic visit and during procedure | 3 months prior to treatment |
| Outcome measures used | PANAS, POMS, PSS Infertility reaction scale, Expected likelihood of achieving a pregnancy scale, Network resource scale, Ways of coping scale. | State Trait Anxiety Inventory  Stress perception scale | State Trait Anxiety Inventory | CART questionnaire | LOT  STAI  Ways of Coping Questionnaires |
| Participants | 151 patients having IVF | 545 couples having IVF | 47 patients having second cycle of IVF | 151 patients having IVF | 97 women having IVF |
| Study | Klonoff-Cohen (2001)(102) | Guinard (2003) (108) | Eugster (2004) (109) | Klonoff- Cohen (2004) (110) | Boivin & Lancastle (2005) (111) |
| No. | 11. | 12. | 13. | 14. | 15. |

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| --- | --- | --- | --- | --- | --- |
| Conclusion | No differences in psychological variables between pregnant and non-pregnant populations | Negative emotion inversely predicted embryo quality among women with poor prognosis but not among good or average prognoses. | Pregnant couples had higher need for parenthood, loss of sexual enjoyment, higher negative view of child free lifestyle and total stress scores. | Women who expressed less negative affect at baseline were less likely to achieve live birth | Significant association between depression/anxiety and pregnancy rate (p=0.034 and p=0.00 respectively). Logistic regression model showed that anxiety/depression affect the outcome of ART significantly. |
| Outcome of IVF | 58 pregnancies | 364 pregnant women | 69 pregnant | 73 patients had live birth | 25 clinical pregnancies |
| Parameters measured | Depressed mood and anxiety  Guilt, Success, anger, Anxiety, satisfaction, depression. powerlessness, competence & control | Positive & negative affect:  Depressive symptoms  Overall life satisfaction Optimism: | Fertility problem inventory:  Social concern Sexual concern Relationship concern Negative view of child free lifestyle Global stress score | Anxiety & Depression  Positive & negative affect Daily record keeping chart | Anxiety & Depression |
| Timing of measurement | 1 month before treatment | Day 3 of the cycle | As a part of psychological evaluation for IVF. | At IVF planning visit within 6 weeks of commencing treatment | Prior to starting medications |
| Outcome Measures used | PGWB  14 items regarding psychological effects of infertility was assessed | PANAS, Centre for Depression Scale, Satisfaction with Life Scale, Attributional style Questionnaire | FPI | Hospital Anxiety and Depression Scale  Daily Record Keeping Chart | Iranian Cattle Anxiety and Beck Depression Inventories (BDI) |
| Participants | 139 women having first time IVF | 595 women having IVF | 129 first time IVF | 289 having first time IVF | 106 First cycle of ICSI |
| Study | Anderheim (2005) (96) | Lee (2006) (112) | Cooper (2007)(113) | de Klerk (2008)(114) | Sohrabvand (2008) (115) |
| No. | 16. | 17. | 18. | 19. | 20. |

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| --- | --- | --- | --- | --- | --- |
| Conclusion | 1 Women who became pregnant reported fewer non-fertility-related negative life-events prior to IVF. 2. Logistic regression analyses revealed that the number of negative life-events remained a significant predictor of pregnancy | Neither baseline nor procedural anxiety, nor depression affected the on-going pregnancy rates | 1. Depression scores were significantly low in pregnant group at baseline and oocyte retrieval. 2. Women with negative pregnancy had higher rating of state anxiety at oocyte retrieval | Stress levels were linearly related to bHCG positivity (OR 1.18, P<0.02) and clinical pregnancy (OR 1.16, p<0.03). | Stress and anxiety levels were lower in the pregnant women all through the cycle. But this difference was statistically significant only at T2(day before oocyte retrieval) |
| Outcome of IVF | 215 clinical pregnancies. | 196 pregnancies | 39 pregnancies |  | 15 pregnancies |
| Parameters measured | Life Events Perceived Stress Depressive symptoms | State anxiety & procedural anxiety Depression | State & Trait anxiety Depression | Self-reported stress on a scale from 1 to10 | State & Trait anxiety  Perceived stress |
| Timing of measurement | During pituitary down regulation | One to two months prior to treatment | Before treatment and at oocyte retrieval | Initial visit to fertility clinic | Prior to ovarian stimulation |
| Outcome measures used | List of recent events, PSS & BDI  2 weeks prior to treatment cycle. | STAI, BDI | STAI, BDI | Infertility-related stress scale | STAI,PSS, Infertility Self-Efficacy Scale (ISES) |
| Participants | 809 first time IVF | 421n fist time IVF | 80 couples with unexplained infertility | 217 consecutive women having first time IVF | 44 women having IVF |
| Author | Ebbesen (2009)(104) | Lintsen (2009)(116) | Gurhan (2009)(117) | Hunter (2010)(118) | Turner (2010)(119) |
|  | 21. | 22. | 23. | 24. | 25. |

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| --- | --- | --- | --- | --- | --- |
| Conclusion | Baseline psychological stress (both anxiety and depression) may negatively influence the clinical pregnancy rate of IVF in women with tubal factor infertility | 1 Women who became pregnant had lower levels of fertility-related stress, state anxiety and depression than women who did not become pregnant.(p<0.001) | No statistically significant correlations between salivary cortisol , FPI scores and clinical pregnancy and live birth. | Pre-IVF anxiety & depression was not significantly different in women whose IVF cycles were successful as compared with those whose cycles failed. | 1. State anxiety and depression negatively correlated with pregnancy and live birth but the scores were not statistically significant. 2. State anxiety positively associated with norepinephrine and cortisol which were significantly low at the time of oocyte retrieval in pregnant women. |
| Outcome of IVF | 50 pregnancies | 41 pregnancies. | 34 pregnancies | 57 clinical pregnancies. | 92 pregnancies |
| Parameters measured | Baseline psychological stress (Anxiety & Depression) | State anxiety Depression Infertility-related stress | Fertility-related stress, salivary cortisol | Anxiety & Depression | Anxiety, Depression, Norepinephrine, Cortisol |
| Timing of measurement | First day of down regulation | Before treatment upto follicular phase | Saliva Cortisol: Day 1,2, 3 of cycle. FPI; Day 2 of cycle | Baseline: First clinic visit | Before the start of treatment (T1) Day of oocyte retrieval (T2),day of pregnancy test (T3), 8 weeks of gestation (T4) |
| Outcome measures used | Zung Self-rating Anxiety (SAS) and  Depression Scales (SDS) | STAI, CES-D, FPI. | Saliva Cortisol, FPI | Center for Epidemiologic Studies Depression scale (CES-D)  State-Trait Anxiety Inventory | STAI, BDI, Norepinephrine, Cortisol |
| Participants | 107 women having first time IVF or ICSI | 160 women having first time IVF or ICSI | 63 women having IVF | 202 women having first time IVF | 264 having first time IVF or ICSI |
| Author | Li XH(2011)(120) | Gourounti (2011)(104) | Nouri (2011)(103) | Pasch (2012)(121) | An Yuan (2013)(122) |
|  | 26. | 27. | 28. | 29. | 30. |

**Table 2.2. Instruments that have been used to measure anxiety and depression**

|  |  |  |  |
| --- | --- | --- | --- |
| **Study** | **Instrument** | **Items** | **Parameters measured** |
| Demyttenaere 1992 | State Trait Anxiety Inventory (STAI) | 40 | State Anxiety |
| Merari 1992 |  |  | Trait Anxiety |
| Visser 1994 |  |  |  |
| Boivin 1995 |  |  |  |
| Harlow 1996 |  |  |  |
| Kee 2000 |  |  |  |
| Smeenk 2001-a |  |  |  |
| Smeenk 2001-b |  |  |  |
| Verhaak 2001 |  |  |  |
| Klonoff-Cohen 2001 |  |  |  |
| Guinard 2003 |  |  |  |
| Boivin 2005 |  |  |  |
| Lintsen 2009  Gurhan 2009 |  |  |  |
| Turner 2010 |  |  |  |
| Gourounti 2011 |  |  |  |
| Pasch 2012 |  |  |  |
| An Yuan 2013 |  |  |  |
|  |  |  |  |
| Kee 2000 | Beck’s depression inventory (BDI) | 21 | Depression |
| Smeenk 2001-a |  |  |  |
| Smeenk 2001-b |  |  |  |
| Verhaak 2001 |  |  |  |
| Sohrabvand |  |  |  |
| Ebbesen 2009 |  |  |  |
| Lintsen 2009 |  |  |  |
| An Yuan 2013 |  |  |  |
|  |  |  |  |
| Lee 2006 | Center for Epidemiological studies- | 20 | Depression |
| Gourounti 2011 | Depression (CES-D) |  |  |
| Pasch 2012 |  |  |  |
|  |  |  |  |
| Demyttenaere 1992 | Zung Depression scale (SDS) | 20 | Depression |
| Demyttenaere 1998 |  |  |  |
| Li XH 2011 |  |  |  |
|  |  |  |  |
| De Klerk 2008 | Hospital Anxiety Depression Scale(HADS) | 14 | Anxiety  Depression |
|  |  |  |  |
| Merari 1992 | Depression Adjective Checklist(DACL) | 34 | Positive mood  Negative Mood |
|  |  |  |  |
| Li XH 2011 | Zung Anxiety scale (SAS) | 20 | Anxiety |
|  |  |  |  |
| Verhaak 2001 | Profile of Mood States | 20 | Positive mood  Negative Mood |

**Table 2.3. Instruments that have been used to measure stress**

|  |  |  |  |
| --- | --- | --- | --- |
| **Study** | **Instrument** | **Items** | **Parameters measured** |
| Klonoff-Cohen 2001 | Perceived Stress Scale (PSS) | 10 | Perceived Stress |
| Ebbesen 2009 |  |  |  |
| Turner 2010 |  |  |  |
| Guinard 2003 |  |  |  |
|  |  |  |  |
| Klonoff-Cohen 2001 | Positive Affect Negative Affect Schedule | 20 | Positive affect |
| Lee 2006 | (PANAS) |  | Negative affect |

**Table 2.4.** Instruments that have been used to measure other general psychological parameters in IVF patients

|  |  |  |  |
| --- | --- | --- | --- |
| **Study** | **Instrument** | **Items** | **Parameters measured** |
| Visser 1994 | Hopkins-Symptoms Checklist | 36 | Symptoms of anxiety and depression |
| Anderheim 2005 | Psychological General Well-being Index\*(PGWB) | 22 | Depressed mood and anxiety |
| Ebbesen 2009 | List of recent events | 37 | Negative life events |
| Lee 2006 | Satisfaction with life scale\* | 5 | Satisfaction with life |
| Lee 2006 | The Attributional Style Questionnaire | 12 | Optimism |
| Demyttenaere 1992 | UCL(Westbrook coping scale) | 7 | Coping strategies |
| Demyttenaere 1998 |  |  |  |
| Klonoff-Cohen 2001 | Ways of Coping scale | 66 | Coping with stressful encounter |
| Boivin 2005 |  |  |  |

**\* Ad-hoc Instrument**

**Table 2.5. Instruments that have been used to measure fertility specific distress**

|  |  |  |  |
| --- | --- | --- | --- |
| **Study** | **Instrument** | **Items** | **Parameters measured** |
| Visser 1994 | Infertility attitude scale | 22 | Insecurity, Fear of failure, Specific anxiety, practical problems |
| Boivin 1995 | Daily record keeping chart | 21 |  |
| De Klerk 2008 | Daily record keeping chart | 21 |  |
| Boivin 1995 | Infertility questionnaire | 21 | self-esteem, guilt/blame, sexuality |
| Klonoff-Cohen 2001 | Infertility reaction scale(IRS) | 5 | perception & feelings twards infertility |
| Klonoff-Cohen 2004 | Concerns during Assisted Reproductive Technologies (CART) Scale | 9 | procedural concerns, missing work, achieving a successful delivery |
| Anderheim 2005 | Psychological effects of infertility | 14 | Psychological stress of infertility |
| Cooper 2007 | Fertility Problem Inventory | 46 | Social concern, sexual concern, |
| Gourounti 2011 |  |  | relationship concern, negative view of childfree life-style, |
| Nouri 2011 |  |  | need for parenthood, global stress |
| Hunter 2010 | Infertility related stress scale (Visual Analogue scale) | 1 | Self-report of stress |
| Turner 2010 | Infertility self-efficacy scale | 16 | Coping with infertility |

**2.4.2 Emotional Distress & IVF outcome**

Emotional distress from all studies was classified into state anxiety, trait anxiety, depression, stress, fertility specific problems and biochemical markers of stress. The effects of each measure on the outcome of assisted conception has been summarised in tables V, VI, VII, VIII & IX.

**State Anxiety:** 23 articles analysed the effects of state anxiety on conception rates. Three studies found state anxiety higher in couples undergoing IVF treatment as compared to fertile controls, while one article reported noted similar state anxiety levels in both groups. Visser *et al* found higher state anxiety in couples prior to IVF treatment than a representative group of local normal population in the age range 16-40 years(76). This finding was also confirmed by Harlow *et al*, where an increase in state anxiety scores was demonstrated in women undergoing gonadotropin-stimulated IVF treatment, in parallel with increases in serum prolactin and cortisol, as compared to a control group having similar laparoscopic surgery (123). However, both these studies reported that women who achieved pregnancy had similar state anxiety scores to those who failed, suggesting that the degree of anxiety observed during IVF treatment is unlikely to influence the conception. Similar results were found by Boivin *et al*, Guinard *et al*, and Lintsen *et al* [Boivin, 1995, STRESS LEVEL ACROSS STAGES OF IN-VITRO FERTILIZATION IN SUBSEQUENTLY PREGNANT AND NONPREGNANT WOMEN](105, 108, 116). In contrast to this, 6 studies found pre-treatment state anxiety to be significantly lower in people who conceived with IVF (69, 95, 97, 106, 107, 109, 115). Demyttenaere *et al* found that a high level of state anxiety at the start of follicular phase was significantly associated with lower IVF success rates. This correlation between state anxiety and IVF outcome was also reported by Kee *et al*, Smeenk *et al*, Sohrabvand *et al* and Gourounti *et al* (95, 106, 115, 124). A similar trend had been observed by other studies but the numbers did not reach statistically significance (84, 108, 116, 117, 119, 121). Merari *et al* on the contrary, observed that raised state anxiety and depression scores were higher in women who successfully conceived with IVF (78). This study found that couples who became pregnant expressed their emotions and concerns more openly than the non-pregnant group. It may be assumed that these couples resorted less to mechanisms such as repression and denial to deal with their stress. A similar trend was observed by de Klerk (2008) in their study, where women who expressed less negative affect at baseline were less likely to achieve live birth(114).

**Trait anxiety**: Two studies found higher trait anxiety in IVF patients than fertile controls (75, 78) while one other study did not confirm this. In the study by Kee *et al,* pre-treatment trait anxiety was noted to be significantly lower in pregnant women (106) as compared to women who did not conceive. Other studies also demonstrated a similar trend towards lower trait anxiety in the pregnant women, but this difference was not statistically conclusive (Table 2.6). In the study by Lancastle & Boivin, trait anxiety by itself was not predictive of the success of treatment, but combined with escapist coping and optimism were significant indicators of an underlying latent psychological construct, which was a better predictor of reproductive outcome than any variable on its own (111).

**Table 2.6. Correlation of anxiety to clinical pregnancy after IVF**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Measure | Study | Instrument | Participants | No of patients | Effect size Correlation | Statistical significance |
| State anxiety | Demyttenaere 1992 | State Anxiety Inventory | Women having IVF | 40 | -0.32 | **p=0.03** |
|  | Merari 1992 | State Anxiety Inventory | Unexplained or Tubal infertility | 113 | 0.14 | Not significant |
|  | Visser 1994 | State Anxiety Inventory | First IVF | 65 | -0.01 | Not significant |
|  | Boivin 1995 | State Anxiety Inventory | Women having first IVF | 40 | -0.18 | Not significant |
|  | Harlow 1996 | State Anxiety Inventory | Women having stimulated IVF | 57 | 0.03 | Not significant |
|  | Kee 2000 | State Anxiety Inventory | Women having IVF | 138 | -0.59 | **p<0.05** |
|  | Smeenk 2001-a | State Anxiety Inventory | First IVF | 237 | -0.01 | **p=0.01** |
|  | Smeenk 2001-b | State Anxiety Inventory | First IVF | 118 | not available | **p<0.05** |
|  | Verhaak 2001 | State Anxiety Inventory | First IVF or ICSI | 207 | -0.11 | Not significant |
|  | Klonoff-Cohen 2001 | State Anxiety Inventory | Women having IVF | 123 | -0.08 | **P=0.04** |
|  | Guinard 2003 | State Anxiety Inventory | Couples having IVF & ICSI | 545 | not available | Not significant |
|  | Eugster 2004 | State Anxiety Inventory | Women having 2nd cycle of IVF/ICSI | 43 | -0.29 | Not significant |
|  | Anderheim 2005 | PGWB Index | First IVF/ICSI | 139 | -0.08 | Not significant |
|  | De Klerk 2008 | HADS | First IVF or ICSI | 289 | 0.01 | Not significant |
|  | Boivin 2005 | State Anxiety Inventory | Women having IVF | 76 | -0.07 | Not significant |
|  | Sohrabvand 2008 | Cattle Anxiety Inventory | Consecutive women with ICSI | 106 | -0.76 | **p=0.0** |
|  | Lintsen 2009 | State Anxiety Inventory | First IVF or ICSI | 421 | -0.01 | Not significant |
|  | Gurhan 2009 | State Anxiety Inventory | Unexplained infertility ICSI | 80 | -0.19 | Not significant |
|  | Turner 2010 | State Anxiety Inventory | First & repeat IVF patients | 36 | -0.21 | Not significant |
|  | Gourounti 2011 | State Anxiety Inventory | First IVF or ICSI | 160 | -0.5 | **p<0.001** |
|  | Li XH 2011 | Zung Anxiety Scale | First IVF or ICSI | 107 | 0.02 | Not significant |
|  | Pasch 2012 | State Anxiety Inventory | First IVF | 202 | -0.06 | Not significant |
|  | An Y 2013 | State Anxiety Inventory | First IVF or ICSI | 353 | -0.11 | Not significant |

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Measure | Study | Instrument | Participants | No of patients | Effect size Correlation | Statistical significance |
| Trait anxiety | Merari 1992 | State Anxiety Inventory | Married couples>2 years infertility | 113 | -0.02 | Not significant |
|  | Boivin 1995 | State Anxiety Inventory | Women having first IVF | 40 | -0.1 | Not significant |
|  | Harlow 1996 | State Anxiety Inventory | Women having stimulated IVF | 58 | 0.0 | Not significant |
|  | Kee 2000 | State Anxiety Inventory | Women having IVF | 138 | -0.69 | **p<0.05** |
|  | Smeenk 2001-a | State Anxiety Inventory | First IVF | 237 | not available | Not significant |
|  | Guinard 2003 | State Anxiety Inventory | Couples having IVF & ICSI | 545 | not available | Not significant |
|  | Eugster 2004 | State Anxiety Inventory | Women having 2nd cycle of IVF/ICSI | 43 | -0.05 | Not significant |
|  | Boivin 2005 | State Anxiety Inventory | Women having IVF | 76 | -0.2 | Not significant |
|  | Gurhan 2009 | State Anxiety Inventory | Unexplained infertility with ICSI | 80 | -0.17 | Not significant |
|  | Turner 2010 | State Anxiety Inventory | Women having IVF | 36 | -0.13 | Not significant |

ǂ when both anxiety & depression scores were added significant negative correlation was noted with clinical pregnancy. p <0.05

\* Combined with optimism and escapist coping, it was a significant predictor of IVF outcome.

**Depression**: Two studies reported higher depression scores in women having IVF as compared to the fertile control group. In our review, 17 studies investigated the effect of pre-treatment depression on outcome of IVF. Of these in 8 studies, a significant correlation between depression and clinical pregnancy was reported (Table 2.7). Demyttenaere *et al* observed that women who became pregnant after IVF had significantly low depression scores. Similar reports were also noted in other studies (95, 97, 106, 107, 115, 117). While the depression scores were not statistically different in the studies by Merari *et al*, Pasch *et al* and An *et al*, the trends remained the same of pregnant group having lower depression scores (78, 116, 121, 122). Although Ebbesen *et al* found depression scores similar in pregnant and non-pregnant groups, people who did not conceive reported more negative life events in the preceding 12 months (104). In contrast to their earlier study in 1992, Demyttenaere *et al* in a later study in 1998, found depression to be higher in pregnant women (77). This study also correlated depression with pregnancy outcome depending on the cause of infertility. They observed that with a female indication for IVF, increased depressive symptoms were associated with lower pregnancy rates, whereas pregnancy rates were higher when the indication was male factor. Li *et al* found depression and anxiety combined together to be a significant predictor of clinical pregnancy than each measure on its own (120). Lee *et al* found depression to be significantly higher in non-pregnant women when they were expected to have a poor response to treatment (112). Overall depression seems to correlate better with treatment outcome than anxiety.

**Table 2.7. Correlation of depression to clinical pregnancy after IVF**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Study | Instrument | Participants | No of patients | Effect size Correlation | Statistical significance |
| Demyttenaere 1992 | Zung Depression | Women from infertility clinic | 40 | -0.25 | **p=0.03** |
| Merari 1992 | Depression adjective checklist | Unexplained or Tubal infertility | 113 | 0.15 | Not significant |
| Visser 1994 | Hopkins-Symptoms-Checklist | First IVF | 65 | 0.19 | Not significant |
| Demyttenaere 1998 | Zung Depression | Women having IVF | 98 | 0.02 | Not significant |
| Kee 2000 | Beck’s depression Inventory | Women having IVF | 138 | 0.44 | **p<0.05** |
| Smeenk 2001 | Beck’s depression Inventory | First IVF | 237 | -0.14 | **p=0.03** |
| Smeenk 2001(2) | Beck’s depression Inventory | First IVF | 156 | not available | **p<0.05** |
| Verhaak 2001 | Beck’s depression Inventory | First IVF & ICSI | 207 | -0.17 | **p<0.05** |
| Anderheim 2005 | PGWB Index | First IVF/ICSI | 139 | -0.02 | Not significant |
| Lee 2006 | CES-D | Women having IVF | 595 | 0.02 | Not significant\* |
| De Klerk 2008 | Hospital Anxiety Depression scale | First IVF or ICSI | 289 | -0.02 | Not significant |
| Sohrabvand 2008 | Beck’s depression Inventory | Consecutive women with ICSI | 106 | -0.72 | **p=0.03** |
| Ebbesen 2009 | Beck’s depression Inventory | First IVF | 809 | 0 | Not significant |
| Lintsen 2009 | Beck’s depression Inventory | First IVF or ICSI | 421 | 0.04 | Not significant |
| Gurhan 2009 | Beck’s depression Inventory | Unexplained infertility ICSI | 80 | -0.22 | **P<0.05** |
| Gourounti 2011 | Depression Adjective Checklist | First IVF or ICSI | 160 | -0.39 | **p<0.001** |
| Li XH 2011 | Zung Depression | First IVF or ICSI | 107 | -0.06 | Not significant |

ǂ Combined anxiety & depression scores had significant negative correlation with clinical pregnancy. P<0.05

\*Negative emotion correlated with failure of IVF among patients with poor prognosis.

**Stress**: General stress levels have measured using Perceived Stress Scale -10 (PSS -10). All four studies did not find stress scores to be significantly different in the pregnant and non-pregnant groups. Ebbesen *et al* observed higher pre-treatment stress in women who subsequently conceived, but this difference was not statistically significant. In the study by Turner *et al*, lower stress corresponded with a trend towards better outcome.

**Table 2.8.** **Correlation of stress to clinical pregnancy after IVF**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Study | Instrument | Participants | No of patients | Effect size Correlation | Statistical significance |
| Klonoff-Cohen 2001 | Perceived Stress Scale (PSS) | Women having IVF | 123 | not available | Not significant |
| Ebbesen 2009 | Perceived Stress Scale (PSS) | First IVF | 809 | 0.03 | Not significant |
| Turner 2010 | Perceived Stress Scale (PSS) | First & repeat IVF patients | 36 | -0.2 | Not significant |
| Guinard 2003 | Perceived Stress Scale (PSS) | Couples with IVF & ICSI | 545 | not available | Not significant |

**Fertility-specific distress**: Fertility specific instruments have been used to assess this measure (Table VIII). Of these, Infertility Attitude scale and Concerns during Assisted Reproductive Technologies (CART) scale and psychological effects of infertility are ad-hoc instruments. Majority of the studies have found significant differences in the fertility related stress scores between pregnant and non-pregnant groups. Anderheim (2005) found no difference in psychological effects of infertility prior to IVF between pregnant and non-pregnant women (96). Klonoff-Cohen *et al* noted thatwomen who were concerned about missing work, finances or about the procedure had up to 20% fewer oocytes retrieved and fertilized, which indirectly affected their pregnancy chances negatively (110). Similarly Gourounti *et al* also observed lower baseline fertility-related stress in pregnant women. In contrast Cooper *et al* and de Klerk *et al* found that higher fertility stress corresponded with successful IVF outcome. Procedural stress during IVF was found to be significantly associated with a higher pregnancy rate in three studies (117, 119, 122), while in one study it did not differ between the two groups (102).

**Table 2.9.** **Correlation of fertility specific distress to clinical pregnancy after IVF**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Study | Instrument | Participants | No of patients | Effect size correlation | Statistical significance |
| Visser 1994 | Infertility attitude scale | First IVF | 86 | 0.1 | Not significant |
| Boivin 1995 | Daily record keeping chart (DRK) | Women having IVF | 40 | 0.23 | Not significant |
| Klonoff-Cohen 2001 | Infertility reaction scale(IRS) | Women having IVF | 151 | -0.5 | **p=0.02** |
| Klonoff-Cohen 2004 | Concerns during Assisted Reproductive Technologies (CART) Scale | Women having IVF | 151 | -0.25 | **p<0.05** |
| Cooper 2007 | Fertility Problem Inventory (FPI) | First IVF | 129 | 0.74 | **p<0.05\*** |
| de Klerk 2008 | Daily record keeping chart (DRK) | First IVF or ICSI | 289 | 0.15 | **p<0.05ǂ** |
| Hunter 2010 | Infertility related stress scale | First IVF | 217 | 0.16 | **p=0.03** |
| Gourounti 2011 | Fertility Problem Inventory (FPI) | First IVF or ICSI | 160 | -0.49 | **p<0.001** |
| Nouri 2011 | Fertility Problem Inventory (FPI) | Women having IVF | 83 | not available | Not significant |

\* Pregnant couples had higher scores on sexual concern and need for parenthood scales.

**ǂ** Baseline negative affect measured by DRK predicted live birth

**Biochemical markers of stress**: Effects of stress on fertility treatment outcome has also been examined using stress markers like prolactin, cortisol and serum adrenaline. Serum prolactin has been shown to increase during periods of stress. High prolactin levels disturb ovarian function and thereby affect the chance of conceiving. Cortisol and catecholamines are secreted by the body in response to stress. In our review, 5 studies used biomarkers prolactin, cortisol, and catecholamines to measure stress (Table IX). Demyttenaere *et al* showed prolactin and cortisol levels to be significantly raised in the non-pregnant women (69) while others did not report similar findings (78, 103). Smeenk *et al* noted a significant positive correlation between adrenaline/creatinine ratio and pre-treatment depression and state anxiety scores (107). All these parameters were significantly higher in the non-pregnant group versus the pregnant group. An Yuan et al found the cortisol and adrenaline levels on the day of oocyte retrieval significantly raised in pregnant women but the pre-treatment levels were statistically similar (122).

**Table 2.10.** **Correlation of biochemical stress markers to clinical pregnancy after IVF**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Measure** | **Study** | **Participants** | **No of patients** | **Effect size correlation** | **Statistical significance** |
| Prolactin | Demyttenaere 1992 | Women having IVF | 40 | -0.25 | **p<0.05** |
|  | Merari 1992 | Unexplained/Tubal infertility | 113 | -0.04 | Not significant |
|  | Nouri 2011 | Women having IVF | 83 | Not available | Not significant |
|  |  |  |  |  |  |
| Cortisol | Demyttenaere 1992 | Women having IVF | 40 | -0.35 | **p<0.05** |
|  | Merari 1992 | Unexplained or Tubal infertility | 113 | 0.18 | Not significant |
|  | Smeenk 2001(2) | First IVF | 118 | Not available | Not significant |
|  | An Yuan 2013 | First IVF or ICSI | 353 | 0.08 | Not significant |
|  |  |  |  |  |  |
| Catecholamines | Smeenk 2001(2) | First IVF | 118 | Not available | **p<0.05** |
|  | An Yuan 2013 | First IVF or ICSI | 353 | 0.11 | Not significant |

**Figure 2.2: Studies showing association of emotional distress to clinical pregnancy**

* 1. **Discussion**

This review was undertaken to assess the information available from the published literature on the association between emotional distress and conception after IVF.

Thirty studies were included in the review that fitted the inclusion criteria. The outcomes of IVF were described separately for different parameters of emotional distress. Anxiety and depression were the main variables predominantly used in most studies. From this literature survey, it appears that both anxiety and depression are significantly higher in IVF patients as compared to the fertile controls. However, these increases in the distress do not seem to affect the clinical pregnancy rate. The number of studies that showed significant results are summarised in Figure 2.2.

Six out of twenty three studies found state anxiety significantly lower in the pregnant group while only one out of ten studies found trait anxiety to have a significant association with pregnancy rate (Table 2.6). Merari *et al* and Harlow *et al* have noted state anxiety and trait anxiety to be higher in conceiving women. These findings are the reverse of the hypothesised relationship but were not statistically significant. Eight out of seventeen studies found depression to have statistically significant correlation to clinical pregnancy after IVF (Table 2.7). None of the four studies that investigated general stress found any significant relationship to clinical pregnancy rate. However, six out of nine studies found significant fertility specific distress in patients who failed to conceive with IVF.

While anxiety and depression are known behavioral markers of stress, they do not appear to be specific or sensitive enough to assess emotional impact of IVF. This could be one of the reasons for the lack of consistency in the studies that have measured these two parameters. Depression seems to be a better indicator of the emotional status as compared with anxiety, as a higher proportion of studies found it to have significant association with clinical pregnancy.

**Strength and limitation of our study:** The strength of our study is that we have adhered to our inclusion criteria of pre-treatment assessment and outcome after one cycle of IVF to investigate the effects of emotional distress on IVF outcome. Pre-treatment anxiety has implicated as the main reason for the passive drop-out rate after the first cycle of IVF in a study by Smeenk *et al* (90) which reduces the cumulative success rate of IVF. Pre-treatment assessment also reduces the confounding factor of treatment related stress.

The limitation of our review was that the results were not consistent due to wide variation in the methodology Due to significant heterogeneity in the studies, meta-analysis was not performed. We were unable to measure effect size correlation for four studies as we did not have data to compare the mean scores of the two groups.

The important factors that varied was (a) the timing of measurement, (b) sample characteristics, and (c) the choice of instruments.

The timing of measurement of emotional distress is very important as it tends to vary over time and duration of infertility. Although all assessments in the review studies were done before or at the start of treatment, there was considerable variation in the actual point of assessment within the infertility pathway. The duration of infertility is also a key factor that can influence the extent of distress faced by the patients. Patients who have had previous treatment are likely to be more stressed due to the prospect of repeated failure of IVF. Two-thirds of the patients (62%) included in 17 studies were having IVF for the first time. Of these a significant relationship between psychological stress and conception rate was established in seven of them. First cycle of IVF is often associated with higher anxiety but reduced negative thoughts as patients are optimistic for a positive result. The emotional distress associated with IVF tends to become more pronounced with failed treatment. In the meta-analysis by Matthiesen et al, first time attendees had a significant association with state anxiety and clinical pregnancy, while no such effect was noted with trait anxiety or depression.

Sample sizes have often been small in most studies and almost invariably been drawn from either patients attending a clinic or self-help groups so they may not necessarily be representative of the whole infertile population. It has been suggested that couples starting IVF treatment may under-report distress because they fear being refused treatment (98). In addition, the variation in psychosocial reactions to infertility may not be captured in small samples (98, 125). This will also make it difficult to generalise the results from these small studies to a larger population. In the study by Demyttenaere et al, aetiology of infertility was a significant factor in the psychological functioning. Two studies in the review included patients with a specific aetiology of infertility thus differentiating them from the rest of the participants.

The generic instruments are valid tools, but too exclusively designed to measure clinical depression or anxiety. Various studies have shown that infertility patients do not suffer from clinical anxiety or depression and consequently they may not be sensitive enough for use in this population (125, 126). For instance, no significant association was found between psychological variables and IVF outcome when a generic measure was used in the study by de Klerk *et al*, but a small significant effect was noted when fertility-specific Daily Record Keeping Chart (DRK) was used (29). Fertility-specific instruments are more sensitive in measuring infertility-related psychological strain experienced by these couples. However there was insufficient information about the psychometric properties of these instruments. Nine studies used different fertility-specific instruments, but the results of these were inconsistent.

* 1. **Conclusion**

Despite the available literature, our results indicate inadequate information about the impact of emotional health on reproductive outcome after IVF treatment . This literature review has therefore highlighted the need for a well-designed, adequately powered prospective cohort study with a fertility-specific instrument to examine the relationship between emotional distress and IVF outcome. Such a study would also give information about the fluctuations of emotional well-being during various aspects of fertility treatment. This data could be then used to provide guidance while designing psychological interventions to reduce the emotional distress faced by patients undergoing IVF. A comprehensive fertility specific tool which can accurately assess the thoughts and feelings of involuntary childlessness would be a better indicator of the overall psychological well-being than anxiety or depression. The next step was to examine the various fertility specific instruments that are available, their construction methods and psychometric properties. This could enable us to choose the most appropriate instruments to measure emotional health durng IVF.

**Chapter 3: Review of Fertility-specific instruments**

|  |
| --- |
| Overview  3.1 Background  3.2 Method  3.3 Psychometric properties  3.4 Results of the review  3.5 Rationale for choosing the instrument |

**3.1 Background:**

From the systematic review of literature it was clear that we needed a prospective adequately powered study using a fertility specific tool to investigate the impact of emotional distress on IVF outcome. The use of generic questionnaires in the assessment of psychological aspects of infertility had produced inconsistent and contradictory results. One possible reason is that generic tools may not be specific enough to capture the emotional and psychological strain associated with infertility. Many of these were originally designed to assess patients with clinically significant psychological illness (126). Condition-specific measurement tools designed for specific diagnostic groups or patient papulation have an advantage in that they measure aspects that are particularly salient to a specific condition or patient group and hence are more sensitive. The results from the previous chapter showed that fertility related stress measured by fertility specific tools showed a more consistent correlation with the reproductive outcome of IVF. We therefore reviewed literature to identify fertility-specific questionnaires that can be used to measure the emotional distress in patients with infertility. The aim of this review was to examine the different fertility specific instruments that are available and to evaluate their psychometric properties so as to choose an appropriate tool for the proposed study.

**3.2 Method**

A review of literature was undertaken in order to identify infertility specific questionnaires that have been developed and validated. An extensive search was done of the following electronic databases. PubMed (1980-2015), ISI Web of Science (1985-2015), Biosis Citation Index (1969-2015), Medline (1950-2015), Psych INFO (1985-2015) and Applied Social Science Index & Abstracts (1987-2015). The search terms used were *anxiety, emotion\*, psychological stress, depressive disorder, depression, and distress* AND *infertility*, *in-vitro* fertilisation, *IVF*, *intracytoplasmic sperm injection,* *ICSI*, *assisted conception, assisted reproduct\*.* Reference lists and bibliography of relevant papers were also hand searched for additional citations.

For reviewing the instruments, we used the criteria set out by the scientific advisory committee of Medical Outcomes Trust name. The following attributes of the questionnaire were evaluated: Item generation, Reliability, Validity, Responsiveness, Interpretability and Burden.

The following inclusion criteria were used to identify the relevant infertility-specific measures.

1. The instrument should be developed and validated in order to assess psychological parameters specific to infertility.

2. The papers should be available in English.

**3.3 Psychometric properties:**

An ideal health status questionnaire should be developed used well-defined construction methods. It should be reliable, valid and sensitive to change and easy to administer (127).

**Item generation**: There should be a conceptual basis for the item content and combination. The target population must be involved in the content derivation. There must be evidence of scale variability and rationale for scale scores. Qualitative interviews are usually considered as gold standard for generating the items(128). They give the patient’s perspective of the impact of the condition on their lives.

Factor analysis should be undertaken to determine the domains of the questionnaire and the variance accounted for by these domains. This can be achieved by component analysis and Varimax rotation(129). This can be carried out by administering the initial questionnaire to a large representative sample of the population for whom it is designed. A large sample is defined as one over the number of candidate items on the questionnaire(130), twice the number of respondents as the candidate items(131) or three times as many respondents as candidate items(132).

**Reliability**: Reliability is the degree to which the questionnaire is free form random error. It can be assessed by internal consistency reliability, (the extent to which items are measuring the same construct) and test-retest reliability (stability of the questionnaire over time).

Internal consistency reliability can be measured with Cronbach’s alpha statistic Cronbach alpha values between 0.7 and 0.9 indicate good internal reliability(133) Other methods of testing reliability are Kuder-Richardson test which analyses inter-item constancy for dichotomous data and the split half method where the questionnaire is divided randomly in half and the two halves are correlated.

Test-retest reliability is assessed by administering the questionnaire to the same sample of participants on two occasions few days apart, thus reducing the chance of the participants remembering how they answered the first time at the same time making sure no real change has taken place. Both the questionnaires should produce similar results. An interclass correlation between the two sets of scores of at least 0.7 indicates good stability (132).

**Validity**: It is the degree to which the instrument measures what it intends to measure(130). It can be assessed in various ways: Face validity, content validity, construct measure validity and criterion validity.

Face validity describes whether the questionnaire appears to measure what it is supposed to measure, whether the items appear to be appropriate and are easily understood(128).

Content validity is an assessment of whether the questionnaire adequately covers the concept under investigation.

Construct validity is assessed by creating hypotheses about the instrument and then testing it against these hypotheses.

Criterion related validity is assessment of how the new instrument correlates with another test of comparison that is considered the gold standard.

**Responsiveness**: Responsiveness is the instrument's ability to detect meaningful change over time. Ideally the measure must detect meaningful change when it has occurred and must remain stable when no change has occurred. This is very important while using a measure in evaluating interventions.

**3.4 List of Fertility specific instruments:**

We identified thirteen instruments that had been developed to measure psychological distress specific to infertility. We divided the instruments into four groups based on the parameter they assessed.

1. Instruments measuring fertility specific distress
2. Instruments measuring adjustment and coping with infertility
3. Instruments measuring treatment related stress
4. Instruments assessing quality of life in patients with infertility

**3.4.1. Instruments measuring fertility specific distress**: This group includes instruments that measure psychological distress associated with infertility. They measured the negative and positive affect, emotional distress and strain associated with infertility. One of the instruments, Emotional Health in Infertility Questionnaire (EM-INFERT) measured the emotional health rather than distress. A summary of the instruments and their psychometric properties are are listed in Table 3.1.

**(i)The Infertility Questionnaire (134)**:

Judith Bernstein and her colleagues developed ‘The Infertility Questionnaire’ with an aim to measure the specific effects of infertility on three major areas: self-esteem, blame/guilt and sexuality”. The questionnaire was developed and validated by a team of experts: nurses, physicians and infertility counselling specialists. The self-esteem scale contained 8 items, guilt/self-blame contained 5 items and sexuality 8 items. The response format was a five point Likert Scale ranging from ‘strongly agree’ to ‘strongly disagree’. The potential score for each item was 1-5 and a score greater than 3 was designated as representing distress. The sample consisted of every third couple attending infertility clinic at the university hospital in New Mexico, who spoke English and had at least two year history of infertility. The response rate was high at 97.5% for women and 77.5% for men. 40 couples completed the study. Internal consistency reliability was assessed using Cronbach’s alpha and it was satisfactory. The questionnaire was assessed for stability using test-retest reliability. Ten couples completed the questionnaire with a completion interval of two months. Six studies were identified which have used the IFQ (47, 105, 135-139).

**Critique**: There was no information about how the items of the questionnaire were derived. The items appear to be appropriate to the three domains of the questionnaire but the statistical methods for item reduction and scale generation were not reported. There was no clinical or statistical data to account for cut off score of 3 representing distress. The overall study sample and the one used to assess reliability were both small.

Face and content validity were not addressed specifically. Construct validity was performed using an item by item correlation matrix, but no prior hypothesis was reported. Criterion validity of the questionnaire was assessed by the participants’ concurrent completion of the Symptom Checklist–90R (SCL-90R) (140). This generic instrument has a number of confounding items for infertility patients (31). Responsiveness to change had not been addressed in this study.

**(ii)The Infertility Reaction Scale (IRS) (141)**

The Infertility Reaction Scale was developed with the objective of determining gender similarities and differences in perceptions of infertility and anticipated treatment stress in couples undergoing IVF(141). Stress was defined as being experienced when ‘transactions with the environment exceed the individuals coping ability, and has psychological and physiological components’ (141).

The IRS initially contained 15 items describing feelings and perceptions related to infertility. The wording of the items were given and the items were said to be scored 1 (never) to 7 (always). Total score was achieved by adding individual items. The questionnaire was used on a cohort of 211 couples entering an IVF programme in a University Hospital in Pennsylvania between January 1989 and May 1990. Two hundred couples returned a full set of data (95% response rate). The IRS items were factor analysed using varimax analysis and orthoganol rotation. Eigen values > 1.0 were used to determine factors. Three factors were identified: (1) ‘the desire to have a child as a major focus of life’, (2) ‘social functioning and work efficiency’, and (3) ‘social pressure to have a child’. Factor scores were compared between men and women and those with children and without children using ANOVA. A stepwise discriminant analysis was performed to find out the contribution of the individual variables to the anticipated stress. The desire to have a child as the major focus of life was the main predictor of anticipated stress for both men and women. The study concluded that women reacted more strongly to infertility, had a stronger desire to have a child and received more social support. The IRS has been used in three studies (102, 142, 143) .

**Critique**: There was no information provided on how the items were generated, but they were based on unpublished observations by Keye *et al* (144) There was no data on reliability, validity, or responsiveness to change for this instrument.

**(iii)The Fertility Problem Inventory (FPI) (145):**

Newton *et al* developed this tool with the aim to have a valid reliable instrument to measure perceived infertility-related stress.

Items were generated from the problematic situations and beliefs reported by patients with infertility that have been published in the scientific literature and from infertility-related themes highlighted by other researchers.

The sample used to develop this questionnaire was taken from a cohort of couples referred for assessment and treatment of infertility at a University Hospital. Data were collected via postal questionnaires approximately three months prior to the first treatment cycle: IVF, intrauterine insemination (IUI), ovulation induction (OI) or donor insemination (DI). 1153 women and 1149 men participated in the study.

The authors initially identified eighty-four items within seven domains initially: social concern, sexual concern, relationship concern, role loss, role failure, need for parenthood and rejection of a child free lifestyle. The item response was a six point Likert scale from ‘strongly agree’ to ‘strongly disagree’. Items were checked for frequency of endorsement and discarded if 95% of male or female respondents had endorsed them at either end of the rating scale (1/2 or 5/6). Items were discarded if there was a marked tendency to answer in a socially desirable way. Scale inter-correlations were performed between the seven original scales. The domains of ‘role loss’ and ‘role failure’ were excluded because they correlated too highly with each other (0.77) and with ‘social concern’ (0.81 and 0.72 respectively). However, no exploratory factor analytical techniques were used

The assessment of face and content validity was not reported. A sequential strategy for scale construction was used to obtain the final questionnaire. Half the responses (n=1151) of the questionnaire were used for item analysis and the other half (n=1151) used to assess reliability and validity.

Internal consistency reliability was assessed using item-total correlation and Cronbach’s alpha statistic. Items were discarded if the item-total correlation was <0.40. The Cronbach’s alpha statistic domain values ranged from sexual concern (α =0.77) to social concern (α =0.87), indicating that the items in the five scales were relatively homogeneous. The final questionnaire had 64 items divided into five domains.

Test-retest reliability assessment was performed on 17 men and 17 women, who completed the questionnaire on two occasions, 30 days apart. The correlation was made on global FPI scores: men (0.84) and women (0.83).

The assessment of construct validity was separated into discriminant and convergent validity. Discriminant validity was assessed using inter-correlations between each of the five remaining scales. These were reported to range from 0.26 to 0.66. The scores indicated that the scales are measuring separate, though related dimensions of infertility stress.

Convergent validity was assessed by concurrently measuring depression (Beck Depression Inventory(146), state anxiety (State-Trait Anxiety Inventory(100), and marital adjustment (Dyadic Adjustment Scale(147), the hypothesis being that there would be positive correlations between the FPI score and anxiety and depression scores, and a negative correlation between marital adjustment and FPI scores.

All correlations were in the expected direction. Higher scores on the FPI for men and women, both on individual scales and globally were associated with higher depression scores. Correlations were greater for social, sexual and relationship concern than for rejection of a childfree lifestyle and need for parenthood. Higher global and individual scale FPI scores were also associated with higher state anxiety scores, but did not reach statistical significance. Statistically significant correlations were observed between marital adjustment scores and scores on the relationship concern and sexual concern scales of the FPI for both men and women. Ten studies have used FPI to assess fertility related distress(113, 124, 145, 148-154)

**Critique:** This instrument has been used more frequently than any other fertility specific measure. It was constructed using a large study sample of both men and women and reliability and validity tests have been reported as satisfactory. However there were some inadequacies in the construction methods. The items for this instrument were generated from publications and researchers but not from qualitative interviews. The authors felt that “it is possible that relevant domains have been omitted” due to the initial item and scale generation methods used and the lack of factor analysis. A large study sample was used but actual response rates were not reported. The assessment of test-retest reliability was based on a small sample of global scores but not of individual domain scores. A larger sample, a shorter time frame and the presentation of data regarding actual change would have increased the credibility of test-retest reliability. The instrument’s responsiveness to change had not been assessed.

**(iv)The Infertility Distress Scale (IDS) (73)**

The aim of this questionnaire was to quantify perceived stress resulting from infertility in men. The development of the IDS has been described in a number of articles of which four were in English language (73, 155-157). 11 items were identified and a five point Likert Scale was used to complete the questionnaire.

Two samples were to construct and validate the questionnaire(73). A sample of 158 men attending a first andrology assessment was used to construct the questionnaire. The second sample consisted of 69 men returning for a second andrology assessment at least 6 months after a first. The andrology assessments were such that all the patients in Sample 2 had a chance of natural conception and were aware of that prior to the study.

Factor analysis, using principal component analysis revealed three factors. The first, ‘infertility distress,’ accounted for 43.5% of the variation. The other two factors were said to be insignificant as they were defined by a very small number of items (the exact data were not given). The final questionnaire consisted of 8 items in a single domain. The items included were: (1) the distress due to the spouse’s last menstruation; (2) the distress due to infertility as a whole; (3) the importance of a child (4) the appraisal that infertility represents a challenge; (5) the appraisal that infertility represents a threat; (6) feelings of helplessness due to infertility; (7) the frequency of thoughts about infertility; and (8) the desire for a child. Internal consistency reliability was assessed in three ways. Item-total correlations were reported to be moderate to strong (r=0.31 – r=0.70). Split-half reliability was given as r = 0.89, and Cronbach’s alpha statistic as 0.90. Test-retest reliability was reported in subsequent articles to have been stable over four months (r = 0.74)(156, 157).

To assess construct validity the German version of the SCL-R 90 was completed by 134 participants from first sample, although no prior hypothesis about the expected correlation was stated. Weak correlations were observed between the IDS and three SCL-R 90 scales: ‘global severity’, ‘depression’ and ‘positive symptom distress.’ The use of the SCL-90R has been criticised for the female infertility population because of confounding items, but no such suggestion has been made for males.

Pook *et al* stated that the IDS correlated well with KINT questionnaire, which was already validated measure of infertility-distress (156). They also reported that the IDS was sensitive to change although no further details were reported. This instrument was by the same author in four studies (73, 155-157).

**Critique**: Origin of the items in the questionnaire were not stated in any of the articles. Factor analysis revealed three factors. But two of the factors were not significant and were defined by very small number of items. Infertility distress was the only factor that accounted for 43.5% of the variation. So the final questionnaire contained 8 items in a single domain. Reliability and validity tests have been satisfactory for this instrument. It had been developed on a study sample of men and hence additional reliability and validity tests have to be performed prior to use in women. Although a good sample size was used for the study, the response rates were not mentioned. There was no data about the sample size of test-retest reliability although it was reported as satisfactory. Similarly sensitivity to change was reported as satisfactory but no details were given.

**(v) Cognitive Appraisal Scale for Infertility (CASI) (158)**

Cognitive Appraisal Scale for Infertility (CASI) was developed to evaluate emotional responses to infertility. The questionnaire was designed from feelings faced by most infertile people as observed by Menning (28) and the emotional responses to infertility described by Craig (159) and based on the authors’ experiences in clinical practice. Content validity and external validity were reviewed by a team of specialists and fertile women in the reproductive age group. This consisted of a faculty member at the department of maternity nursing, a specialist in female psychology, clinicians, nurses, embryologists, and medical secretaries. This instrument was piloted on 40 women, who were being treated for infertility at the institution.

The final tool asked the women to write down their perceptions and feelings about infertility on a 4-point Likert scale for 35 items containing eight subscales: difficulty in accepting infertility; despair; denial; guilt; decrease in self-esteem; loss of libido and deterioration in marital relationship; self-imposed; acceptance or coming to terms with new self-identity (reversed items). High scores indicated a negative response to infertility, whereas low scores indicated the opposite.

Principal factor analysis with promax oblique rotation was done. Accepted factors had eigenvalues of 1 with factor loadings of greater than 0.35. Internal consistency was evaluated by Cronbach’s α. Eight factors with 35 items were extracted: (i)difficulty accepting infertility (shock, anger, depression, and anxiety) (11items); (ii) decrease in self-esteem (5 items); (iii) acceptance/ coming to terms with new self-identity (reversed items) (5 items); (iv)despair (4 items); (v) loss of libido and deterioration in marital relationship (4 items); (vi) guilt (2 items); (vii) denial (2 items); and (viii) self-imposed isolation (2 items). Internal consistency (Cronbach’s α) for factors 1 and 2 was 0.88 and 0.82, respectively; for factors 3 to 8, internal consistency was marginal or poor (smaller than 0.7).

Test–retest reliability was assessed using paired t-tests by correlating the first responses with responses obtained 2 weeks later. The mean number of days of test–retest method was 16.7 -13.7. Correlations ranged from α of 0.87 up to 0.9 indicating high reliability.

Concurrent validity was assessed by correlating the eight individual CASI scores with scores from the Japanese versions of the STAI and SDS(160). There was a moderate correlation between two factors and other inventory scores (STAI and SDS), suggesting satisfactory validity.

**Critique:** The items in this questionnaire were based on author’s experiences rather than patient generated. It was developed using a relatively small sample of infertile women resulting in insufficient statistical validity. The internal consistency of domains 3-8 was low indicating poor reliability. But two domains had good internal reliability. Test-retest reliability and concurrent validity were found to be satisfactory. CASI was developed for a small clinic population of Japanese infertile women and hence additional studies need to be done to assess the validity in other populations.

**(vi)Emotional Health in Infertility Questionnaire (EM-INFERT) (161)**

This instrument was developed in order to evaluate the emotional health of infertile couples undergoing IVF. The concept of emotional health was used for the first time in the context of infertile couples. Emotional Health in Infertility Questionnaire **(**EM-INFERT) is a comprehensive 40 item questionnaire which covers nine domains of people’s lives that can be influenced by infertility and its treatment namely personal strain, partner relationship strain, sexuality, social support, confidence in treatment, guilt and blame, financial strain, need for privacy and couple concordance. These domains were designed to assess the wide range of effects of infertility on (a) self ( challenges to self-esteem, regret, self-blame and guilt) (b) on relationships (with partners, family, friends and work colleagues) and (c) on life plans (challenge to the place of parenthood, impact of treatment on work and family finances and loss of control over their lives). It was developed by researchers in Oxford to assess psychological distress specifically associated with infertility.

Qualitative methods were used to generate items for the developmental version of the questionnaire, and the initial construction and validation of the EM-INFERT. The analysis of the qualitative study resulted in a large item pool from which the initial 64 items were drawn. The 64 item version of the questionnaire was piloted with a large sample (n = 381) of couples undergoing IVF in Oxford Fertility Unit.

Face and content validity was satisfactory. Internal consistency among the domains was tested with Cronbach Alpha and the scores ranged from 0.93 (personal strain) to 0.55 (need for privacy). All item-total correlation coefficients were also satisfactory. The instrument was scored using a 5-point Likert scale where 0=definitely true, 1=mostly true, 2=not true, 3=mostly untrue, 4= definitely untrue. The individual domain scores were computed and total EM-INFERT scores were calculated by summing up the nine domain scores. Initial scores ranged from a minimum score of 0 to a maximum score of 160. The scores were rescaled from 0 to 100 for optimal comparison. High EM-INFERT scores corresponded with better emotional health.

**Critique**: The items were generated from qualitative interviews inferring that the target population was involved in the content derivation and it was piloted on a large sample. Nine domains involving various psychological aspects of infertility has been included in the study making it a comprehensive measure. However test-retest reliability, construct validity and sensitivity to changes had not been reported for this questionnaire. This instrument had not been used in any other studies.

**(vii) Screen IVF (162)**

SCREENIVF was designed in order to screening patients going through assisted reproduction in order to identify patients at risk of developing significant emotional problems in response to unsuccessful IVF treatment. Verhaak *et al* identified five risk factors for increased emotional problems: (i) pre-treatment anxiety and (ii) pre-treatment depression, (iii) helplessness and (iv) less acceptance of fertility problems and (v) a lack of social support.

A short questionnaire was designed to assess these five risk factors. This resulted in questionnaire with 34 items , of which 10 items assessed state anxiety, 7 items assessed depression, 6 items assessed helplessness, 6 items assessed lack of acceptance and 5 items assessed perceived social support. The items that assessed anxiety were based on a short version of Spielberger State and Trait Anxiety Inventory(163) . The depression items were the 7 items of the short Beck Depression Inventory version for patients of general practitioners (164). The items on helplessness regarding fertility problems and acceptance of fertility were from the Illness Cognition Questionnaire for IVF patients(165, 166). Perceived social support was assessed by five items derived from the Inventory of Social Involvement (167).

The different scales showed good reliability: anxiety α= 0.88; depression α= 0.82; helplessness α= 0.87; acceptance α= 0.92 and social support α=0.89. SCREENIVF was handed out to be completed at pre-treatment information (Time, T1) and again asked to complete the follow-up assessment 3–5 weeks after the pregnancy test (Time, T2). Patients were defined as at risk when their scores on one of the five risk factors showed clinically relevant problems. SCREENIVF resulted in a dichotomous score on each of the five risk factors: score was 0 if the patient scored below the cut off and 1 when the patient scored equal to or above the cut off. The score range on SCREENIVF was 0–5: 0 indicating no risk factors and 5 indicating 5 risk factors. The contruct validity was done with confirmatory factor analysis. SCREENIVF identified 34% of the women as at risk at pre-treatment (T1). The sensitivity was 69%, the specificity 77%. The positive predictive value was 48, the negative predictive value was 89, indicating that SCREENIVF was better at identifying patients without emotional distress. The overall efficiency of SCREENIVF was 75.

**Critique:** Although this questionnaire was projected as fertility specific and has been validated on fertility patients, the items in the questionnaire were all derived from generic instruments. Even the items on helplessness regarding infertility ad acceptance of infertility were based on Illness Cognition Questionnaire which was designed for patients with chronic illness.This tool was mainly developed to identify patients at risk of developing psychological distress during IVF. It is reported to have a good sensitivity of 69% and high negative predictive value of 88%. The Guideline Development Group at ESHRE have therefore recommended use of Screen IVF to screen patients undergoing IVF so as to identify the patients who will benefit with additional psychological support. Emotional distress related to infertility gets worse with the duration of infertility. Screen IVF has bee validated on a sample of patients undergoing their first IVF cycle when they are more likely to be optimistic.

The other limitation is the high attrition rate. Only 50% of the total number of patients participated in the questionnaire at time 2. The drop outs’ emotional state has therefore not been included in the study. The study focused only on women, which restricts the use of this tool in men. The realibility and validity tests have not been reported for this instrument.

**Table 3.1.Instruments measuring fertility associated distress**

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Screen IVF (2010)** | 34 item questionnaire | 10 items assessing state anxiety from STAI, 7 items assessing depression BDI , 6 items assessing helplessness, and 6 items assessing lack of acceptance from Illness Screening for risk factors for emotional problems and 5 items assessing perceived social support from the Inventory of Social Involvement. | 239 women having their first IVF cycle | Not done | Not reported | Assessed | Not reported | Done with Confirmatory factor analysis | Not reported | Not reported |
| **Emotional Health in Infertility Questionnaire (2007)** | 40 items in nine domains personal strain; partner relationship strain; sexuality; social support; confidence in treatment; guilt and blame; financial strain; need for privacy and couple concordance | Qualitative analysis using 23 largely unstructured interviews | 179 couples and 23 women | Principal component analysis and varimax rotation Factors with Eigen values<1 discarded | 10 patients (5 couples)6 members from staff & research team. | Satisfactory | Not reported | Not reported | Not reported | Not reported |
| **Cognitive Appraisal Scale for Infertility (CASI)(2009)** | Item questionnaire subdivided into 8 factors | Emotional responses to infertility and authors’ clinical experience35 | 40 infertile women undergoing treatment | Principal component analysis and varimax rotation Factors with Eigen values<1 discarded | Not done | Not satisfactory | Assessed | Assessed | Not reported | Not reported |
| **The Infertility distress scale (1999)** | 8 items in the questionnaire in a single domain | Not reported | 158 men attending for first andrology assessment | Factor analysis with principal component analysis | Not reported | Assessed | Assessed | Done with SCL-R90 | Not reported | Assessed |
| **The Fertility Problem Inventory (1999)** | 46 items measuring seven domains: social concern, sexual concern, relationship concern, role loss, role failure, need for parenthood and rejection of child-free lifestyle. | Popular & Scientific literature and infertility related themes highlighted by other researchers | 1153 women and 1149 men. One half was used for item analysis and the other half to assess reliability and validity | Items were written to fit domains | Not reported | Satisfactory | Satisfactory | Satisfactory | Not reported | Not reported |
| **The Infertility reaction scale (1992)** | 15 items describing feeling and perceptions related to infertility | Unpublished observations by Keye et al (129) | 211 couples entering IVF programme | Factor analysis using varimax analysis and orthogonal rotation | Not reported | Not reported | Not reported | Not reported | Not reported | Not reported |
| **The Infertility questionnaire (1985)** | 21 item measuring three domains self-esteem, blame/ guilt & sexuality | Developed by panel of experts: nurses, physicians & counsellors | Forty couples attending infertility clinic | Not specified | Not reported | Satisfactory | Assessed | Assessed using item by item correlation matrix | Assessed using Symptom Checklist-90R | Not done |
| Name of the instrument | Questionnaire Items | Initial Item generation | Sampling | Item reduction and factor analysis | Face & Content validity | Internal reliability | Test-retest reliability | Construct validity | Criterion validity | Sensitivity to change |

**3.4.2. Instruments developed to measure adjustment and coping with infertility**

These instruments have been developed to examine the adjustment to fertility problems and coping with it Table 3.2. Individual vary in their fertility adjustment and coping at different stages of treatment. This depends on the interpersonal variation in capacity to cope with stressful situations. In this group there are four instruments. The first one examines the adjustment to fertility problems that includes cognitive behavioural and emotional aspects(168) while the other three measure coping with infertility.

**(i)The Fertility Adjustment Scale (FAS) (168)**

This instrument was developed by Glover *et al* as a standardised measure of psychological adjustment to infertility. Psychological adjustment was defined as ‘a heterogeneous concept comprising cognitive, behavioural and emotional components related to the way in which individuals acknowledge and process information about the course of their fertility problem, its investigation, treatment and possible outcomes’.

Items were generated from qualitative pilot interviews of couples at various stages of investigation and treatment and from the clinical experience of the authors. The number of qualitative interviews was not stated. 12 items were selected for the questionnaire,

1. I will continue with investigations/treatment until I succeed in having a child

2. There are both advantages and disadvantages to having a child.

3. I cannot plan for the future until I know for certain whether or not I can have a child.

4. I can talk to my partner about the possibility of not having a child.

5. I want a child of my own more than anything else in life.

6. I have made plans for a possible future life without a child.

7.I seem to live my life from month to month.

8. I will always feel unfulfilled if I am unable to have my own child.

9. I think I could adjust to a future life without a child.

10. I make sure that I carry on with my normal life activities.

11. I cannot imagine a future without a child.

12. I think life could be rewarding either with or without children.

Six positive and six negative items were written to reduce item response bias. Positive items were reverse scored. The item response was a six point Likert scale from ‘strongly agree’ to ‘strongly disagree’.The scores were summed to achieve a global adjustment score. The minimum possible score was 12 and the maximum score was 72. A higher score indicated poorer adjustment.

The sample was drawn from couples attending two London hospital clinics. One was a general infertility clinic and the other was a specialised male infertility clinic. Consecutive patients over a six month period were eligible to participate. The sample size for analysis of 50 men and 50 women was adequate for a 12 item questionnaire, although response rates were not reported. More women were recruited from the general clinic (34 v. 16) and more men from the other clinic (14 v. 33). The authors compared the demographic characteristics of the sample from the male clinic with those obtained from a separate study in the same clinic which had elicited a high response. On the basis of that comparison they claimed the sample was representative of the population attending the clinic.

Internal consistency reliability was assessed using Cronbach’s alpha statistic (ά=0.8557) indicating a high degree of homogeneity between the items.

Test-retest reliability was assessed by a relatively small sample of 30 people completing the questionnaire with a two week interval. The response rate was 30/37 (81%). The correlation coefficient between the time points was 0.88, suggesting stability over this time frame, albeit in a small sample.

Construct validity was assessed by concurrently administering the Hospital Anxiety and Depression Scale (HADS) (169) and a 10cm visual analogue scale (VAS) of infertility distress. Significant correlations (p<0.0001) were reported between the FAS scores and anxiety, depression and fertility distress.

Two studies have used FAS to assess the infertility related psychological adjustment (170, 171).

**Critique**: There was no data reported on how the 12 items were selected for the questionnaire or the size of the original pool. The assessment of face and content validity was not reported. The relaibility and validity were satisfactory but responsiveness to change was not addressed.

**(ii)The Coping Scale for Infertile Couples (CSIC) (136)**

This instrument was developed with a view to exploring gender differences in coping among infertile couples. The authors stated that the 20 initial items were derived from a qualitative study (172) in which in-depth interviews were used to explore how infertile women coped with their infertility. The 20 items were positively and negatively balanced to reduce item response bias. The items require a response indicating how often particular strategies are employed on a five point Likert Scale from ‘never’ (1) to ‘almost always’ (5).

The questionnaire was validated on a sample of 138 couples (n=276) drawn from a medical centre in Taiwan. Selection criteria were that the couples were married and had been diagnosed with infertility of at least one year duration.

Content validity was assessed by a panel of five experts: a statistician, two fertility physicians, a university professor, and a fertility nurse specialist. 15 items comprised the final questionnaire, which was tested with the 138 couples in the sample. Principal factor extraction and Varimax rotation were performed. A factor load of 0.3 and an Eigen value of ≥ 1.0 were used to determine factors. Four factors were extracted: ‘increasing space’ (5 items), ‘regaining control’ (5 items), ‘being the best’ (3 items) and ‘sharing the burden’ (2 items). Factor loadings of all the items are given and range from 0.51 to 0.85.

Internal consistency reliability was assessed using Cronbach’s alpha statistic. Stability is claimed from test-retest reliability over a two week period (0.73). Construct validity was assessed using the IFQ (134), the Perceived Stress Scale (PSS) (173) and the Jalowiec Coping Scale (JSC) (174).

There were no statistically significant differences between total mean scores of husband and wife. However, when individual scales were compared, it was observed that wives scored higher on ‘increasing space’ (p<0.05) and ‘sharing the burden’ (p< 0.01), whereas husbands scored more highly on ‘being the best’ (p<0.05). These findings were similar to the ones reported by Jordan and Revenson(175). They found significant gender differences with higher incidence of women ‘seeking social support’ and ‘escape-avoidance’ behaviour.

**Critique:** The qualitative study to generate items for the questionnaire focused only on women when the aim of the questionnaire was to detect gender differences. Two Items were deleted by the advice of expert panel who examined content validity, but no information was given about what these items were. The remaining 18 items were pilot tested on 30 couples. Item analysis was used to delete inadequate items, but no methods or statistics were given.

The authors stated that factor analysis was undertaken to establish construct validity. But this is not a typical method used to determine construct validity. Seven of the 15 items on the final questionnaire contain more than one construct, making them ambiguous. Two of the items contain four constructs at the same time: “I confide my frustrations, disappointments, fears and hopes with other infertile patients” and “Although I cannot control my infertility, I keep myself in the best condition by controlling my weight, diet and appearance”.

Construct validity was assessed using IFQ, PSS and Jaloweic Coping Scale. But there was no information about the psychometric properties of these scales. Although moderate correlations were reported but no specific results were given. The results of the internal consistency test indicated that the four scales were relatively homogeneous. An alpha score for the whole questionnaire was given, even though it was stated that separate and discrete factors had been identified. Test-retest reliability was satisfactory but no sample size was given. Responsiveness to change was not assessed. No further studies were undertaken using this instrument..

**(iii)The Copenhagen multi-centre psychosocial infertility research programme (COMPI) questionnaire (176)**

The COMPI questionnaire was developed for use in a prospective cohort study of infertile couples. The aim of the study was to “examine how people seeking fertility treatment cope with their situation, how they communicate about their situation and their attitudes to, and evaluation of, treatment”

The total questionnaire consists of 187 items covering:

(a) Demographic information (1 item)

(b) Reproductive history (5 items)

(c) Infertility history (5 items)

(d) Current treatment (3 items)

(e) The desire to have a child (3 items)

(f) Psychosocial consequences of infertility (18 items),

(g) Expectations and wishes about treatment (23 items)

(h) Coping with infertility and treatment (28 items for women, 29 for men)

(i) Communication about infertility and treatment (20 items),

(j) General health and wellbeing (14 items),

(k) Physical stress reactions (9 items)

(l) Sense of coherence (9 items)

(m) Social relationships and social position (48 items).

Nominal and ordinal data were collected. Response categories ranged from yes/no with follow up if yes, to different length (3, 4, 5 and 6 point) and differently worded Likert scales.

The questionnaire items were derived from a number of sources: standardised questionnaires - SF36, (177); The Ways of Coping Questionnaire (178) other infertility questionnaires (179) qualitative interviews, and previous papers (180-182). Face and content validity were assessed by piloting the whole questionnaire with a sample of 68 infertile women and 54 infertile men and by a series of 8 telephone interviews carried out by the main investigator. Participants were invited to comment on the content of the questionnaire, response categories, themes they thought had been omitted, and ambiguity of wording. Items originally in English were translated into Danish by two people and translated back into English by two others to check for accuracy. A wide distribution of scores was reported to have been observed across different response categories.

The main study sample consisted of 2250 people (1069 couples, plus 100 women and 12 men whose partners declined to take part) immediately prior to undergoing the first IVF ± ICSI cycle in five clinics (4 public, 1 private) in Denmark. The response rate was 83.1% for women and 76.9% for men. The characteristics of the non-responders were assessed: there were some differences between the groups, but they were not thought to have affected the results. It was also noted that the patients attending the public clinics may have had different expectations about treatment because their treatment was funded, than those attending the private clinic. A sample bias was acknowledged as there were far fewer patients attending the private clinic in the study. The authors describe the factor analysis of 16 items related to psychosocial consequences of infertility. But the final version contained the following 18 factors: ‘marital benefit’ (2 items), ‘marital stress’ (4 items), ‘social stress’ (4 items) and ‘personal stress’ (6 items). Different response scales were used. A four point Likert Scale: (1) ‘none at all’ to (4) ‘a great deal’ was used for social stress, personal stress and 2 items from marital stress. The remaining items were answered with a five point Likert Scale: (1) ‘strongly disagree’ to (5) ‘strongly agree’. Subscale items were summed to produce total scores.

Cronbach’s alpha coefficients were computed for each sub-scale, indicating homogeneity within the subscales: marital benefit (α = 0.83), marital stress (α = 0.73), social stress (α = 0.82) and personal stress (α = 0.82).

**Critique**: This was a study with large sample size and good response rates. The items were generated from a variety of sources incluing qualitative interviews. The final version contained 18 items after factor analysis and it is not clear which items were removed. There is no discussion on whether the different response scales for the items would have any effect on the results.

Test-retest reliability was not reported. No other validity tests were undertaken. Participant acceptability may have also been an issue due to the length of the questionnaire.

**(iv) Infertility Self-Efficacy scale (ISE) (183)**

Self-efﬁcacy is a fundamental construct in mental health that has not yet been measured in the area of fertility and it is crucial to how an individual experiences and copes with infertility. The aim of this study was to develop and validate a scale of perceived self-efficacy for people coping with infertility treatment.

A 16-item ISE scale was developed by Cousineau *et al*, that tapped an infertility patient's perception about his or her ability to engage in a set of cognitive, emotional, and behavioural skills related to the medical treatment of infertility. Item generation involved an extensive literature review of the psychological aspects of infertility, followed by a review of the qualitative interview data from a previous study. The research team members (ﬁve) and three project consultants, having expertise in infertility and health psychology, generated an initial list of more than 70 items, which was further reﬁned with feedback from a patient focus group and expert opinion from health professionals.

93 participants (69 women and 24 men) were recruited for the pilot phase of the questionnaire development. Participants were recruited in following ways: a flyer announcement at a fertility clinic, an announcement posted in the newsletter of an infertility support organization, infertility linked internet message board, and at a public website that accepted posts for clinical trials. Potential participants called or e-mailed a research coordinator who screened them for eligibility by telephone. Inclusion criteria were: 2 years of infertility, ability to read and write English and ability to consent to the study. Consent forms were then posted to eligible recruits. After receiving the consent, the participants were e-mailed a link to access the assessment on a secure internet website. The subjects completed a demographic questionnaire, the 76-item ISE, and three other previously validated infertility related questionnaires,Fertility Problem Inventory(FPI), Perceived Stress Scale(PSS) and Ways of Coping (WOC) scale.

Item-level analyses were done to reduce the number of questions for further scale development. Items were eliminated if they met the following criteria: (i) 30% or more responses recorded as very conﬁdent (ii) inter item correlations < 0.35 or > 0.8, and (iv) corrected item-total correlation < 0.5 or squared multiple correlations > 0.9. This reduced the total number of items from 76 to 43.

The next step was to repeat the test in another patient sample in order identify the underlying components, to assess the criterion validity, and to determine the test–retest reliability. A total of 113 patients participated in this part of the study with the same recruitment process as before. Of these 29 patients were randomised to undertake test–retest reliability. A principal components analysis (PCA) with varimax rotation was undertaken. An item-level analysis was undertaken and the number of variables were further reduced to 22 with a view to improve the item-to-subject ratio. Further refining of the items through PCA led to a ﬁnal set of 16 items. The variability within the 16 items was good and none exhibited floor or ceiling effects. Inter item correlations were satisfactory and ranged from 0.26 to 0.71. The PCA extracted a single component with an Eigen value of 8.89, explaining 55.55% of the variance. Component loadings ranged from 0.64 to 0.88; communalities ranged from 0.40 to 0.78.

The Cronbach’s α estimate of internal consistency reliability was 0.94 and the item-total correlations was between 0.59 to 0.86. The test–retest reliability was correlated at 0.91 (p<0.01).

Correlations with similar construct measured by the FPI, PSS, positive reappraisal, self controlling, and escape avoidance WOC subscales were satisfactory and in the expected direction, indicating good convergent validity.

The lack of correlation between the mean ISE score and age, race,ethnicity, income level, cause of infertility, and the WOC confrontive copingsubscale indicates good discriminant validity. The ISE has been used in six studies so far (184-189).

**Critique:** This studyused online recruitment which may be biased toward patients with internet access or seeking information from the internet, and hence may have higher stress levels. The methodology of item-generation and psychometric scale development was robust but sample size was small with predominantly women. The sample size used for test-retest reliability was small and there was no data on the duration between the two tests. Sensitivity to change was not examined by this study.

**Table 3.2 Instruments developed to measure adjustment and coping with infertility**

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Infertility Self-Efficacy scale (2006)** | 16 Item scale tapped an infertility patient's perception about his or her ability to engage in a set of cognitive, emotional, and behavioural skills related to the medical treatment of infertility. | Item generation involved an extensive literature review of the psychological aspects of infertility, followed by a review of the qualitative interview data from a previous study. | 138 married couples with infertility for at least 1year | Item-level analyses followed by principal component analysis with Varimax rotation done | Not reported | Assessed | Assessed | Assesed | Not reported | Not reported |
| **Copenhagen Multi- Centre Psychosocial Infertility (COMPI) research programme (2001)** | 187 items covering thirteen domains of which one was psychosocial consequences of infertility with 18 items. | Other standardised questionnaires, infertility questionnaires , qualitative interview and previous papers | 2250 people (1069 couples, plus 100 women and 12 men) prior to undergoing first IVF. | Factor analysis of psychosocial consequences (18 items) done. | Pilot study on 68 infertile women and 54 infertile men and by telephone interviews | Assessed | Not reported | Not reported | Not reported | Not reported |
| **The Coping Scale for Infertile Couples (2000)** | 15 item questionnaire | Qualitative interviews | 138 married couples with infertility for at least 1year | Principal factor extraction & Varimax rotation used | Not reported | Assessed | Assessed | Done with factor analysis | Not reported | Not reported |
| **The Fertility Adjustment Scale (1999)** | 12 items including six positive and six negative items | Qualitative pilot interviews of infertile couples | 50 men and 50 women | Not specified | Not reported | Assessed | Assessed | Assessed | Not reported | Not reported |
| Name of the instrument | Questionnaire Items | Initial Item generation | Sampling | Item reduction factor analysis | Face & Content validity | Internal reliability | Test-retest reliability | Construct validity | Criterion validity | Sensitivity to change |

**3.4.3 Instruments developed to examine treatment related distress**

We identified one instrument that was designed to measure treatment related stress. IVF is physically demanding treatment and the uncertainties and challenges at every step of this treatment process can itself equally affect the emotional well-being.

**Concerns during Assisted Reproductive Technologies (CART) Scale (110, 190)**

The aim of this study was to develop an instrument that addresses the concerns of patients during IVF treatment.

The study cohort consisted of women attending seven infertility clinics in Los Angeles, Orange and San Diego counties between July 1993 and June 1998. All women above 20 years of age, either married or co-habitating and diagnosed with primary or secondary infertility. Women with pre-existing illnesses were excluded.

Most of the items came from the first 70 women participating in a larger prospective study (102). Participants were asked to identify questions that were vague and important topics that they felt had been omitted. Almost unanimously, all the 70 women reported that the stress they were experiencing had been omitted and they gave various examples of that stress. After reviewing the content of the other scales, and consultation with the reproductive physicians, the items suggested by the women were combined into a scale. This scale was pilot tested on 30 patients wth infertility, who were undergoing IVF.

The final scale asked women in the study to rate their concern on a three-point Likert-type scale (not concerned, moderately concerned and very concerned) for each of the following nine items: anaesthesia; surgery; length of recovery; side-effects; finances; missing work; pain from the procedure; not being given enough information; and giving birth to a healthy baby. There was one question on each topic so as to not increase the length of the questionnaire.

The scale was administered twice to all participants: first at baseline or initial visit prior to treatment, and second at the time of embryos transfer. Women underwent only one treatment cycle during the course of the study.

Factor analysis was done using principal component analysis with an orthogonal rotation; factors retained were based on eigenvalues greater than one, a screen plot and factor loadings greater than 0.40. These results are presented in along with mean score, standard deviation and factor loading for each of the items. As shown, three factors were identified: (1) procedural concerns (six items, accounting for 24 percent of the variance); (2) work related concerns (two items, accounting for 12 percent of the variance); and (3) success in achieving the desired outcome namely, a live birth(two items, accounting for 8 percent of the variance). Only one item (concern about recovery time) loaded on more than one factor.

Cronbach’s alpha was satisfactory for factor one (0.78), borderline for factor two (0.68) and low for factor three (0.40). Responses to each were treated separately in subsequent analyses because of the low Cronbach’s alpha values for factors two and three. Scores for factor one was obtained by calculating the mean of the six procedural items.

Concurrent validity was assessed by correlating the four individual CART scores with an instrument measuring general stress (POMS) and another measuring general fertility-related concerns (Infertility Reaction Scale). Correlations between CART and POMS ranged from 0.26 to 0.28 (*p* = 0.001), while correlations between the CART and the Infertility Reaction Scale ranged from 0.06 to 0.45 (*p* < .0001), suggesting adequate validity.

Test–retest reliability was computed by correlating baseline responses with responses at the time of the embryo transfer which was two to four weeks later. Correlations were 0.75 for procedural concerns, 0.74 for financial concerns, 0.66 for achieving the desired live birth and 0.65 for missing work (*p* < .0001).

CART scale was used in two studies.(191, 192)

**Critique:** The study used to develop the items in the questionnaire was small (70). 151 women completed the questionnaire at baseline, but only 132 completed it at the time of the procedure. We do not have information about the emotional concerns of the drop outs. Only women were used in the study. The internal consistency was poor for factors 2 and 3 The test-restest scores were unreliable due to the confounding factor of ovarian stimulation with gonadotrophins during the time interval between the tests. A comparitive paried t test between these two time points confirmed siginficantly different scores in three of the four factors. For three of the four scores, responses at the time of the procedure were significantly lower than responses at baseline. Sensitivity to change was not measured.

**3.4.4 Instruments developed to measure quality of life:**

Health related quality of life is considered a good tool for outcome measurement in most conditions. Quality of life measurement in infertility includes health status measurement, psychological wellbeing, physical and social functioning as well as environment factors. Psychosocial studies have shown a higher prevalence of negative emotions with regards to infertility and its treatment which can affect the overall life satisfaction and emotional well-being. Only one instrument has been developed to measure quality of life in patients having infertility..

**The Fertility Quality of Life Tool (FertiQoL) (193)**

FertiQoL was developed as an international instrument in order measure fertility quality of life, FertiQoL, in men and women experiencing fertility problems. It has been translated FertiQoL into multiple languages for use in different countries.

Couples experiencing infertility with and without medical experience were sampled from one clinic each in Australia, Canada, New Zealand, and the United Kingdom and two clinics in the United States. Patient support websites in these countries hosted the online survey. The study recruited 291 women and 75 men from the clinics and the 1,014 women and 34 men online making up a total of 1,414 people with infertility.

Item-generation involved generating items, eliminating irrelevant items, validating the instrument, and assess acceptability and feasibility of the tool. A comprehensive literature review and discussion with psychosocial experts in infertility created an initial pool of 302 items affecting the quality of life in infertile patients in 14 areas. These were further classified into three levels of concept speciﬁcity: dimensions, domains and facets that can capture related aspects of quality of life. Classiﬁcation and subsequent focus groups reduced this pool to 102 items, which were submitted to the acceptability and feasibility study.

Items were deleted for several reasons (i.e., highly skewed distribution, high inter correlations (>0.80 among item set, poor scale coherence, interpretive issues). Other items were deleted because they measured broad constructs that could be better captured by measures designed for that purpose. Factor analyses (orthogonal rotation) was performed and items with factor loadings<0.30 and eigenvalues <1 were eliminated. The ﬁnal FertiQoL instrument consisted of 24 items from the core set and 10 items from the optional treatment module. The 24 core items were categorised into emotional, mind-body, relational, and social domains. The 10 optional treatment items were classified into treatment environment and treatment tolerability. Two additional items measuring satisfaction with quality of life and physical health were retained for the FertiQoL measure, but they were not included in the factor analysis.

FertiQoL survey were randomly presented and rated on a scale of 0 to 4, where higher scores indicated more favourable QoL. Cronbach reliability statistics were satisfactory, in the range of 0.72 and 0.92. Sensitivity analyses showed expected correlation between quality of life and gender, parity, and support seeking. The FertiQoL has been used in the following papers (191, 194-202).

**Critique:** The sample size used to develop this questionnaire was large but predominantly contained women. There was a large number of patiets recruited online and sgnificant differences were noted between the scores of clinic sample and online recruits. The items in this questionnaire were not from qualitative analysis or patient generated. In an attempt to have an international tool, FertiQoL was translated into 20 languages with each translation verified by local fertility experts**.** No test-retest reliability or validity tests have been stated for this instrument. Sensitivity to change has also not been performed.

**Table 3.3 Instruments developed to examine fertility treatment related distress & Quality of Life**

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| |  |  |  |  |  |  |  |  |  |  |  | | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | | **The Fertility Quality of Life Tool (FertiQoL) (2010)** | 24 items from the core set of items and 10 items from the optional treatment module. | A comprehensive literature review and consultation with psychosocial infertility experts generated an initial pool of 302 items on consequences of fertility problems on QoL in 14 areas | The clinical sample consisted of 291 women and 75 men, and the online sample consisted of 1,014 women and 34 men giving a total of 1,414 people with fertility problems. | Exploratory factor analysis | Not reported | Assessed | Not reported | Not reported | Not reported | Not reported | | **Concerns during Assisted Reproductive Technologies (CART) Scale (2004)** | 10 items covering 4 domains: concerns regarding medical aspects of IVF, work related concerns and concerns regarding achieving a successful result | Surveying scientific literature on stress and IVF | 151 women completed the study at baseline and 132 at the time of the procedure. | Factor analysis with principal component analysis with orthogonal rotation | Not reported | Satisfactory | Assessed | Done with POMS and Infertility Reaction scale | Not reported | Not reported | | **Name of the instrument** | Questionnaire Items | Initial Item generation | Sampling | Item reduction factor analysis | Face & Content validity | Internal reliability | Test-retest reliability | Construct validity | Criterion validity | Sensitivity to change | |  |  |  |  |  |  |  |  |  |  |
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**3.5 Discussion:**

We identified and reviewed thirteen fertility-specific instruments to assess suitability for use in our study. All the instruments appeared to have limitations in their construction methods or validation data. The instruments measured different psychological aspects of fertility specific distress. We classified them according to the variables they measured into the ones that assessed fertility related emotional distress, those that evaluated coping skills, fertility treatment related distress and quality of life. Initial item generation tends to be haphazard and random and qualititative interview were used in five of the quetsionnaires to generate items. Sample sizes have also been variable. Few studies were very large (FPI, COMPI and FertiQol) while others were much smaller (eg: 40 couples in Infertility Questionnaire). Several of the studies did not give response rates either (eg: Newton *et al*(FPI), Glover *et al* (FAS)). Only Schmidt *et al* (COMPI)mentioned data regarding the non-responders.

Face and content validity was mentioned for only two questionnaires (COMPI & EM-INFERT). Item reduction and factor analysis was not specified for four instruments (IQ, FPI, ScreenIVF and FAS). Bernstein *et al* (IQ)and Newton *et al* (FPI)appeared to have created the scales first and then written items to fit the scales.

Internal reliability was addressed and satisfactory in most of the papers using Cronbach’s alpha except in Infertility Reaction Scale (IRS) and Cognitive Appraisal Scale for Infertility(CASI ). But some authors having stated that their questionnaires contained separate and discrete scales then provided alpha statistic for the whole questionnaire.

Test-restest reliability was assessed in in about half of the studies but some of the samples were small (eg: Bernstein *et al* IQ) or not mentioned (Lee *et al* CSI). In some others the time intervals were too long (Netwon *et al* FPI) or occurred during confounding factor of ovarian stimulation potentially biasing results with actual change having taken place(CART).

Construct validity was addressed six questionnaires as per the definition given in the test construction literature. Construct validity is when the questionnaire is tested against a prior hypothesis about how scores correlate with the hypothesis. In some of the studies no prior correlation about the the expected correlation was stated (eg: Pook *et al* correlated Infertility Distress scale with SCL-09-R, Glover *et al* correlated Fertility Adjustment scale with Hospital Anxiety and Depression Scale).

Only one paper addressed sensitivity to change but even that was reported in German article. (Pook *et al* in Infertility Distress Scale).

This review was undertaken to select an appropriate instrument to estimate the emotional distress related to infertility at the start of the IVF cycle. Instruments measuring adjustment and coping with infertility, treatment related distress and quality of life were not appropriate for our study. Adjustment and coping with infertility are skills used by patients to deal with the distress.While patient report of quality of life is an important outcome of the fertility treatment offered to them, it does not give us information about the pre-treatment distress that we intend to measure.

Screen IVF has been recommended by the ESHRE guideline as a means to assess the risk of developing clinical levels of psychological distress following treatment. However this questionnaire measures anxiety, depression and fertility associated helplessness using items from generic tools. Fertility related distress cannot be adequately measured using generic tools meant for clinical diagnosis of anxiety or depression or those used in chronic illness.

EM-INFERT is an instrument that is said to measure emotional health rather than distress. EM-INFERT had been developed using qualitative interviews for item generation, and standardised methods for item reduction and scale generation. All item correlations was satisfactory. It had good internal reliability and face and content validity. Though this instrument was constructed using robust methodology, test-retest reliability, construct validity and sensitivity to change had not been reported for this questionnaire. We planned to undertake our study using EM-INFERT and use the data to evaluate the psychometric properties of this instrument.

**3.6 Fertility specific instrument for the study:**

Emotional health or wellbeing rather than distress is a concept that had never been studied before in infertility patients. Emotional health is a state of psychological well-being in which an individual is able to use his or her cognitive and emotional capabilities to the fullest, function in society, and meet the ordinary demands of everyday life(203). The inability to conceive impacts all aspects of people lives including social relationships and self-esteem. Measurement of the emotional health in these patients will help us to understand the true impact of infertility. It was a very comprehensive instrument measuring nine domains of peoples’ lives and 40 item tool that is also easy to administer.

FPI is a multidimensional 46 item questionnaire with satisfactory psychometric properties. Although it was well validated, and had been used in previous studies, the construction methods especially item generation, item reduction with factor analysis was not satisfactory. Face and content validity for this instrument has not been reported.

For our study, we therefore planned to use both FPI and EM-INFERT to enable us to measure emotional health and distress in the patients undergoing IVF. Although fertility associated distress before and during IVF has been measured previously, this would be the first time that emotional health related to infertility would be assessed. The next chapter describes the aim, hypothesis and the study protocol in detail.

**Chapter 4: The Study**

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| --- |
| Overview  3.1 Background  3.2 Study Hypothesis, Aims & Objectives  3.3 Methods  3.4 Results  3.5 Discussion |

**4.1 Background:**  In the first chapter we discussed the emotional aspects of infertility and the reasons why we need to investigate the impact of emotional distress on IVF outcome. In the second chapter we systematically analysed the evidence that was published and identifed the need to perform a well-designed adequately powered study using a fertility specific tool, that will help to correlate the pre-treatment emotional distress with the IVF outcome. In the third chapter we reviewed all the available fertility specific instruments and identifed EM-INFERT and FPI as suitable tools to assess fertility specific distress. In this chapter the study protocol is described in detail including the aims and objectives.

**4.2 Study hypothesis, aim and objectives**:

In our study we planned to assess the emotional health and distress of patients who are undergoing IVF prior to treatment and investigate their impact on the pregnancy outcome after IVF.

**Study hypothesis** : Our hypothesis was that better emotional health at the start of the treatment cycle leads to better success after assisted conception. In other words people who had high emotional health at the start of the treatment had significantly better pregnancy rates after one cycle of IVF.

**Aim and objectives of the study:** The aim of our study was to measure emotional health in women undergoing IVF at the start of the cycle and and correlate it with pregnancy rates after one cycle of IVF.

The primary objective of the study was to compare the pregnancy rates from IVF in women with poor and high pre-treatment emotional health. The secondary objectives were to measure changes in emotional health during the IVF treatment cycle, to find out whether differences are found in male and female respondents, to compare emotional health in first, second and third or later cycles and to determine the responsiveness of the questionnaire to events such as success or failure of IVF treatments.

**4.3 Methods**:

**4.3.1 Study Design:** A quantitative prospective investigation of emotional health assessed by EM-INFERT scores and its potential association with pregnancy rates following assisted conception**.** Three other questionnaires FPI, Perceived stress score (PSS) and positive and negative affect schedule (PANAS) were also used for the study. Eligible couples undergoing IVF at Jessop fertility were recruited to the study between June 2011 to February 2015. Researcher (VT) undertook the study while working as Clinical Research Fellow at Jessop fertility and later on as a specialty trainee at the Jessop wing. As many couples as possible were approached by the researcher on the days recruitment was being done.

**4.3.2 Ethical approval, Research Governance & Funding**: Ethical approval for the project was granted by the National Research Ethics Committee in August 2010 and an amendment in May 2011 approved the appointment of chief investigator as Dr. Patrick Magill and researcher as Dr. Vidya Tamhankar. Research Governance was provided by Sheffield Teaching Hospitals NHS Trust Research Department. The study had part funding from Sheffield Teaching Hospitals Obstetrics, Gynaecology and Neonatology small grants scheme.

**4.3.3 Study sample:** The study sample was from all couples undergoing IVF at the Jessop Fertility Unit.

The inclusion criteria for this project were:

1. Age above 18 years
2. Command of the English language sufficient to understand the questionnaire and its implications; and
3. Ability to understand the patient information and willingness to provide written consent.

The exclusion criteria were:

1. Couples taking part in any interventional research; and
2. Occurrence of an event of major emotional significance (for example, bereavement, major surgery or the diagnosis of major illness) six months or less before giving informed consent.

**4.3.4 Recruitment of women**

Eligible couples attending Jessop Fertility were contacted by the researcher (VT) during one of the assessment consultations. Information about the study was provided at the time and consent was obtained for contact by phone to provide further details of the research and to answer questions arising from the information sheet. Couples were given ample time to consider whether to participate and were encouraged to discuss the research with each other and with friends. Those willing to take part were asked to complete the questionnaires at three time points during the IVF treatment cycle (at the start of ovarian stimulation, at egg collection and 48 hours after receiving the result of the pregnancy test).

**Figure 4.1: Flow chart for recruitment of infertile couples**

Eligible couples booked for IVF treatment identified from the database at the Assisted Conception Unit, Jessop wing

Couples approached at the medical or nurse consultation and ensured that inclusion and exclusion criteria were met. The research project was discussed and information leaflets were given and consent was obtained for telephone contact to further discuss details of the project

Couples who agreed to participate gave their written consent for the study

On receiving the consent form a questionnaire pack was given to the couples at the start of the cycle during their initial assessment visit with the names written in pencil.

They were advised to complete the first questionnaire before any medication was administered and encouraged to leave the questionnaire at a pre-arranged area of the IVF Unit as soon as they were completed.

The second questionnaire was completed on the day of egg collection at home by the couple and handed over when they attend the unit for embryo transfer.

The third questionnaire was completed atleast 2 days after the pregnancy test and was posted to the researcher in a self addressed envelope already provided in the questionnaire pack.

All the received questionnaires are anonymised by exchanging the name for unique study ID

**4.3.5 Instruments used:**

**1. Emotional Health in Infertility Questionnaire (EM-INFERT)**

The primary questionnaire that was used to measure the emotional health of infertile couples undergoing IVF couples was the Emotional Health in Infertility Questionnaire **(**EM-INFERT). EM-INFERT is a comprehensive 40 item questionnaire which covers nine domains of people’s lives that can be influenced by infertility and its treatment namely personal strain, partner relationship strain, sexuality, social support, confidence in treatment, guilt and blame, financial strain, need for privacy and couple concordance. The instrument was scored using a 5-point Likert scale where 0=definitely true, 1=mostly true, 2=not true, 3=mostly untrue, 4= definitely untrue. The individual domain scores were computed and total EM-INFERT scores were calculated by summing up the nine domain scores. Initial scores ranged from a minimum score of 0 to a maximum score of 160. The scores were rescaled from 0 to 100 for optimal comparison. High EM-INFERT scores corresponded to better emotional health.

**2. The Fertility Problem Inventory (FPI)** focuses upon the stress of infertility. It has 46 items and contains five scales measuring Social concern, Sexual concern, Relationship concern, Need for parenthood, and Rejection of childfree lifestyle. The instrument was scored using a 6-point Likert scale and a total measure of Global stress can also be calculated by summing the five scales. High scores of individual domain indicate feelings of social alienation, loss of enjoyment of sexual relations, concerns about the future of relationships, negative view of childfree lifestyle. Higher scores of global stress indicate overall high level of infertility-related stress. The FPI has demonstrated good reliability, discriminant and convergent validity(145).

**3. The Perceived Stress Scale (PSS)** is a measure of the degree to which situations in one’s life are appraised as stressful. Items were designed to tap how unpredictable, uncontrollable, and overloaded respondents find their lives(173). The 10-item version was used in this study. The questions in the PSS ask about thoughts and feelings during the last month. In each question the respondent is asked how often they felt a certain way. The 10 items are scored using a 5 point Likert scale from 0 to 4. PSS-10 scores are obtained by reversing the scores on the four positive items, 4, 5, 7 and 8 and then summing across all 10 items

**4. The Positive and Negative Affect Schedule (PANAS)** consists of 10 positive affects (interested, excited, strong, enthusiastic, proud, alert, inspired, determined, attentive, and active) and 10 negative affects (distressed, upset, guilty, scared, hostile, irritable, ashamed, nervous, jittery, and afraid) (204). Participants are asked to rate items on a scale from 1 to 5, based on the strength of emotion where 1 = "very slightly or not at all," and 5 = "extremely". High score of positive affect indicates the extent to which the individual feels enthusiastic, active and alert, while a high negative affect indicates the extent to which the individual feels aversive mood states and general distress.

**4.3.6 Assessments:** The following demographic data was recorded: BMI, age, cause & duration infertility, previous treatment and obstetric history. The treatment related paramenters that were assessed are total number of days taken to achieve ovarian stimuation, number of oocytes retrieved, fertilisation rate and number of embryos replaced/ stored frozen.

**4.3.7 In vitro fertilisation**: The treatment commenced usually with the menstrual cycle and consisted of controlled ovarian stimulation with FSH or HMG (Human Menopausal Gonadotropin) and GnRH agonist or antagonist. A few had regimen of long protocol which started with pituitary downregulation using GnRH agonist from the 21st day of the previous menstrual cycle for two weeks followed by ovarian stimulation by FSH. After baseline blood tests and ultrasound scan on the second day of the menstrual cycle, all patients went through a variable period of ovarian stimulation with FSH during which they underwent blood and ultrasound monitoring. When they met the criteria, (minimum of 3 follicles more than 17mm on transvaginal ultrasound) ovulation was triggered with chorionic gonadotrophin and transvaginal oocyte recovery was performed after 36 hours. Oocytes were fertilised using IVF or intracytoplasmic sperm injection (ICSI) depending on the cause of infertility and sperm parameters. Embryos were then transferred inside the uterus anytime between day 3 to Day 5 depending on the number and quality of embryos. Pregnancy test using serum Beta HCG was done 14 days after egg collection.

**4.3.8 Outcomes**: Treatment outcome was classified as follows:

**Cancelled cycles**: Patients who had their IVF treatment cycles cancelled before reaching the stage of egg collection due to under or over response to stimulation.

**Failed Fertilisation**: Patients whose egg did not fertilise to form embryos. Their treatment cycles ended at this stage and a medical follow up was arranged to discuss the possible reasons for failure of fertilisation.

**Freezing of all embryos**: In some patients it was deemed not suitable to proceed to embryo transfer either due to risk of developing ovarian hyperstimulation syndrome due to over-response or due to some other medical reasons like presence of endometrial polyp or infection following egg collection.

**Non pregnant**: Patients whose Serum HCG levels on Day 14 after egg collection were negative. Patients with a biochemical pregnancy and ectopic pregnancy were also included in this group. Biochemical pregnancy is when there is a positive serum HCG on day 14 after egg collection but it becomes negative prior to confirmation of clinical pregnancy by ultrasound scan .

**Clinical pregnancy**: Patients who had a positive serum HCG on day 14 after egg collection followed by confirmation of ultrasound scan of a intrauterine pregnancy.

**Biochemical pregnancy**: Biochemical loss was defined as positive BHCG >20 IU/L on day 14 of luteal phase with no ultrasound evidence of pregnancy. In almost all cases the level of HCG starts falling within a week.

**Ectopic pregnancy**: Ectopic pregnancy was defined when pregnancy has implanted extrauterine in the fallopian tube or ovary. It is usually diagnosed by suboptimally rising BHCG and or ultrasound scan.

**Miscarriage**: Pregnancy loss after confirmation of intrauterine pregnancy by ultrasound scan. It can occur in the first or second trimester.

**Live birth**: Pregnancy that results in the live birth of the baby.

**4.3.9 Power calculation**: The strength of the relationship between EM-INFERT scores and pregnancy rates following assisted reproduction, if it exists, is not known. A difference in pregnancy rates per cycle between the top and bottom thirds of EM-INFERT scores of 15 percentage points (35% and 20% respectively) would be clinically significant. Power of greater than 80% to detect this difference would be achieved by 138 observations (assuming that female partner scores are the more relevant) taken at the start of the treatment cycle (before ovarian response potentially impacts on emotional perceptions) using a two tailed test at the 5% level of statistical significance. This calculation implies 138 couples undergoingIVF in each third or 414 couples in total. Therelative risk (RR) of achieving pregnancy is 1.75 which represents a difference of 15 percentage points between the top and bottom thirds of the study population ranked by EM-INFERT scores (estimated pregnancy rates of 35% in the top third compared with 20% in the bottom third). This is a moderate effect. If 10% of couples are lost to follow-up then a total of 460 couples will need to be recruited to achieve a sample size of 414 evaluable couples.

**4.3.10 Plan for data analysis**

**Descriptive statistics:**

The demographic variables age, BMI and duration of infertility of the study group were to be described using descriptive statistics of mean and standard deviation for normally distributed data and median and interquartile range for non-normally distributed parametric data.

The categorical variables previous pregnancies, previous failed IVF, cause of infertility were to be described using number and percent.

The treatment variables compared between groups should include number of days of stimulation, eggs retrieved, and number of eggs fertilized. All these would be described using median and inter-quartile range. The number of embryos transferred is either 1 or 2 and hence described as a categorical variable.

**Main Hypothesis:**

The plan to investigate the main hypothesis was to divide pre-treatment scores from EM-INFERT into three tertiles based on their emotional health score and compare the pregnancy rates between the top and bottom tertile. Chi square test of proportion was to be used to compare the tertile groups. Statistical significance had been set at p<0.05. Statistically significant difference in the pregnancy rate between the top tertile and bottom tertile would disprove the null hypothesis . Intention to treat analysis was planned. Hence all cycles including the ones that are cancelled, would be analysed. The groups would be also compared for any difference in the demographic variables of age, BMI, duration of infertility, previous pregnancy, previous failed IVF and cause of infertility. Independent samples‘t’ test was to be used to compare the means between groups for age, BMI and duration of infertility. Chi square test was to be used to compare previous pregnancy, previous failed IVF and cause of infertility. We would be comparing the biochemical pregnancy rate, miscarriage rate and live birth rate between the three tertiles of EM-INFERT scores by Chi square test. Mean scores of FPI, PSS and Panas would also be compared between the three tertiles using Independent samples ‘t’ test.

Our next question is can we predict pregnancy rates using EM-INFERT scores? To answer this a logistic regression model was to be fitted with clinical pregnancy as dependent variable and pre-treatment EM-INFERT scores as independent variable and multivariable logistic regression would be performed, adjusting for woman’s age, BMI and duration of infertility. Wald statistic would be used to assess if a particular variable was a significant predictor of clinical pregnancy.

**Secondary analysis:**

We planned to compare the biomedical variables age, BMI, duration of infertility, previous live birth, days of stimulation, number of eggs retrieved, fertilised eggs and psychological variables of FPI, PSS and PANAS median scores between pregnant and non-pregnant groups. A p value of <0.05 was considered to be statistically significant.

**Changes in EM-INFERT scores during IVF treatment:**

In order to understand the impact of IVF on emotional health, EM-INFERT questionnaire scores at all three time points will be compared with each other using ANOVA for repeated measures. A further comparison between time points 1 and 2 and then between time points 2 and 3 would be done using using paired samples ‘t’ test. This would be done again separately for pregnant and non-pregnant groups. Similar test would be repeated for FPI, PSS and PANAS questionnaires.

**Gender based comparison**:

Comparison of mean EM-INFERT scores and domain scores would be done at three time points between men and women using student‘t’ test with a p value of 0.05 to be considered as significant. We planned to compare the EM-INFERT scores between men and women for pregnant and non-pregnant groups and for male and female cause of infertility. Similar analysis was also planned using FPI, PSS and PANAS questionnaire. The aim was to assess if there is any the difference in emotional health between men and women in response to infertility and assisted conception.

**Changes in Emotional health due to cause and duration of infertility**:

The entire cohort was to be divided into groups according to the cause of infertility. The groups would be compared using age, BMI, duration of infertility, number of eggs retrieved, previous live birth. Comparison of mean and domain EM-INFERT scores between all causes of infertility would be done using ANOVA comparison of multiple means. These tests would be repeated with FPI, PSS and PANAS questionnaires. The results of this would indicate if the emotional health is significantly different in any of the causes of infertility.

The next step was to compare mean and domain scores of EM-INFERT, FPI, PSS and Panas between patients undergoing first cycle of IVF and repeat cycles. The results would also indicate whether duration of infertility and its treatment has any impact on the emotional state of the patients.

**Psychometric Tests on EM-INFERT:**

**Test-retest reliability**:

Test-retest reliabilityis the [variation](https://en.wiktionary.org/wiki/variation) in [measurements](https://en.wikipedia.org/wiki/Measurement) taken by a single person or [instrument](https://en.wikipedia.org/wiki/Measuring_instrument) on the same item, under the same conditions, and in a short period of time. If the correlation between separate administrations of the test is high (e.g. Cronbach's alpha >0.7), then it has good test–retest reliability. We planned to ask patients whether they experienced any change in their health or emotion between the pre-treatment questionnaire and the test done at egg collection stage. On comparison of patients who had no change in health or emotion between this time interval were compared with Cronbach alpha. A score of 0.7 or more on would confirm reliability of EM-INFERT.

**Construct validity**

Construct validity indicates the degree to which observations actually represent the measure or construct being investigated. In our study, this can be done by correlating EM-INFERT questionnaires with other established validated measure of fertility associated stress like FPI, PSS and Panas

**Sensitivity to change**

Any tool that is used to measure efficacy of a particular intervention has to be responsive to change. If we are to use EM-INFERT to measure the change in emotional health after intervention, then it needs to demonstrate sensitivity to change.

**4.4. Recruitment Results**:

460 patients, who met the inclusion criteria, were approached and invited to participate in the study from June 2011 till February 2015. Of these 457 were couples and 3 were single females going through IVF. Out of 457 couples 46 couples declined to participate giving a recruitment rate of 90%. 29 partners of women who had consented to participate declined the study. So 414 women and 380 men completed the study at time point 1 (T1). Treatment of 12 patients was cancelled prior to egg collection due to medical reasons and 3 IVF cycles were converted to IUI due to poor response in the ovarian stimulation phase. 399 patients reached the stage of egg collection. Of these, 237 were IVF cycles and 162 cycles had fertilisation using ICSI. In 36 couples surgical sperm aspiration was done to retrieve sperm for treatment.

Out of 399 patients, 20 did not have embryo transfer. 10 patients had failed fertilisation and all embryos were frozen in 10 patients due to ovarian hyperstimulation syndrome. 379 patients completed their IVF treatment cycle as planned. Of these only 282 women and 244 men completed questionnaire at Time point 2 (T2). This rate further decreased and only 194 women and 168 men completed the study at time point 3 (T3).

**Figure 4.2: Study population**

**Declined to participate**

**Couples 46 M: 29**

**Cycles cancelled prior to EC n=12**

**Patients who reached EC 399**

**Patients with completed IVF 379**

**No embryo transfer= 20**

**Failed fertilisation =10**

**Freeze all =10**

**Completed questionnaire at T2**

**282 W 244 M**

**Completed questionnaire at T3**

**194 W 168 M**

**Patients approached 460 (couples 457 + 3 single) )))))))))female)**

**Consented for study**

**414 W 380 M**

**Completed questionnaire T1 414 W 380M**

**Cycles converted to IUI n=3**

**T1: Time point 1 W: Female partner**

**T2: Time point 2 M: Male partners**

**T3: Time point 3 EC: Egg collection**

**IVF: In vitro Fertilisation IUI: Intrauterine insemination**

**Characteristics of the study population:**

Summary statistics of the demographic variables of study population was done using mean, standard deviation; median and interquartile ranges were calculated for the demographic variables of the study population. The variables that were studied were female age, male age, female BMI, previous IVF, duration of infertility, previous pregnancies, previous live births, cause of infertility. The causes of infertility were further divided into tubal, ovulatory cause, male factor, poor ovarian reserve, endometriosis and unexplained cause.

The clinical pregnancy rate at the end of the IVF cycle of the study population was 31.4% (130/414) (Table 4.1). 98 pregnancies resulted in a live birth (23.7%). 30 pregnancies (7.2%) ended in a miscarriage and 1 was a stillbirth. 284 cycles did not result in a clinical pregnancy. Of this 21 treatment cycles ended in a biochemical pregnancy (5%) and 3 (0.7%) were diagnosed with ectopic pregnancy

**Table 4.1: Demographic parameters of study sample**

|  |  |
| --- | --- |
| Female age\* | 33.8 (4.5) |
| Male age\* | 38.5 (7.0) |
| Female BMI \* | 24.7(3.7) |
| Duration of infertility \* | 3.1 (1.6) |
| Previous pregnancies | 66 (16%) |
| Previous children | 52 (12.5%) |
| First time IVF | 243 (58.7%) |
| Cause of Infertility  Anovulation  Male factor  Tubal factor  Endometriosis  Unexplained  Same sex relationship | 12 (6.2%)  82 (42.3%)  34 (17.5%)  17 (8.8%)  47 (24.2%)  2 (1%) |
| Number of days of stimulation \* | 8.9 (1.6) |
| Number of follicles \* | 9.8 (4.1) |
| Number of eggs \* | 9 (4.5) |
| Number of embryos transferred \* | 1.4 (0.5) |
| Pregnancy outcome | |
| Biochemical pregnancy | 21 (5%) |
| Clinical pregnancy | 130 (31.4%) |
| Miscarriage | 30 (7.2 %) |
| Ectopic | 3 (0.7%) |
| Stillbirth | 1(0.2%) |
| Livebirth | 98 (23.7%) |

\* - Results expressed as Mean (Standard Deviation)

**Completion of questionnaires**:

There was a high attrition rate in completion of questionnaire by the time of pregnancy tests. Out of 379 women who had completed the first questionnaire and undergone a full cycle of IVF, 282 patients (74.4%) completed questionnaire at egg collection stage and only 194 (52%) completed the third questionnaire. This in itself could be due to a possible refection of the stressful nature of the treatment. In men, the response rate was poorer with 64% of response for the second questionnaire and 44% response for the third questionnaire.

The most common reason cited for non-completion was ‘lack of time’ or ‘forgot to bring it’. The following were the responses of the patients who had not completed the questionnaire.

'I felt too stressed after doing the questionnaire. It made our IVF treatment worse'.

'I had to think about the questions which made me uncomfortable.’

‘Initially the questionnaire was OK but then later I found it a chore'.

‘I work long hours and have to fit the treatment in between and then having to do the questionnaire was a lot of work for me’

‘I did not do the last questionnaire as I had a failed cycle.’

58.5% of patients who had a positive outcome completed all three questionnaires while only 40% of the patients with negative outcome completed the study. This difference is not quite statistically significant (p=0.06)

**Non-participation in the study**

Stress was the commonest factor cited as the reason for not participating in the study. Although the uptake rate for the study was good, we feel that it may have failed to include patients who have poor emotional health as they would have declined to participate leading to a selection bias.

The reasons cited for non-participation was as follows

‘I feel that my stress will get worse on doing the study as the questions might cause more distress’.

‘I am very busy with work and cannot spend time doing the questionnaire.’

‘I don’t want anything to interfere or distract us from treatment and hence do not want to participate.’

‘I don’t want to do anything else except treatment.’

All but one patient who declined, had undergone previous IVF treatments. One patient was having her first IVF, but had undergone 6 IUI cycles previously. This she said was the main reason for declining.

**Chapter 5: Result (I) Impact of emotional health on IVF outcome**

|  |
| --- |
| Overview  3.1 Background  3.2 Method  3.3 Results  3.4 Results  3.5 Impact of Emotional Health on pregnancy |

**5.1 Background**

We have seen from the previous chapters that studies reporting the impact of psychological distress on IVF outcome are inconsistent due to heterogeneity in the study design, the instruments used and the methodology. The timing of measurement of emotional distress in relation to the IVF cycle is very important. Stress is often higher closer to the onset of the treatment cycle(205). In this chapter, we present the results of the main part of the study, which is the impact of emotional health measured by EM-INFERT at the start of the IVF cycle on pregnancy outcome.

**5.2 Method**:

We designed a prospective longitudinal cohort study to assess the impact of pre-treatment emotional health on pregnancy rates after IVF. The study protocol and methods has been described in detail in Chapter 4. As per the statistical plan, pregnancy rates were compared between the three tertiles of EM-INFERT scores. Emotional health between pregnant and non-pregnant groups was also compared to see if emotional health at the start of the cycle can predict the probability of pregnancy.

**5.3 Results:**

EM-INFERT scores for 414 women, at the start of the treatment cycle were calculated by adding up all the responses of individual 40 questions. A score of 100 represented the best emotional health and a score of 0 was the worst. The EM-INFERT scores ranged from a minimum of 13.13 to a maximum of 97.5. Based on the EM-INFERT scores, the entire study population was divided into three tertiles as per the study protocol: Group I had the lowest tertile of EM-INFERT scores (EM-INFERT 13.13-56.88; n=140) corresponding to poor emotional health, Group II had scores in the middle tertile (EM-INFERT 57.5-71.88; n=139) corresponding to average emotional health and Group III had the highest tertile of EM-INFERT scores (72.5-97.50; n=135) consistent with best emotional health . The three groups were similar with regards to female age, BMI, previous live births and proportion of patients having their first IVF. Only significant parameter that was different between the groups was duration of infertility, which was lowest in the top tertile and highest in the middle tertile (p=0.029). The primary outcome of clinical pregnancy and secondary outcome of live birth rate was similar between the three tertiles (p=0.34 & p=0.33). We tested our hypothesis by comparing the difference in clinical pregnancy rates between top tertile and bottom tertile. This difference was not significant. (27.9% vs. 31.1% p=0.597). This means that our assumption that better emotional health leads to higher pregnancy rates was wrong. The clinical pregnancy rate in bottom tertile was lowest (27.9%), but the highest pregnancy rates were found in the middle tertile in patients with average emotional health (36.2%). This difference was also not significant (27.9% vs.36.2 % p=0.199).

**Table 5.1 Domains of EM-INFERT**

|  |  |
| --- | --- |
| Personal strain | |
| Q.2 | I feel upset when people make insensitive comments about childless couples |
| Q.5 | My life is on hold because of fertility treatment. |
| Q.8 | I find it hard to cope with our fertility problem. |
| Q.11 | I resent having to put other aspects of my life on hold because of infertility. |
| Q.17 | Infertility has taken over my life. |
| Q.22 | I find it painful when family members and/or friends become pregnant |
| Q.23 | I will feel incomplete as a person if I cannot have my own child. |
| Q.25 | Infertility makes me feel I have lost control of my life. |
| Q.33 | I am exhausted by the emotional roller coaster of infertility. |
| Q.34 | I find trying to balance fertility treatment with my other commitments stressful. |
| Q.36 | I feel angry that I may not be able to have a / another child. |
| Q.37 | Each birthday without a / another child is more upsetting. |
| Partner relationship strain | |
| Q.12 | I find it hard to help my partner cope with our fertility problem. |
| Q.14 | Infertility strains my relationship with my partner. |
| Q.21 | I find it difficult to talk to my partner about our fertility problem without one of us getting upset or angry. |
| Q.24 | Sometimes I think that infertility could lead to us separating. |
| Q.28 | I feel my partner is obsessed with trying to have children |
| Couple concordance | |
| Q.26 | I disagree with my partner about how much money to spend on treatment. |
| Q.31 | I feel my partner is not as committed to having children as I am. |
| Sexuality | |
| Q.16 | I feel pressured to have sex at the ‘right time’ even when I don’t feel like it. |
| Q.19 | I feel that sex is more about conceiving than expressing our love for each other. |
| Q.20 | Fertility treatment makes me feel like a ‘thing’ rather than a person. |
| Q.29 | Sex is less enjoyable now that I know about our fertility problem. |
| Q.35 | I feel less sexually attractive since discovering our fertility problem. |
| Social support | |
| Q.3 | I get upset when family and/or friends talk about their children.. |
| Q.13 | I avoid seeing family and/or friends who have children. |
| Q.18 | I feel unsupported by family and/or friends. |
| Q.27 | I avoid places where there might be pregnant women or children. |
| Confidence in treatment | |
| Q.1 | I feel that information given by staff is sometimes inadequate. |
| Q.10 | At times I feel we are not getting the best treatment. |
| Q.15 | I feel that decisions about treatment are out of my control. |
| Guilt and Blame | |
| Q.7 | I feel my partner blames me for our fertility problem. |
| Q.30 | I blame myself for our fertility problem |
| Q.38 | I feel guilty that my past actions may have affected my fertility. |
| Q.39 | Having a fertility problem makes me feel inadequate. |
| Financial Strain | |
| Q.4 | I may have to stop treatment sooner than I would like because of the financial cost. |
| Q.40 | Finding the money for treatment is a constant worry. |
| Need for privacy | |
| Q.6 | I find it hard to share my feelings about infertility with my family and/or friends. |
| Q.9 | Trying to maintain privacy during treatment is stressful. |
| Q.32 | I find it hard to agree with my partner whether to tell family and/or friends about our fertility problem. |

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | Lowest Tertile  (EM-INFERT 13.13-56.88) | Middle Tertile  (EM-INFERT 57.5-71.88) | Top Tertile  (EM-INFERT 72.5-97.50) |  |
| Number of patients | 140 | 139 | 135 |  |
| Female mean age (SD) | 33.9 (4.4) | 34.0 (4.4) | 33.6 (4.6) | p=0.718 |
| Female mean BMI (IQR) | 24.9 (3.9) | 24.4 (3.7) | 24.9 (3.3) | p=0.554 |
| Mean duration (years) of infertility (SD) | 3.16 (1.6) | 3.36 (1.8) | 2.82 (1.3) | **p=0.029** |
| Previous live births (%) | 17 (12.1) | 17 (12.2) | 16 (11.9) | p=0.97 |
| First time IVF (%) | 78 (55) | 77 (57.2) | 85 (63.8) | p=0.31 |
| Completed cycles | 129 | 134 | 122 |  |
| Failed fertilisation | 4 (2.9) | 3 (2.2) | 3 (2.2) |  |
| Clinical pregnancy (%) | 39 (27.9) | 49(35.3) | 42 (31.1) | p=0.34 |
| Biochemical pregnancy (%) | 8 (5.7) | 7 (5) | 6 (4.4) |  |
| Ectopic (%) | 0(0) | 1 (0.7) | 2 (1.5) |  |
| Miscarriage (%) | 10 (7.1) | 11 (7.9%) | 9 (6.7%) |  |
| Live birth (%) | 29(20.7) | 38 (27.3) | 31 (23) | p=0.33 |

**Table 5.2: Comparison between the three tertiles of EM-INFERT scores**

The EM-INFERT scores from the three groups were further divided into nine domains as follows: personal strain, partner relationship, sexuality, social support, confidence in treatment, guilt and blame, need for privacy, financial strain and couple concordance. The scores of individual domains were computed and compared between the three tertiles. Rest of the questionnaire scores were also compared between the three groups.

After IVF cycle, we compared pregnant women with the non-pregnant group with regards to demographics and other treatment variables. We compared means using independent ‘t’ test and chi-square test for categorical variables. The results showed that younger women were more likely to conceive (32.91 vs. 34.24; p=0.009). Pregnant women also had higher number of oocytes as compared to non-pregnant women (10.1 vs.8.28 p=0.000). Rest of the parameters including BMI, previous unsuccessful IVF, previous live births, duration of infertility, number of embryos transferred did not differ between the two groups (Table 5.4). Change in emotional health in the first half of cycle between pregnant and non-pregnant women was similar indicating no impact of the fluctuation in emotional health on pregnancy rates.

|  |  |  |  |
| --- | --- | --- | --- |
|  | Lowest Tertile  (EM-INFERT 13.13-56.88) | Middle Tertile  (EM-INFERT 57.5-71.88) | Top Tertile  (EM-INFERT 72.5-97.50) |
| Personal strain | 25.65 (11.93) | 46.28 (12.71) | 70.56 (13.58) |
| Partner relationship | 62.43 (19.62) | 79.71 (14.24) | 94.44 (7.37) |
| Sexuality | 48.96 (21.87) | 72.41 (19.24) | 90.56 (11.41) |
| Social support | 62.28 (18.94) | 81.43 (15.67) | 92.92 (9) |
| Confidence in treatment | 65.42 (15.58) | 76.02 (16.53) | 88.95 (12.83) |
| Guilt and blame | 48.62 (23.07) | 68.93 (19.21) | 87.18 (15.35) |
| Financial strain | 30.54 (26.83) | 51.71 (31.36) | 67.87 (29.2) |
| Need for privacy | 44.05 (21.19) | 59.41 (18.6) | 76.54 (20.03) |
| Couple concordance | 67.32 (24.94) | 81.74 (18.87) | 93.15 (10.66) |
| FPI |  |  |  |
| Social concern | 37.33 (7.1) | 30.86 (7.74) | 24.31 (6.28) |
| Sexual concern | 26.49 (7.55) | 19.8 (6.82) | 13.69 (5.16) |
| Relationship concern | 28.96 (8.49) | 23.67 (6.85) | 19.53 (4.6) |
| Rejection of childfree lifestyle | 33.27 (7.51) | 29.56 (7.36) | 26.24 (7.82) |
| Need for parenthood | 46.01 (7.83) | 41.16 (9.2) | 34.98 (9.28) |
| Global stress | 171.14 (25.7) | 144.88 (23.58) | 118.49 (21.83) |
| Perceived stress | 21.38 (5.22) | 18.28 (5.95) | 14.13 (5.82) |
| Positive affect | 29.32 (7.92) | 30.02 (6.86) | 34.84 (7.67) |
| Negative affect | 29.05 (8.87) | 23.72 (6.97) | 20.35 (6.81) |

**Table 5.3: Comparison of EM-INFERT domains between the three tertiles**

**Table 5.4: Demographic and treatment variables in pregnant and non-pregnant women**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Variable | After IVF treatment | | Mean Difference (95%CI) | Test |
|  | Non pregnant n=284 | Pregnant n=130 |  |  |
| Female age years  Mean (SD) | 34.24 (4.4) | 32.91 (4.5) | 1.33(0.39,2.26) | **p=0.005** |
| Female BMI  Mean (SD) | 24.5 (3.6) | 25.3 (3.6) | -0.86(-1.73,0.004) | p=0.05 |
| Duration of infertility (years) Mean (SD) | 3.11(1.6) | 3.13 (1.65) | -0.02 (-0.38,0.33) | p=0.87 |
| Previous IVF  No  Yes | 156  126 | 82  45 |  | p=0.08 |
| Previous pregnancies  Yes  No | 26 % (74)  74% (210) | 20% (26)  80% (104) |  | p=0.21 |
| Previous live births | 35 (12.3%) | 15 (11.5%) |  | p=0.8 |
| Completed IVF cycle | 249 | 130 |  |  |
| Number of oocytes Mean (SD) | 8.28 (4.7) | 10.1(4.05) | -1.9(-2.86,-0.94) | **p= 0** |
| Embryos transferred Mean (SD) | 1.34 (0.66) | 1.36 (0.48) | -0.04(-0.17,0.08) | p=0.5 |

**Table 5.5: Comparison of emotional health and fertility related distress between pregnant and non-pregnant women**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | Non pregnant n=284 | Pregnant n=130 | Mean Difference (95% CI) | Independent ‘t’ test |
| EM-INFERT | 64.3 (16.3) | 64.06 (17.03) | 0.24 (-3.24,3.71) | p= 0.893 |
| Personal Strain  Mean (SD) | 47.9 (22.32) | 45.7 (22.5) | 2.21 (-2.43,6.86) | p= 0.35 |
| Partner relationship  Mean (SD) | 78.7 (19.6) | 78.4 (20.3) | 0.36 (-3.73,4.46) | p= 0.862 |
| Sexuality  Mean (SD) | 70.5 (62.5-93.75) | 70.1 (20.56) | 0.41 (-4.76,5.59) | p= 0.875 |
| Social support  Mean (SD) | 78.6(19.6) | 78.9 (20.51) | -0.29 (-4.4,3.83) | p= 0.892 |
| Confidence in treatment  Mean (SD) | 75.8 (17.52) | 78.3 (18.3) | -2.55 (-6.26,1.17) | p= 0.178 |
| Guilt and Blame  Mean (SD) | 67.5 (24.86) | 68.9 (24.4) | -1.43 (-6.64,3.79) | p= 0.591 |
| Need for Privacy  Mean (SD) | 59.5 (24.01) | 60.2 (24.1) | -1.67 (-8.52,5.19) | p= 0.633 |
| Financial Strain  Mean (SD) | 49.2(33.3) | 51.8 (31.84) | -0.66 (-5.65,4.33) | p= 0.794 |
| Couple Concordance  Mean (SD) | 80.4 (22.3) | 80.9 (21.4) | -0.55 (-5.1,4) | p= 0.813 |
|  | Non pregnant n=284 | Pregnant n=130 | Mean Difference (95% CI) | Independent ‘t’ test |
| FPI Stress  Mean (SD) | 144.08 (31.9) | 147.48 (32.22) | -3.4 (-10.06,3.26) | p= 0.316 |
| Social concern  Mean (SD) | 30.79 (8.8) | 31.12 (8.94) | -0.32 (-2.17,1.52) | p= 0.731 |
| Sexual concern  Mean (SD) | 20.23 (8.1) | 19.68 (9.04) | 0.55 (-1.2,2.31) | p= 0.537 |
| Relationship concern  Mean (SD) | 24.16 (8.17) | 23.95 (7.15) | 0.21 (-1.43,1.85) | p= 0.801 |
| Rejection of childfree lifestyle  Mean (SD) | 29.19 (8.27) | 30.86 (7.53) | -1.67 (-3.35,0.01) | p= 0.051 |
| Need for parenthood  Mean (SD) | 40.26 (10.05) | 41.88 (9.36) | -1.62 (-3.67,0.43) | p= 0.122 |
| Perceived Stress  Mean (SD) | 17.74 (6.5) | 18.41 (6.13) | -0.66 (-2,0.67) | p= 0.329 |
| Positive Affect  Mean (SD) | 31.64 (8.1) | 30.92 (7.35) | 0.72 (-0.95,2.39) | p= 0.398 |
| Negative affect  Mean (SD) | 24.36 (8.54) | 24.24 (8.08) | 0.12 (-1.66,1.9) | p= 0.894 |

The total EM-INFERT scores between pregnant and non-pregnant groups were similar. (64.06 vs.64.3; p=0.893). There was no difference in the domain scores of EM-INFERT or in the rest of questionnaires indicating that emotional heath and fertility related distress was similar at the start of the cycle between patients who conceived and those who did not get pregnant.

Logistic regression analysis was conducted to identify if EM-INFERT can predict the occurrence of clinical pregnancy. Female age was used in the prediction model as univariate analysis showed that to be significantly different between pregnant and non- pregnant women. The odds ratio for EM-INFERT was 0.999 with 95% Confidence interval 0.986 to 1.011. This indicated that emotional health as measured by EM-INFERT cannot predict the occurrence of pregnancy.

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Table 5.6: Prediction of Clinical pregnancy using Logistic regression** | | | | | | | | | |
|  | | B | S.E. | Wald | df | Sig. | Exp(B) | 95% C.I.for EXP(B) | |
| Lower | Upper |
| Step 1a | Femaleage | -.066 | .024 | 7.658 | 1 | .006 | .936 | .893 | .981 |
| EM-INFERT | -.001 | .006 | .053 | 1 | .818 | .999 | .986 | 1.011 |
| Constant | 1.536 | .918 | 2.803 | 1 | .094 | 4.647 |  |  |
| a. Variable(s) entered on step 1: Femaleage, TotalEM-INFERTT1. | | | | | | | | | |

**5.4 Impact of emotional health on pregnancy:**

The main aim of this study was to explore the relationship between emotional distress due to infertility and the outcome after IVF. Infertility on its own leads to significant amount of psychological stress(206). Couples undergoing assisted conception are additionally exposed to the physical and emotional burden of IVF (207). We evaluated the effect of pre-treatment emotional health on the pregnancy rates after IVF. We hypothesised that pre-treatment emotional distress can significantly affect the outcome of IVF cycle.

According to our hypothesis, patients with the top EM-INFERT scores should have the best emotional health and the highest pregnancy rates while the bottom tertile will have the lowest pregnancy results after IVF. Our study has shown that patients in the lowest tertile of EM-INFERT scores do have the least success with IVF (clinical pregnancy of 27.9%). But the comparison between this group and the other two tertiles has failed to show any significant difference. According to our study we can infer that pre-treatment emotional health as measured by EM-INFERT does not affect the success rate of IVF. There does seem to be a trend that patients with better emotional health, were more likely to conceive but this difference was not statistically sigificant. We also considered the effects of other confounding variables on the success of IVF like age, BMI, duration of infertility, history of previous pregnancies, number of retrieved and fertilised oocytes and number of embryos replaced. Age and number of oocytes retrieved were the only factors that were significantly different between pregnant and non-pregnant groups.

Our results are consistent with other recent studies (96, 116, 121, 208) and meta-analysis by Boivin *et al* (85) but contrasts with other studies which showed that psychological distress correlated with negative outcome of IVF (95, 102, 122). It also differs from the meta-analysis by Matthiesen *et al* which showed a small but significant effect of stress and distress on pregnancy rates after IVF (86). There may be several reasons for the discrepancies between our study and others. Most of the studies that differed from us were mainly done using generic measures of state and trait anxiety and depression. But Gourounti *et al* used both fertility specific (FPI) and generic measures to examine pre-treatment distress and found it to be negatively associated with pregnancy rates (124). However in their study the sample size was one third of ours. The end point was positive pregnancy test which was different from ours. 5% of our study group who has positive pregnancy result had a biochemical pregnancy.

One of the other factors that led to different results could be overall good emotional health of our study group with a mean score of 64.37 although there were large inter-individual differences. It is possible that patients’ responses were more positive than what they actually felt due to scoial desirability bias. They might have suppressed their worries and anxiety because they wanted to show that they were functioning well psychologically (77) so as to ensure that they are able to access IVF treatment. Our study was conducted just at the start of the treatment cycle, when patients often have unrealistically high expectations about the likelihood of a successful IVF (47, 76). This could have influenced their responses to the questionnaire. Another explanation is that only psychological well-adjusted couples will choose to confront the emotional demands of IVF treatment (56). Our results are consistent with the systematic review by Verhaak et al, who found no increase in pre-treatment anxiety and depression over the norm groups just before the start of the cycle.(79). He also concluded that women starting with IVF may see the treatment as a solution to their fertility problems and a possibility to regain control over the fulfilment of an important life goal.

EM-INFERT is a comprehensive tool which taps into nine domains that involves fertility- specific distress. The composite EM-INFERT score measures emotional wellbeing of patients pertaining to fertility. This study has helped to identify a group of patients who have poor emotional health at the start of treatment cycle. These patients are more likely to get worse after an unsuccessful treatment cycle. Studies have shown that Pre-IVF distress is a strong predictor of increase in anxiety and depression after treatment especially if it is not successful (121). Verhaak et al also reported that, while the vast majority of IVF patients seem to adjust well to the considerable stress of successive unsuccessful treatment, a small group are at risk for significant emotional disturbances as a result of failed treatment cycle(79). Although there is no direct evidence of impact of psychological factors on pregnancy outcome, indirectly it has been related to be the reason for pre-mature drop out of treatment. (90, 209, 210). A review of psychosocial interventions by Boivin *et al* showed overall positive effect on emotional well-being of infertile couples (211). This instrument will help us to identify such a group of emotionally vulnerable women who will benefit from such support, facilitating their emotional adjustment to treatment and reducing their dropout rates (212).

We used three other questionnaires to assess psychological distress in IVF patients. There was no significant difference in their scores between pregnant and non-pregnant groups. Despite the overall positive emotional health of the group from EM-INFERT scores, the global distress scores from FPI were high with a median of 145 (IQR 121-169). This was higher than other published studies (124, 213). All the individual domain scores were also higher than other similar studies. The biological mechanism linking psychological stress and IVF outcome is quite complex. Stress activates HPA axis which lead to premature LH stimulation which then interferes with follicle maturation and and endometrial receptivity. However in our study we did not find any difference in stress levels between pregnant and non-pregnant groups.

**5.5 Discussion**

This study confirms the extent of the effects of infertility experience and anitcipation of IVF treatment. The most marked impact is that of on-going treatment which is measured as domain of personal strain. Table 5.6 enlists the items in the domain of personal strain. It describes patient’s feelings of loss of control, denial of parenthood, putting life on hold, balancing work and treatment, uncertain future especially in cases of failed treatment and impact on relationship with wider family, friends and colleagues. On the other hand couple concordance scored very high even in patients with low emotional health in the bottom tertile.

Couple concordance examines the agreement between couples about the perception of the severity of infertility. Levin *et al* in their study concluded that if perception of infertility and coping strategy differ among partners, this can impact the psychological functioning and lead to reduction in the marital satisfaction (40). Peterson *et al* in their study showed that couples who have similar thoughts about the issue of infertility and its treatment, report higher marital satisfaction as compared to those where there is a disagreement about the impact of infertility on their lives.(194). Our study confirmed high scores for couple concordance through all tertiles of emotional health. Consequently this also mirrored partner relationship which was equally strong in all groups of patients despite variation in their individual emotional health.

The other domain of distress to IVF patients is financial worries. The access to NHS funded IVF treatment depends on the patient’s individual circumstances and area where they live. Hence one of the constant source of concern is affordability of further cycles in case of negative result.

To conclude this study has shown that success of IVF treatment is not affected by the psychological stress. This is an important finding that should be conveyed to the patient undergoing IVF in order to reassure her. This in itself may assist in reducing the stress of IVF as patients are less likely to blame themselves if their treatment fails. However the findings from this study also highlights the need to reduce the stress of IVF so that patients are able to cope better if the treatment fails. This study enables us to focus on multiple domains and we can tailor the psychological interventions as per individual patient factors.

|  |
| --- |
| Overview  3.1 Background  3.2 Method  3.3 Methods  3.4 Results  3.5 Impact of IVF on Emotional Health |

**Chapter 6: Results (II): Impact of IVF on the Emotional Health**

**6.1 Background:**

The inability to conceive causes significant psychological distress which has been well documented in literature(91). The stress from long-standing infertility has also been compared to that from chronic illness such as cancer (214). The stress from infertility can also reduce the chances of successful pregnancy due to its effects on fertility(215). In the previous chapter we investigated impact of pre-treatment emotional distress on the outcome of IVF. The results (Chapter 5) have shown that emotional health at the start of IVF does not affect the pregnancy rates. However, in addition to the chronic pre-treatment stress due to the diagnosis of infertility, there is the acute procedural stress related to the medical process of IVF treatment. The impact of IVF treatment on the psychological functioning of the patient is very complex. There is the initial increase in optimism at the start of the cycle(76), anxiety prior to every stage including egg collection and embryo transfer (54), anticipation after the embryo transfer(105) and feeling of sadness and depression when there is negative outcome(79). Most patients consider the psychological stress during IVF to be a worse burden than the physical stress(216). This psychological distress can also lead to patients prematurely dropping out of treatment (87).

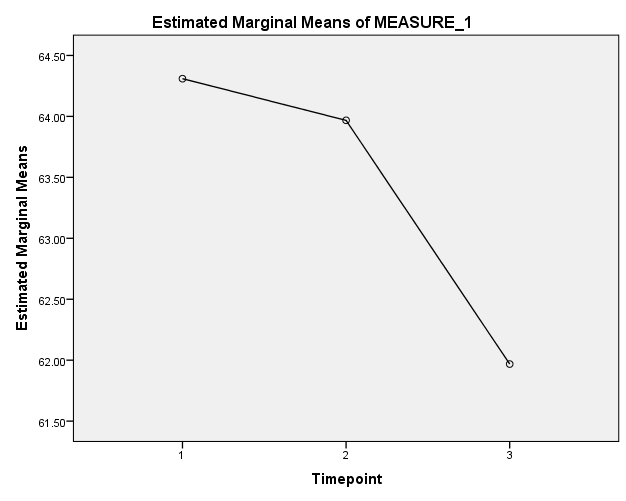
The different stages of the IVF-procedure can negatively influence the psychosocial functioning of couples(207). Stress and anxiety have been shown to be raised at several points in the IVF cycle, including at the start of the cycle(54, 76), before egg collection (102, 217) before pregnancy test(78), waiting for the results (105) and after a failed cycle (166). A number of studies have looked at the stress during the course of the IVF cycle, however, the time points examined and instruments used varied, and analysis of change over time was not uniformly performed. It is very important to determine the most stressful time point during IVF cycle as this information will help to plan the direction of future interventional studies. In this chapter we present the results of impact of the various stages of IVF treatment on the emotional health of the patients. To explore this, we compared the emotional health at three time points during IVF cycle: the pre-treatment stage, at egg collection and after the pregnancy test. We also correlated the change in the emotional health during ovarian stimulation to the biological endpoints of treatment: number of oocytes retrieved, number of days of stimulation, endometrial thickness, oestradiol levels and fertilisation rate.

**6.2 Method**: The study design, method and recruitment process has been described in detail in Chapter 4. To understand the impact of IVF on the emotional health, EM-INFERT scores have been compared between the three time points.

**6.3 Results**: Out of the 414 couples who participated in the main study, 382 patients went on to complete their IVF cycle. Out of these 194 women completed questionnaires at all three time points during their IVF cycle: at the start of the cycle, at egg collection and 2 days after pregnancy test. The clinical pregnancy rate in this study group was 39.1%.

A repeated measures ANOVA with a Greenhouse-Geisser correction determined that EM\_INFERT scores differed statistically significantly between the three time points (F(1.797, 323.486) = 6.774, p =0.002). Post hoc tests using the Bonferroni correction revealed that emotional health scores had reduced slightly from the start of the IVF cycle till egg collection (64.8 ±16.81 vs 63.96 ±18.3,respectively), which was not statistically significant (p = 1). However, emotional health at the end of the cycle had dropped to 61.96±19.17 which was statistically significantly different to the start of the cycle (p =0.01) and midpoint of the cycle at egg collection (p = .009). In the first part of the IVF cycle, analysis of the individual domain scores revealed that social support and partner concordance seems to have significantly reduced. Similarly positive affect of PANAS also significantly reduced during this phase. Global stress score of FPI, perceived stress and negative affect of PANAS was relatively stable, need for parenthood had significantly increased between time point 1 and time point 2. These results have been described in Table 6.1.

**Figure 6.1: Changes in emotional health during the three time points**



**Table 6.1: Impact of ovarian stimulation on emotional health of patients**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| EM-INFERT | Time point 1 (Start of cycle)  Mean scores (SD) | Time point 2 (Egg collection)  Mean scores (SD) | Mean Difference  (95%CI) | Paired 't' test |
| Personal Strain | 48.5(23.1) | 48.1(23.7) | 0.3 (-1.1,1.7) | p= 0.64 |
| Partner relationship | 80 (19.2) | 80.3 (19.3) | -0.3 (-1.7,1.1) | p= 0.64 |
| Sexuality | 71.0 (25.2) | 70.7 (26.6) | 0.3 (-1.1,1.7) | p= 0.65 |
| Social support | 79.1 (20.2) | 76.0 (18.4) | 3 (1.7,4.3) | **p= 0** |
| Confidence in treatment | 76.8 (18.4) | 76.8 (18.6) | -0.1 (-2.1,2) | p= 0.96 |
| Guilt & Blame | 69.6 (25.0) | 70.7 (24.8) | -1.1 (-2.6,0.5) | p= 0.19 |
| Financial strain | 51.7 (33.0) | 51.9 (32.2) | -0.3 (-2.4,1.9) | p= 0.8 |
| Need for privacy | 60.1 (24.3) | 59.7 (26) | 0.4 (-1.5,2.3) | p= 0.7 |
| Couple Concordance | 81.4 (20.4) | 77.8 (21.7) | 3.5 (1.8,5.3) | **p= 0** |
| Total EM-INFERT score | 65.3 (16.9) | 64.8(17.9) | 0.5 (-0.4,1.4) | p= 0.29 |
| **FPI** | | | | |
| Social concern | 30.6 (9.1) | 30.4 (9.8) | 0.2 (-0.4,0.8) | p= 0.56 |
| Sexual concern | 19.6 (8.4) | 19.9 (9.4) | -0.2 (-0.7,0.3) | p= 0.38 |
| Relationship concern | 23.5 (7.5) | 23.9 (7.8) | -0.3 (-0.9,0.3) | p= 0.32 |
| Rejection of childfree life | 29.3 (8.1) | 28.7 (8.2) | 0.6 (0,1.1) | **p= 0.04** |
| Need for parenthood | 40.4 (10.0) | 41.3 (9.9) | -1 (-1.6,-0.3) | **p= 0.003** |
| Global Stress score | 143.9 (32) | 144.4 (34.5) | -0.8 (-2.5,0.9) | p= 0.36 |
| **PSS** | | | | |
| Perceived stress | 17.9 (6.2) | 18.6 (6.8) | -0.8 (-1.3,-0.2) | **p= 0.006** |
| **PANAS** | | | | |
| Positive Affect | 31.4 (7.8) | 30.5 (8.5) | 0.8 (0.1,1.6) | **p= 0.03** |
| Negative Affect | 23.9 (8.4) | 25.4(8.8) | -1.5 (-2.3,-0.6) | **p= 0** |

Table 6.2 describes the change in the questionnaire scores from time point 2 at egg collection till time point 3 after the pregnancy test. In contrast to the previous time frame, this period is associated with a significant reduction of EM-INFERT scores and two of its domains. The score for social support continues to diminish after the pregnancy test, but the marital discordance does not get worse. The confidence in treatment also diminishes significantly after the pregnancy test. Global stress scores in FPI increase after the pregnancy test but not quite statistically significant. Similar to the EM-INFERT instrument the scales on social and sexual concern show a significant increase from time point 2. Perceived stress, positive and negative affect all show an increase in emotional distress from egg collection till the pregnancy test .

In view of the significant decrease in the emotional health at time point 3, we further analysed the impact of pregnancy result on the psychological distress scores. We divided the entire cohort into pregnant and non-pregnant groups. While all questionnaire scores showed increased psychological distress in the non-pregnant group, the emotional health of the pregnant women got better after positive pregnancy results.

Total EM-INFERT scores and all except two domain scores were significantly lower at time point 3 in the non-pregnant women as compared to the pregnant group. The two domains that were unaffected by the pregnancy result were couple concordance and need for privacy. In the pregnant group most of the questionnaire scores were statistically similar except for financial strain which was better as patients did not have to worry about funding for fertility treatment

**Table 6.2: Change in emotional health from egg collection until pregnancy test**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| EM-INFERT | Time point 2  (At Egg collection)  Mean (SD) | Time point 3  (After pregnancy test)  Mean (SD) | Mean Difference  (95%CI) | Paired 't' test |
| **Personal Strain** | **47.9(24.5)** | **45.1(24.9)** | **2.8 (1.2,4.4)** | **p= 0.001** |
| Partner relationship | 79.4 (19.5) | 77.9 (19.5) | 1.5 (-0.5,3.5) | p= 0.14 |
| Sexuality | 68.3 (25.1) | 67.2 (27.3) | 1.2 (-0.7,3) | p= 0.21 |
| **Social support** | **75.9 (21.9)** | **73.2 (23.6)** | **2.7 (0.6,4.8)** | **p= 0.01** |
| **Confidence in treatment** | **76.6 (19.3)** | **71.9 (23.6)** | **4.7 (1.9,7.6)** | **p= 0.001** |
| Guilt & Blame | 70.1 (25.3) | 68.7 (26.7) | 1.4 (-0.7,3.5) | p= 0.2 |
| Financial strain | 50.9 (32.4) | 50.1 (33.1) | 0.8 (-2,3.7) | p= 0.5 |
| Need for privacy | 57.1 (25.0) | 57.5 (23.8) | -0.4 (-2.7,2) | p= 0.76 |
| Couple Concordance | 76.7(22.0) | 75.7 (22.1) | 1 (-1.8,3.7) | p= 0.49 |
| **Total EM-INFERT score** | **63.8 (18.3)** | **61.8(19.1)** | **2 (0.7,3.3)** | **p= 0.003** |
| **FPI** | | | | |
| **Social concern** | **30.2(9.1)** | **31.7 (9.8)** | **-1.4 (-2.3,-0.6)** | **p= 0.001** |
| **Sexual concern** | **20.1 (9.9)** | **20.9 (9.7)** | **-0.7 (-1.5,0)** | **p= 0.04** |
| Relationship concern | 24.1 (7.6) | 23.8 (7.6) | 0.3 (-0.5,1.1) | p= 0.47 |
| Rejection of childfree life | 28.4 (8.4) | 28.6 (8.8) | -0.2 (-0.9,0.5) | p= 0.63 |
| Need for parenthood | 40.9 (10.0) | 41.3 (10.3) | -0.4 (-1.1,0.4) | p= 0.36 |
| Global Stress score | 143.9 (35.2) | 146.4 (37.1) | -2.5 (-5.1,0) | p= 0.05 |
| **PSS** | | | | |
| Perceived stress | 18.2 (6.9) | 20.08 (7.6) | -1.9 (-2.7,-1.1) | **p= 0** |
| **PANAS** | | | | |
| Positive Affect | 30.8 (7.8) | 28.3 (8.5) | 2.4 (1.1,3.7) | **p= 0** |
| Negative Affect | 24.3 (8.7) | 29.3(13.8) | -5 (-6.9,-3.1) | **p= 0** |

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **Non-pregnant n=118** | | | | **Pregnant n=76** | | | |
| EM-INFERT | Egg collection | After pregnancy test | Mean Difference  (95%CI) | Paired 't' test | Egg collection | After pregnancy test | Mean Difference  (95%CI) | Paired 't' test |
| **Personal Strain** | **48.5** | **42.6** | **5.7 (3.6,7.7)** | **p= 0** | 47.1 | 48.4 | -1.8 (-4.1,0.4) | p= 0.10 |
| **Partner relationship** | **80.2** | **76.6** | **3.3 (0.7,5.9)** | **p= 0.01** | 78.3 | 79.7 | -1.5 (-4.5,1.5) | p= 0.31 |
| Sexuality | 68.6 | 66.3 | 1.9 (-0.6,4.4) | p= 0.13 | 67.9 | 68.3 | -0.1 (-2.5,2.4) | p= 0.95 |
| **Social support** | **76.4** | **71.4** | **3.9 (0.9,6.9)** | **p= 0.01** | 75.3 | 75.6 | 0.8 (-1.8,3.4) | p= 0.53 |
| **Confidence in treatment** | **76.2** | **67.9** | **8.2 (4.3,12.1)** | **p= 0** | 77.1 | 77.3 | -1 (-4.7,2.7) | p= 0.60 |
| **Guilt & Blame** | **70.8** | **67.3** | **3.3 (0.5,6.2)** | **p= 0.02** | 69.1 | 70.6 | -1.8 (-4.7,1.1) | p= 0.22 |
| **Financial strain** | **50.1** | **45.7** | **4.2 (0.4,8)** | **p= 0.03** | 52.1 | 56.1 | -4.7 (-8.8,-0.7) | **p= 0.02** |
| Need for privacy | 57.3 | 57.1 | 0.5 (-2.4,3.4) | p= 0.72 | 57.0 | 58.1 | -1.8 (-5.9,2.2) | p= 0.36 |
| Couple Concordance | 76.9 | 75.8 | 2.3 (-1.4,6) | p= 0.22 | 76.4 | 75.6 | -1.3 (-5.1,2.6) | p= 0.51 |
| **Total EM-INFERT score** | **64.3** | **60.0** | **4.1 (2.3,5.8)** | **p= 0** | 63.3 | 64.4 | -1.4 (-3.1,0.2) | p= 0.09 |
| **FPI** | | | | | | | | |
| **Social concern** | **30.0** | **32.7** | **-2.5 (-3.6,-1.4)** | **p= 0** | 30.5 | 30.3 | 0.3 (-0.7,1.4) | p= 0.53 |
| **Sexual concern** | **20.3** | **21.6** | **-1.2 (-2.2,-0.2)** | **p= 0.012** | 20.0 | 20.0 | 0 (-1.1,1.1) | p= 0.97 |
| Relationship concern | 24.1 | 24.2 | -0.2 (-1.3,1) | p= 0.77 | 24.0 | 23.2 | 1 (-0.1,2.2) | p= 0.06 |
| Rejection of childfree life | 28.1 | 29.0 | -0.6 (-1.7,0.4) | p= 0.20 | 28.7 | 28.0 | 0.6 (-0.2,1.4) | p= 0.13 |
| Need for parenthood | 40.4 | 41.7 | -0.9 (-2,0.1) | p= 0.08 | 41.6 | 40.7 | 0.6 (-0.5,1.6) | p= 0.27 |
| **Global Stress score** | **142.7** | **149.0** | **-5.5 (-9.2,-1.9)** | **p= 0.003** | 145.6 | 143.0 | 2.5 (-0.3,5.3) | p= 0.08 |
| **PSS** | | | | | | | | |
| **Perceived stress** | **18.1** | **21.2** | **-3 (-4,-2.1)** | **p= 0** | 18.2 | 18.4 | 0.1 (-1.2,1.4) | p= 0.89 |
| **PANAS** | | | | | | | | |
| **Positive Affect** | **31.2** | **26.6** | **4.2 (2.5,5.9)** | **p= 0** | 30.2 | 30.6 | -0.3 (-2.3,1.6) | p= 0.74 |
| **Negative Affect** | **24.4** | **31.7** | **-7.2 (-10,-4.3)** | **p= 0** | 24.3 | 26.2 | -1.6 (-3.2,0) | p= 0.05 |

**Table 6.3: Comparison of change in emotional health between pregnant and non-pregnant groups**

EM-INFERT: Emotional Health in infertility questionnaire

FPI: Fertility problem inventory

PSS: Percieved Stress scale

PANAS: Positive affect and Negative affect schedule

**6.4 Impact of IVF on Emotional Health**:

The process of IVF is stressful and impacts on the emotional wellbeing of patients. IVF treatment involves three stages: (i) ovarian stimulation; (ii) oocyte retrieval and embryo transfer; and (v) the luteal phase ending in a pregnancy test.

**Impact of IVF treatment on the emotional health of infertile women**

Ovarian stimulation is the first phase of IVF treatment. It involves administration of human chorionic gonadotrophin for stimulation of ovarian follicles. It is also physically intense with daily injections, blood tests and ultrasound scan. Our study showed that emotional health and global stress did not significantly alter during this phase. This is in contrast to others studies which have reported a negative impact of ovarian stimulation on the psychological functioning. They worried whether they were injecting themselves properly, whether they were achieving the correct dose of medication and whether the treatment would be successful. Logistics of daily injections and the associated psychological burden made it very stressful for most women (218). Huisman *et al* (2009) in his study noted that over half of patients reported that ovarian stimulation had an impact on their daily lives and nearly one-third felt that daily injections limited their everyday activities(219). In our study, although the overall emotional health (EM-INFERT score) had not significantly altered, but social support and couple concordance had reduced significantly during this phase.

The domain of social support included the following questions ‘I get upset when family and/or friends talk about their children’, ‘I avoid seeing family and/or friends who have children’, ‘I avoid places where there might be pregnant women or children’, and I feel unsupported by family and friends’. Infertility has been described as lifetime crisis that causes social isolation causing a strain relationships with family and friends(220). It mainly stems from an inability to achieve a desired social role (221). Previous studies have reported that women try not to be in places with children so as to avoid questions related to having a child (222),(142).These feelings seem to have become more distressing during the first half of the treatment cycle.

Couple concordance had also reduced significantly in the first part of the IVF cycle during ovarian stimulation. Our results in contrast with the study by Holter *et al* (2006) where 90% of the study group answered ‘not at all’ to the question ‘Do you find it more difficult to talk to each other now than before childlessness became an important issue?’(223). Infertility has been known to increase marital conflicts but does not lead to a decline in marital satisfaction(221). Similarly in our study, even though couple concordance decreased, the domain of partner relationship remained stable during the first half of the treatment cycle.

FPI also did not show any difference in the global stress scores in the first phase of IVF, but stress due to rejection of childfree life and need for parenthood had increased significantly during this period. Correspondingly perceived stress and negative affect had increased sigificantly while positive affect had reduced. The construct of social support in EM-INFERT describes feelings of social isolation from the fertile world which compounds the distress due to lack of parental role. It also deals with the difficulties in disclosing to family and friends about their treatment and distress due to insensitive remarks made by them.

**Impact of IVF outcome on emotional health of infertile women**

In contrast to the first phase of IVF, EM-INFERT scores reduced significantly between the stage of egg collection and pregnancy test. There is consistent with other studies that have reported that the waiting period after embryo transfer is the most stressful time of the IVF cycle (105, 224). In the retrospective study by Dudok de Wit (1992), stress levels decreased with embryo transfer and increased prior to pregnancy test (225). In the study by Boivin and Takefman(1996) also, higher stress scores were recorded in the luteal phase on the daily symptom scoring chart (105). This is also the time period during which the patients have least interaction with clinic staff. Yong *et al* in his study found that women were most vulnerable in the duration leading up to the pregnancy test and suggested that they should be offered psychological support after the embryo transfer(226).

In our study, the domains of social support and confidence in treatment were most affected in EM-INFERT and the stress of social concern increased in FPI. These differences in emotional health was more pronounced in the event of a negative cycle. In patients who had a failed cycle, EM-INFERT scores and all but two domain scores reduced significantly at time point 3. The domains that were unaffected by the pregnancy test result was need for privacy and couple concordance. This is consistent with other studies where marital relationship has not only been unaffected, but has been strengthened by failed IVF cycles. Similarly in FPI, global stress scores and all but one domain scores are significantly increased after a negative IVF cycle indicating increased psychological distress. The domain that was unaffected was relationship concerns which was similar to the results from EM-INFERT questionnaire. Perceived stress and negative affect increased significantly while positive affect substantially reduced in non-pregnant patients. This result is similar to other studies which have shown higher anxiety, depression and negative emotions in patients after failed IVF (79, 121).

In pregnant patients the emotional health actually improved but this was not statistically significant (63.3 versus 64.4;p=0.1). The domain of financial strain showed significant improvement due to a positive pregnancy test after IVF (52.1 versus 56.1;p=0.04).

The FPI also showed reduction in the global stress and domain scores in pregnant women, but this difference was not statistically significant (145.6 versus 143.0; p=0.05). The perceived stress and PANAS did not change significantly in patients who had a successful IVF.

**6.5 Discussion**

The impact of IVF on psychological wellbeing is a very important issue that needs to be addressed. Ours is a prospective study that has followed patients from the start of IVF cycle to after the pregnancy test. This gives a better indicator of the specific effect of each stage of IVF on the emotional wellbeing. However out of 382 patients, who entered the study, only 194 patients completed all three questionnaires . The emotional health of the drop-outs is unknown which is a drawback of the study. It is possible that these people could not complete the study due to considerable emotional distress.

The phase of ovarian stimulation although did not reduce the overall emotional health or global stress, had some effect on the psychological functioning of the individual. There has been a suggestion that certain IVF treatment protocols may be associated with lower distress while maintaining the pregnancy rates(227). In the study by Merari *et al* women reported highest anxiety levels just before oocyte retrieval(78). However in our study, luteal phase was the most stressful period during IVF. Interventions and increased emotional support during the luteal phase(228) may be helpful in not only reducing the emotional suffering but also decrease the number of patients discontinuing their treatment(229, 230). Emotional health was least at time of pregnancy test possibly due to the concerns about success or failure of treatment.

The emotional health of IVF patients is lowest at the time of the pregnancy test especially in the ones with negative result. They also felt that screening women during this time period would be most helpful to identify patients at risk of significant psychological distress. Skiadas *et al* examined the benefit of brief intervention in the form of two telephonic calls between embryo transfer and pregnancy test in patients undergoing their first cycle of IVF(228). Although the stress scores on the questionnaire did not change significantly, a majority of the patients felt the need for added emotional support during this period.

To conclude this study has emphasized the importance of reducing the stress during IVF cycle so that patients can cope better during treatment and in the event of failed cycle. It helps us to assess the psychological health of patients throughout their IVF cycle and identifies optimum time for emotional support in these women. It also helps us to pinpoint particular aspects of psychological distress that are more relevant than others so that we can offer targeted psychological interventions. Research has shown that if such support was to be available majority of the patients will opt for it (180). More importantly patients feel reassured when they know that support is available if they need it, even if they don’t use it (231).

**Chapter 7: Results (II): Gender based comparison of emotional health among IVF couples**

|  |
| --- |
| Overview  3.1 Background  3.2 Method  3.3 Results  3.4 Gender differences in Emotional health  3.5 Conclusion |

**7.1 Introduction & Aim**

Infertility affects both male and female partners. However most of the studies on the psychological distress of infertility have focused on women. The experience of infertility tends to more stressful for women than for men (232) . Both men and women are perceive infertility differently and exhibit different reactions and coping mechanisms (141, 233). Studies in infertile couples have reported higher levels of anxiety, depression and low self-esteem in women as compared to men(54, 233, 234). Women are more likely to blame themselves for the infertility and feel socially isolated (51, 125, 235).

Women are less inclined than men to accept childlessness(139). Newton *et al*  in their study observed that women without children, who had failed IVF had significantly higher anxiety than women with children while men reported increased anxiety after failed IVF regardless of whether they had children(234). In addition to the chronic stress of infertility, women undergoing IVF also have the added treatment related stress due to the complex procedures involved . Beaurepaire *et al* in his study of couples undergoing IVF found increased levels of depression and state anxiety in women as compared to their male partners (47). The emotional distress associated with infertility can differ between men and women depending on the cause of infertility.

Connolly *et al* (1992) noted higher levels of distress in men with male cause of infertility(42). Psychological stress in infertile men can be a cause (74, 236, 237) or consequence of infertility(238) in these patients. Increase in stress hormones like cortisol and ACTH can inhibit the conversion of androstenedione into testosterone, which then reduces the level of testosterone. This can interfere with semen volume, sperm concentration and motility (239, 240). Several stress related factors like increased nitric oxide, reduction in arginase activity and increase in superoxide dismutase have been implicated in poor sperm quality (241, 242). Male partners of women undergoing IVF are known to have high levels of stress and anxiety which can affect the sperm parameters (74)and thereby indirectly cause an impact of the success of treatment.

Due to all the above mentioned factors, it is important to address the psychological health of men as well during infertility treatment and IVF. The aim of this part of the study was to investigate the emotional health of male partners during IVF and correlate it with pregnancy rates. We also wanted to explore the differences between male and female partners in terms of their emotions, attitudes and responses associated with IVF treatment. This information would also be vital while designing psychological interventions to reduce the stress from IVF.

**7.2 Method**:

The study protocol has been described in chapter 4. Both men and women completed four questionnaires EM-INFERT, FPI, PSS and PANAS at three time points in the IVF cycle at the start of the treatment, at mid-point and at egg collection. In this part of the study we compared the mean emotional health and fertility distress in men between pregnant and non-pregnant groups using independent samples ‘t’ test. We also compared the mean emotional health throughout the cycle and change in emotional health after pregnancy test between men and women using independent samples ‘t’ test and paired ‘t’ test respectively.

**7.3 Results:**

409 couples were participated in the study of which 2 were same sex couples. The mean age of women were significantly lower than mean age of men in our study group.(33.8 (4.5) vs.38.5 (5.2); p=0) . 20% of patients had unexplained cause of infertility while 80% had male or female cause of infertility.

Table 7.1 represents the comparison of emotional health and fertility distress in men between pregnant and non-pregnant couples at all three time points. The overall emotional health including most of the domain scores, as measured by EM-INFERT are similar in both groups at the first two time points indicating that emotional health before and during IVF does not have any impact on conception rates. The domain of sexuality scored significantly lower in the non-pregnant group at the start of the cycle.The fertility related and perceived stress, and positive and negative affect scores were similar in both groups confirming that psychological distress in men does not affect pregnancy rates after IVF.

Table 7.2 shows the comparison of questionnaire scores between men and women at all three time points during the IVF cycle. The overall emotional health and the majority of the domain scores in men were consistently higher than women at the start of the cycle, at egg collection and after the pregnancy test. Correspondingly, most of the fertility related stress scores measured by FPI were significantly lower in men through all the domains indicating men experienced lower emotional distress as compared to women at all three time points.

**Table 7.1: Comparison of psychological distress in men between pregnant and non-pregnant couples after IVF**

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Egg collection** | Paired 't' test | p= 0.909 | p= 0.843 | p= 0.585 | p= 0.142 | p= 0.237 | p= 0.513 | p= 0.418 | p= 0.11 | p= 0.666 | p= 0.543 |  | p= 0.855 | p= 0.211 | p= 0.962 | p= 0.489 | p= 0.562 | p= 0.496 | p= 0.971 | p= 0.848 | p= 0.992 |
| Mean Difference (95%CI) | 0.25(-4.04,4.54) | 0.6(-5.32,6.51) | 1.59(-4.13,7.3) | 4.33(-1.46,10.1) | -2.97(-7.91,1.96) | -1.68(-6.72,3.36) | 2.4(-3.43,8.23) | -6.86(-15.3,1.58) | -1.42(-7.91,5.07) | 1.23(-2.76,5.23) |  | -0.22(-2.65,2.2) | -1.24(-3.19,0.71) | 0.05(-2.05,2.16) | -0.72(-2.75,1.32) | -0.84(-3.67,2) | -2.96(-11.53,5.6) | 0.03(-1.84,1.9) | 0.21(-1.97,2.4) | 0.01(-1.96,1.98) |
| Pregnant n=81 | 73.9(15.5) | 66.3(23.8) | 74.9(23.4) | 75.9(23) | 87.1(16.6) | 79.3(19.1) | 76.7(20.7) | 63.3(30.3) | 66.8(25.1) | 86.3(14.7) |  | 24.5(9.1) | 17.3(7.5) | 22.6(8.5) | 27.6(7.6) | 34.2(11.2) | 126.2(32.6) | 15.4(7.2) | 34.7(8) | 20.5(7) |
| Non-Pregnant  n=164 | 73.9(15.5) | 66.9(21.4) | 76.5(20.4) | 80.2(21.1) | 84.1(19.4) | 77.6(18.8) | 79(22.5) | 56.4(32.3) | 65.3(24) | 87.5(15) |  | 24.3(9) | 16(7.2) | 22.7(7.5) | 26.9(7.6) | 33.4(10.3) | 123.2(31.7) | 15.5(6.9) | 34.9(8) | 20.5(7.4) |
| **Start of the cycle** | Paired 't' test | p= 0.492 | p= 0.492 | p= 0.544 | **m** | p= 0.323 | p= 0.965 | p= 0.612 | p= 0.291 | p= 0.778 | p= 0.545 |  | p= 0.875 | p= 0.856 | p= 0.669 | p= 0.526 | p= 0.613 | p= 0.849 | p= 0.584 | p= 0.873 | p= 0.667 |
| Mean Difference (95%CI) | 1.22 (-2.27,4.7) | 1.61 (-0.99,6.21) | 1.59 (-3.5,6.72) | **5.42 (0.7,10.14)** | -1.87 (-5.6,1.85) | -0.09 (-4.2,4.08) | 1.28(-3.6,6.22) | -3.76(-10.7,3.23) | 0.78 (-4.65,6.21)  ) | 1.11(-2.5,4.72) |  | -0.15(-1.96,1.67) | -0.15(-1.76,1.46) | 0.36(-1.31,2.04) | -0.54(-2.2,1.12) | -0.59(-2.89,1.71) | -0.64(-7.28,6) | -0.42(-1.95,1.1) | -0.14 (-1.84,1.56) | -0.35 (-1.93,1.24) |
| Pregnant  n=120 | 73.6(15.9) | 72.5(23.4) | 65.7(21.4) | **74.8(24.1)** | 86(17.1) | 77.4(18.6) | 76.4(21.8) | 58.5(33.9) | 63.8(26.4) | 86.1(18.1) |  | 24.4(8.6) | 16.3(7.7) | 22.9(7.7) | 28(7.2) | 34.6(10.4) | 125.7(29.6) | 15.2(6.8) | 34.3(7.5) | 19.7(6.6) |
| Non-pregnant  n=259 | 73.6(15.9) | 74.2(23.7) | 67.4(21.1) | **80.2(20.5)** | 84.7(17.2) | 77.6(19.5) | 78.1(23.2) | 54.7(31.3) | 64.8(24.3) | 87.3(15.9) |  | 24.1(8.1) | 16.3(7.1) | 23.2(7.6) | 27.4(7.7) | 33.9(10.5) | 124.8(30.4) | 14.7(6.9) | 34.1(7.7) | 19.2(7.3) |
|  |  | EM-INFERT | Personal Strain | Partner relationship | **Sexuality** | Social support | Confidence in treatment | Guilt & Blame | Financial strain | Need for privacy | Couple Concordance | FPI | Social concern | Sexual concern | Relationship concern | Rejection of childfree life | Need for parenthood | Global Stress score | Perceived stress | Positive Affect | Negative Affect |

**Table 7.2: Comparison of psychological distress between men and women having IVF**

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Pregnancy test** | Independent samples ‘t’ test | **p= 0** | **p= 0** | **p= 0.033** | **p= 0.001** | **p= 0** | p= 0.454 | **p= 0** | **p= 0.08** | **p= 0.007** | **p= 0** |  | **p= 0** | **p= 0** | p= 0.742 | **p= 0.049** | **p= 0** | **p= 0** | **p= 0** | **p= 0** | **p= 0** |
| Mean Difference (95%CI) | **-9.94(-13.74,-6.14)** | **-19.73 (-24.7,-14.73)** | **5.04 (0.41,9.67)** | **-8.99(-14.38,-3.6)** | **-11.34(-15.81,-6.86)** | -1.77(-6.4,2.87) | **-9.47(-14.49,-4.45)** | **-5.96(-12.63,0.71)** | **-6.92(-11.98,-1.86)** | **-9.38(-13.46,-5.3)** |  | **6.96 (4.92,8.99)** | **4.25 (2.36,6.15)** | 0.28(-1.38,1.94) | **1.74 (0.01,3.48)** | **7.53 (5.32,9.74)** | **21.42 (3.97,28.87)** | **3.75 (2.19,5.32)** | **-5.38(-7.4,-3.35)** | **6.8(4.36,9.24)** |
| Male  n=167 | **71.7(17.3)** | **64.6(23.4)** | **72.9(23.9)** | **76(24.3)** | **84.4(18.7)** | 73.6(21.3) | **78.2(21.4)** | **56.5(31.6)** | **64.5(25)** | **85.3(15.8)** |  | **24.9(9.4)** | **17(8.4)** | 23.7(8.4) | **27(8)** | **33.9(11)** | **126.4(34.5)** | **16.1(7.6)** | **34(9.3)** | **22.3(8.6)** |
| Female  n=195 | **61.8(19.2)** | **44.8(24.8)** | **77.9(20.9)** | **67.1(27.5)** | **73(23.8)** | 71.8(23.3) | **68.8(26.3)** | **50.5(32.8)** | **57.6(23.9)** | **75.9(22.5)** |  | **31.9(10.1)** | **21.2(9.8)** | 24(7.7) | **28.8(8.8)** | **41.5(10.3)** | **147.8(36.9)** | **19.9(7.5)** | **28.6(9.8)** | **29(13.5)** |
| **Egg collection** | Independent samples ‘t’ test | **p= 0** | **p= 0** | **p= 0.011** | **p= 0** | **p= 0** | p= 0.396 | **p= 0** | **p= 0.015** | **p= 0.004** | **p= 0** |  | **p= 0** | **p= 0** | **p= 0.08** | **p= 0.02** | **p= 0** | **p= 0** | **p= 0** | **p= 0** | **p= 0** |
| Mean Difference (95%CI) | **-9(-12,-6.1)** | **-18.6(-22.6,-14.7)** | **4.5 (1,8)** | **-8.1(-12.2,-3.9)** | **-9.1 (-12.6,-5.6)** | --1.4(-4.6,1.8) | **-7.5(-11.5,-3.5)** | **-6.8(-12.3,-1.3)** | **-6.3(-10.6,-2)** | **-9.2(-12.4,-5.9)** |  | **6 (4.4,7.7)** | **3.4 (2,4.9)** | **1.2 (-0.1,2.6)** | **1.6 (0.3,3)** | **7.8 (6,9.5)** | **20 (14.3,25.8)** | **3.2 (2,4.4)** | **-4.1 (-5.6,-2.7)** | **4.8 (3.4,6.3)** |
| Male  n=245 | **73.8(16)** | **66.7(22.1)** | **75.9(21.4)** | **78.8(21.7)** | **85.1(18.5)** | 78.1(18.8) | **78.2(21.8)** | **58.7(31.7)** | **65.8(24.3)** | **87(14.9)** |  | **24.4(9)** | **16.4(7.3)** | **22.7(7.8)** | **27.1(7.5)** | **33.6(10.5)** | **124.2(31.9)** | **15.4(6.9)** | **34.8(8)** | **20.5(7.2)** |
| Female  n=282 | **64.8(17.9)** | **48.1(23.7)** | **80.4(19.2)** | **70.7(26.5)** | **76(22)** | 76.8(18.5) | **70.8(24.5)** | **51.9(32.4)** | **59.5(25.8)** | **77.9(21.8)** |  | **30.4(9.7)** | **19.9(9.4)** | **23.9(7.8)** | **28.7(8.1)** | **41.4(9.9)** | **144.2(34.5)** | **18.7(6.7)** | **30.7(8.5)** | **25.3(8.8)** |
| **Start of the cycle** | Independent samples ‘t’ test | **p= 0** | **p= 0** | **p= 0.001** | **p= 0** | **p= 0** | p= 0.505 | **p= 0** | **p= 0.008** | **p= 0.006** | **p= 0** |  | **p= 0** | **p= 0** | **p= 0.078** | **p= 0** | **p= 0** | **p= 0** | **p= 0** | **p= 0** | **p= 0** |
| Mean Difference (95%CI) | **-8.9(-11.2,-6.6)** | **-19.7(-22.7,-16.6)** | **5.1(2,8.1)** | **-8.1(-11.4,-4.8)** | **-6.5(-9,-3.9)** | -0.9(-3.5,1.7) | **-9.5(-12.8,-6.1)** | **-6.1(-10.7,-1.6)** | **-4.8(-8.2,-1.4))** | **-6.3(-9,-3.6)** |  | **6.8(5.5,8)** | **3.8(2.7,4.9)** | **1(-0.1,2.1)** | **2.1(1,3.2)** | **6.6(5.2,8)** | **20.4 (16,24.8)** | **3.1(2.2,4)** | **-2.7(-3.8,-1.6)** | **4.9(3.8,6.1)** |
| Male  n=379 | **73.1(16)** | **66.9(21.1)** | **73.7(23.6)** | **78.5(21.8)** | **85.1(17.2)** | 77.5(19.2) | **77.5(22.7)** | **55.9(32.2)** | **64.5(25)** | **86.9(16.6)** |  | **24.2(8.3)** | **16.3(7.3)** | **23.1(7.6)** | **27.6(7.5)** | **34.2(10.5)** | **125.1(30.1)** | **14.9(6.9)** | **34.2(7.6)** | **19.4(7.1)** |
| Female  n=414 | **64.2(16.7)** | **47.2(22.3)** | **78.7(19.7)** | **70.4(24.8)** | **78.7(19.7)** | 76.6(17.9) | **68.1(25)** | **49.7(32.9)** | **59.7(23.9)** | **80.6(21.8)** |  | **30.9(8.8)** | **20.1(8.4)** | **24.1(7.9)** | **29.7(8.1)** | **40.8(9.9)** | **145.5(31.9)** | **17.9(6.3)** | **31.4(7.9)** | **24.3(8.4)** |
|  |  | **EM-INFERT** | **Personal Strain** | **Partner relationship** | **Sexuality** | **Social support** | Confidence in treatment | **Guilt & Blame** | **Financial strain** | **Need for privacy** | **Couple Concordance** | FPI | Social concern | Sexual concern | Relationship concern | Rejection of childfree life | Need for parenthood | Global Stress score | Perceived stress | Positive Affect | Negative Affect |

In the above table the domain scores of confidence in treatment remained similar for men and women throughout the cycle indicating both partners had similar feeling about the treatment they were receiving. In FPI questionnaire, stress due to relationship concerns were statistically similar in both men and women. Perceived stress and negative affect were higher in women and positive affect was higher in men at all three time time points.

Table 7.3 compares the change in emotional health in men and women after the pregnancy result. While women experience a significant drop in their emotional health and increase in their stress levels after pregnancy result, in men both EM-INFERT and FPI scores do not change significantly after the pregnancy result. However the perceived stress and negative affect do still increase after the pregnancy result in men. Table 7.4 and 7.5 describe the emotional health and distress scores in non-pregnant and pregnant couples. Both in non-pregnant men and women, emotional health significantly reduced after the pregnancy result. When the pregnancy test was positive, men’s emotional health improved significantly. However, in women no significant difference was noted in the emotional health despite a positive result.

**Table 7.3: Change in emotional health after pregnancy test**

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Males | Paired 't' test | p= 0.331 | p= 0.978 | p= 0.269 | p= 0.552 | **p= 0.02** | p= 0.66 | p= 0.468 | **p= 0.046** | p= 0.385 | p= 0.497 |  | p= 0.178 | p= 0.495 | p= 0.118 | p= 0.609 | p= 0.242 | p= 0.166 | **p= 0.003** | p= 0.575 | **p= 0** |
| Mean Difference (95%CI) | 1 (-1,3) | 0 (-2.2,2.1) | 1.1 (-0.9,3.1) | 0.6 (-1.5,2.7) | **3.3 (0.5,6.1)** | -0.5 (-2.7,1.7) | -1.3 (-4.7,2.2) | **-3 (-5.9,-0.1)** | 1 (-1.3,3.4) | 0.5 (-0.9,1.9) |  | -0.6 (-1.5,0.3) | -0.3 (-1.1,0.5) | -0.7 (-1.6,0.2) | 0.2 (-0.7,1.1) | -0.7 (-1.8,0.5) | -2 (-4.9,0.8) | **-1.4 (-2.4,-0.5)** | -0.3 (-1.5,0.8) | **-2.9 (-4,-1.8)** |
| After the pregnancy test | 64.6(23.4) | 72.8(23.9) | 76(24.2) | 84.4(18.7) | **73.5(21.2)** | 78.2(21.4) | 56.4(31.5) | **64.4(25)** | 85.3(15.7) | 71.7(17.3) |  | 24.9(9.4) | 16.9(8.4) | 23.8(8.3) | 27(7.8) | 34(11.1) | 125.9(34.3) | **16.2(7.5)** | 33.8(9.2) | **22.2(8.6)** |
| At start of cycle | 65.6(22) | 72.8(23.9) | 77.1(22.7) | 85(16.9) | **76.8(17.7)** | 77.7(21.7) | 55.2(30.9) | **61.5(25.4)** | 86.3(17.6) | 72.2(16.3) |  | 24.3(8.6) | 16.7(7.8) | 23(7.9) | 27.2(7.5) | 33.3(10.2) | 123.9(31.3) | **14.8(6.9)** | 33.5(7.7) | **19.3(6.7)** |
| Females | Paired 't' test | **p= 0.02** | p= 0.324 | p= 0.528 | **p= 0** | **p= 0.007** | p= 0.649 | p= 0.086 | p= 0.688 | **p= 0.001** | **p= 0.003** |  | p= 0.095 | **p= 0.024** | p= 0.418 | p= 0.381 | **p= 0.002** | **p= 0.032** | **p= 0** | **p= 0** | **p= 0** |
| Mean Difference (95%CI) | **2.5 (0.4,4.7)** | 1.1 (-1.1,3.3) | 0.6 (-1.4,2.6) | **5.2 (3.1,7.3)** | **3.6 (1,6.2)** | 0.5 (-1.8,2.9) | 2.7(-0.4,5.8) | 0.5 (-2,3) | **4.5 (1.9,7.1)** | **2.2 (0.7,3.7)** |  | -0.7 (-.6,0.1) | **-0.9 (-1.6,-0.1)** | -0.4 (-1.3,0.5) | 0.4 (-0.5,1.3) | **-1.3 (-2.1,-0.5)** | **-3 (-5.7,-0.3)** | **-2.1 (-3,-1.1)** | **3.3 (1.9,4.7)** | **-5.7 (-7.6,-3.8)** |
| After the pregnancy test | **44.8(24.7)** | 77.9(20.9) | 67(27.4) | **73(23.8)** | **71.8(23.3)** | 68.8(26.3) | 50.5(32.8) | 57.6(23.8) | **76(22.5)** | **61.8(19.1)** |  | 31.9(10.1) | **21.2(9.7)** | 24(7.7) | 28.8(8.7) | **41.5(10.3)** | **147.8(36.9)** | **19.9(7.4)** | **28.5(9.8)** | **29.2(13.5)** |
| At start of cycle | **47.4(23.3)** | 79(19.7) | 67.6(25.8) | **78.2(20.4)** | **75.4(18)** | 69.3(24.9) | 53.2(31.6) | 58.1(23.4) | **80.4(20.3)** | **64(17)** |  | 31.2(8.9) | **20.4(8.6)** | 23.6(7.2) | 29.2(8.3) | **40.3(9.8)** | **144.8(32.5)** | **17.8(6.3)** | **31.9(7.7)** | **23.5(8.5)** |
|  | EM-INFERT | **Personal Strain** | Partner relationship | Sexuality | **Social support** | **Confidence in treatment** | Guilt & Blame | Financial strain | Need for privacy | **Couple Concordance** | **Total EM-INFERT score** | FPI | Social concern | **Sexual concern** | Relationship concern | Rejection of childfree life | **Need for parenthood** | **Global Stress score** | **Perceived stress** | **Positive Affect** | **Negative Affect** |

**Table 7.4: Impact of pregnancy result on emotional health in non-pregnant couples**

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | Paired 't' test | p= 0.025 | p= 0.153 | p= 0.027 | p= 0.874 | p= 0 | p= 0.614 | p= 0.074 | p= 0.965 | p= 0.051 | p= 0.007 | p= 0.801 | p= 0.985 | p= 0.158 | p= 0.498 | p= 0.872 | p= 0.639 | p= 0.006 | p= 0.619 | p= 0 |
|  | Mean Difference (95%CI) | 3.1 (0.4,5.9) | 2.3 (-0.9,5.5) | 2.8 (0.3,5.2) | 0.2 (-2.2,2.6) | 6.6 (3.1,10.1) | 0.8 (-2.3,3.9) | 4.2 (-0.4,8.8) | 0.1 (-3.9,4) | 3 (0,6) | 2.6 (0.7,4.4) | -0.2 (-1.4,1.1) | 0 (-1.1,1.1) | -1 (-2.3,0.4) | 0.4 (-0.8,1.7) | -0.1 (-1.5,1.3) | -1 (-5.3,3.3) | -1.9 (-3.3,-0.6) | 0.4 (-1.2,2) | -3.1 (-4.8,-1.5) |
|  | After pregnancy test | 65.6(22.2) | 72.4(24.8) | 77.9(22.3) | 85.4(17.8) | 71.6(20.6) | 78.2(22.6) | 52.3(30.8) | 64.1(24.6) | 85(16.3) | 71.9(16.6) | 23.6(8.4) | 16.3(7.9) | 24(8.7) | 26.6(8.2) | 32.5(10.1) | 122.7(34.2) | 16.1(7.7) | 33(9.5) | 21.5(8.8) |
| Men | At the start of the cycle | 68.8(21.1) | 74.7(23.9) | 80.7(21.6) | 85.5(16.6) | 78.2(17.5) | 79(22.8) | 56.5(29.4) | 64.2(24.7) | 88(16.1) | 74.5(15.8) | 23.4(7.9) | 16.3(7.6) | 23(8.2) | 27(8.2) | 32.4(10) | 121.6(31.8) | 14.2(6.7) | 33.4(7.8) | 18.4(6.8) |
|  | Paired 't' test | p= 0 | p= 0.079 | p= 0.086 | p= 0 | p= 0 | p= 0.065 | p= 0 | p= 0.272 | p= 0.002 | p= 0 | p= 0.006 | p= 0.005 | p= 0.174 | p= 0.351 | p= 0 | p= 0.001 | p= 0 | p= 0 | p= 0 |
|  | Mean Difference (95%CI) | 6.2 (3.6,8.9) | 2.6 (-0.3,5.6) | 2.4 (-0.3,5.2) | 6.3 (3.4,9.2) | 6.9 (3.2,10.5) | 2.8 (-0.2,5.8) | 7.8 (3.6,12.1) | 1.7 (-1.3,4.7) | 5.8 (2.2,9.4) | 4.7 (2.8,6.6) | -1.6 (-2.8,-0.5) | -1.5 (-2.5,-0.4) | -0.8 (-2,0.4) | -0.6 (-1.8,0.7) | -2.2 (-3.3,-1.1) | -6.8 (-10.5,-3) | -3.6 (-4.8,-2.3) | 5.2 (3.4,7.1) | -7.8 (-10.8,-4.9) |
|  | After pregnancy test | 42.9(23.6) | 76.9(20.9) | 66.2(26.1) | 72(23.2) | 68.3(24.9) | 67.2(26.6) | 46.4(32.7) | 57.2(24.7) | 74.9(23) | 60.2(18.3) | 32.7(10.2) | 21.8(9.4) | 24.3(7.6) | 29.1(8.9) | 41.6(10.2) | 149.6(36.3) | 20.9(7.6) | 27.3(10.2) | 31.5(15.7) |
| Women | At the start of the cycle | 49.1(24.1) | 79.6(19.1) | 68.6(24.2) | 78.3(19.6) | 75.1(17.8) | 70(24.7) | 54.2(31.7) | 58.9(23.4) | 80.7(20.1) | 64.9(16.7) | 31.1(8.7) | 20.3(8.1) | 23.5(7.2) | 28.5(8.7) | 39.4(9.7) | 142.9(31.2) | 17.3(6.6) | 32.6(7.9) | 23.7(8.6) |
|  | EM-INFERT | Personal strain | Partner relationship | Sexuality | Social support | Confidence in treatment | Guilt and blame | Financial strain | Need for privacy | Couple concordance | Total EM-INFERT | Social concern | Sexual concern | Relationship concern | Rejection of childfree lifestyle | Need for parenthood | Global stress | Perceived stress scale | Positive Affect | Negative Affect |

**Table 7.5: Impact of pregnancy result on emotional health in pregnant couples**

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Men | Paired 't' test | **p= 0.026** | p= 0.221 | p= 0.543 | p= 0.516 | p= 0.643 | p= 0.156 | **p= 0.001** | **p= 0.002** | p= 0.413 | **p= 0.024** |  | p= 0.047 | p= 0.255 | p= 0.505 | p= 0.92 | p= 0.143 | p= 0.053 | p= 0.208 | p= 0.157 | p= 0.001 |
| Mean Difference (95%CI) | **-3.1 (-5.9,-0.4)** | -1.9 (-4.8,1.1) | -1 (-4.4,2.4) | 1.2 (-2.5,4.9) | -1 (-5.5,3.4) | -2.2 (-5.2,0.9) | **-8.5 (-13.3,-3.7)** | **-7.1 (-11.3,-2.8)** | -1.6 (-5.3,2.2) | **-2.3 (-4.3,-0.3)** |  | -1.2 (-2.4,0) | -0.6 (-1.7,0.5) | -0.4 (-1.4,0.7) | -0.1 (-1.2,1.1) | -1.5 (-3.4,0.5) | -3.4 (-6.8,0) | -0.8 (-2.1,0.5) | -1.2 (-2.9,0.5) | -2.6 (-4.1,-1.1) |
| After pregnancy test | **63.2(25)** | 73.4(23) | 73.5(26.6) | 83.2(19.9) | 76.2(21.9) | 78.2(20) | **62(31.9)** | **64.9(25.8)** | 85.8(15.2) | **71.4(18.4)** |  | 26.8(10.5) | 17.9(9.1) | 23.5(7.9) | 27.6(7.4) | 36(12.1) | 130.3(34.3) | 16.4(7.4) | 34.8(9.1) | 23.1(8.5) |
| At the start of the cycle | **61.3(22.7)** | 70.3(24) | 72.5(23.5) | 84.4(17.6) | 75.1(17.9) | 76(20.3) | **53.5(33)** | **57.9(26.3)** | 84.2(19.3) | **69.1(16.6)** |  | 25.6(9.5) | 17.2(8.1) | 23.2(7.7) | 27.6(6.6) | 34.6(10.5) | 126.9(30.8) | 15.6(7.2) | 33.5(7.8) | 20.5(6.7) |
| Women | Paired 't' test | p= 0.458 | p= 0.057 | p= 0.136 | **p= 0.016** | p= 0.385 | p= 0.129 | **p= 0.006** | p= 0.558 | p= 0.192 | p= 0.133 |  | p= 0.255 | p= 0.838 | p= 0.618 | p= 0.001 | p= 0.745 | p= 0.101 | p= 0.81 | p= 0.551 | p= 0.002 |
| Mean Difference (95%CI) | -1.2 (-4.5,2.1) | -3.1 (-6.3,0.1) | -2.1 (-4.8,0.7) | **3.5 (0.7,6.3)** | -1.4 (-4.6,1.8) | -2.9 (-6.7,0.9) | **-5.2 (-8.9,-1.5)** | -1.3 (-5.7,3.1) | 2.4 (-1.2,6.1) | -1.6 (-3.8,0.5) |  | 0.7 (-0.5,1.9) | 0.1 (-0.9,1.1) | 0.3 (-1,1.7) | 1.9 (0.8,2.9) | 0.2 (-0.9,1.2) | 2.9 (-0.6,6.3) | 0.2 (-1.2,1.6) | 0.6 (-1.4,2.6) | -2.7 (-4.4,-1) |
| After pregnancy test | 47.8(26.4) | 79.4(21) | 68.3(29.6) | **74.7(24.7)** | 77.2(19.6) | 71.2(26) | **56.8(32.2)** | 58.1(22.7) | 77.6(21.9) | 64.3(20.2) |  | 30.7(10) | 20.4(10.2) | 23.6(7.9) | 28.3(8.5) | 41.4(10.6) | 145(37.9) | 18.5(7.1) | 30.3(9.2) | 26(8.9) |
| At the start of the cycle | 44.7(22.1) | 78.1(20.8) | 66.2(28.2) | **78.2(21.9)** | 75.8(18.6) | 68.3(25.5) | **51.6(31.6)** | 56.8(23.6) | 80(20.7) | 62.6(17.4) |  | 31.4(9.5) | 20.5(9.4) | 23.9(7.4) | 30.1(7.8) | 41.5(10) | 147.9(34.4) | 18.6(6.1) | 30.8(7.4) | 23.3(8.6) |
|  | EM-INFERT | Personal strain | Partner relationship | Sexuality | **Social support** | Confidence in treatment | Guilt and blame | **Financial strain** | Need for privacy | Couple concordance | Total EM-INFERT | FPI | Social concern | Sexual concern | Relationship concern | Rejection of childfree lifestyle | Need for parenthood | Global stress | Perceived stress scale | Positive Affect | Negative Affect |

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Males | Paired 't' test | p= 0.099 | p= 0.717 | p= 0.559 | p= 0.447 | p= 0.466 | p= 0 | p= 0.092 | p= 0.042 | p= 0.112 | p= 0.014 |  | p= 0.6 | p= 0.427 | p= 0.997 | p= 0.712 | p= 0.24 | p= 0.302 |  | p= 0.385 | p= 0.936 | p= 0.012 |
| Mean Difference (95%CI) | -3.9 (-8.6,0.7) | 1 (-4.3,6.2) | -1.4 (-6.2,3.4) | -1.5 (-5.5,2.5) | 1.6 (-2.7,6) | -22.9 (-27.4,-18.4) | -6.3 (-13.6,1) | -5.8 (-11.4,-0.2) | -3.1 (-6.9,0.7) | -4.5 (-8,-0.9) |  | 0.5 (-1.3,2.3) | 0.7 (-1,2.3) | 0 (-1.7,1.7) | 0.3 (-1.4,2) | 1.4 (-0.9,3.7) | 3.4 (-3.1,9.9) | | -0.7 (-2.3,0.9) | -0.1 (-1.9,1.7) | 2.1 (0.5,3.8) |
| Female cause of infertility | 68.7(21.1) | 73.6(23.4) | 80.4(20.8) | 85.5(17.7) | 76.8(19.8) | 87.2(18) | 57.2(31) | 67.9(24.4) | 88.2(16.1) | 75.3(15.8) |  | 23.8(8) | 15.3(6.8) | 23.1(7.6) | 27.3(7.1) | 33.7(9.9) | 122.7(27.7) | | 15.1(7.1) | 34.4(8.1) | 18.6(6.5) |
| Male cause of infertility | 65.2(19.8) | 74.7(23.2) | 79.3(21.5) | 84.5(17.9) | 78.7(18.9) | 64.6(22) | 51.4(33.6) | 61.9(25.5) | 85.1(17.6) | 71(15.5) |  | 24.3(7.9) | 16.1(7.2) | 23(7.4) | 27.7(7.4) | 35.1(10.3) | 126.2(28.3) | | 14.5(6.4) | 34(7.1) | 20.7(7.6) |
| Females | Paired 't' test | p= 0.255 | p= 0.247 | p= 0.079 | p= 0.337 | p= 0.033 | p= 0 | p= 0.901 | p= 0.672 | p= 0.936 | p= 0.023 |  | p= 0.712 | p= 0.105 | p= 0.414 | p= 0.155 | p= 0.827 | p= 0.312 |  | p= 0.151 | p= 0.992 | p= 0.827 |
| Mean Difference (95%CI) | 2.8 (-2,7.6) | 2.5 (-1.8,6.9) | 4.9 (-0.6,10.4) | 2.1 (-2.1,6.2) | 4.2 (0.3,8) | 19.4 (14.3,24.4) | 0.5 (-6.8,7.7) | -1.1 (-6.4,4.1) | 0.2 (-4.5,4.9) | 4.2 (0.6,7.8) |  | 0.4 (-1.6,2.3) | -1.5 (-3.3,0.3) | -0.7 (-2.5,1) | -1.3 (-3,0.5) | -0.2 (-2.4,1.9) | -3.6 (-10.5,3.4) | | 1 (-0.4,2.4) | 0 (-1.8,1.8) | -0.2 (-2.1,1.7) |
| Female cause of infertility | 46.4(21.9) | 77.5(21) | 69.1(25.9) | 78(19.4) | 75.2(18.8) | 59.7(24.9) | 48.9(32.8) | 60.3(24.4) | 80.8(21.2) | 62.7(16.9) |  | 30.6(9.1) | 20.5(8.5) | 24.5(8.6) | 30.2(7.9) | 41.2(9.5) | 147.2(31.6) | | 17.3(6.5) | 31.7(7.7) | 24.5(8.8) |
| Male cause of infertility | 49.2(22.1) | 80(18.2) | 74(23.9) | 80.1(18.7) | 79.2(15.7) | 79.1(21.1) | 49.2(33.4) | 59.2(23.4) | 80.9(21.8) | 66.8(15.7) |  | 30.9(8.7) | 19(8) | 23.8(7.2) | 29(7.9) | 40.9(9.8) | 143.6(31.1) | | 18.4(6.2) | 31.6(8) | 24.3(7.8) |
|  | EM-INFERT | Personal Strain | Partner relationship | Sexuality | Social support | Confidence in treatment | Guilt & Blame | Financial strain | Need for privacy | Couple Concordance | Total EM-INFERT score | FPI | Social concern | Sexual concern | Relationship concern | Rejection of childfree life | Need for parenthood | Global Stress score | | Perceived stress | Positive Affect | Negative Affect |

**Table 7.6: Comparison of psychological distress according to gender based infertility.**

Table 7.6 shows comparison of male and female emotional health according to the cause of infertility. Women with female cause and men with male cause of infertility overall have significantly lower emotional health as compared to the women with male cause and men with female cause of infertility respectively. The domain scores of guilt and blame are significant lower in this group of patients. Women with female cause appear to have lower confidence in their fertility treatment while men with male factor infertility feel a greater need for privacy and less likely to confide in others.

**7.4 Discussion**

The results of our study has shown that the overall emotional health of men undergoing IVF and their fertility associated distress does not have any impact on pregnancy rates. The negative impact of sexual dysfunction is significantly higher in men with non-pregnant partners. This is similar to published literature where sexual dysfunction were more prevalent in men going through IVF causing considerable distress (243, 244). Peterson *et al* found increased sexual stress in men having IVF which was related to performance anxiety(152). The loss of spontaneity, the medical approach to conception, the pressure to produce a semen sample when required and loss of privacy all these can contribute to impaired sexual functioning in men. Various studies have reported that high anxiety levels prior to IVF can cause a reduced of sperm motility(245, 246). Similar decline in sperm quality in relation to psychological stress had been noted by Clarke *et al*(74). Sperm motility and morphology have been linked to outcome of IVF by previous studies (247-249). Hence it is imperative that all efforts must be taken to reduce the psychological distress of men as well during IVF.

The other part of the study was to investigate difference in emotional response and coping of men and women to infertility and IVF. In our study we found that women had lower emotional health and higher psychological distress than men through all stages of their IVF cycle. Similar findings have been reported by other studies (180, 234, 250). The EM-INFERT tool reported significantly positive psychological health in men with regards to personal strain, relationship with partner, social support,sexuality,guilt and blame, financial stress, couple concordance and need for privacy. Both men and women had similar feelings with regards to confidence in the treatment process. On the other hand in the FPI tool, relationship concern was the only domain that has no impact of gender. This could be as both partners are equally worried about the impact of IVF o their marital relationship. Other studies have also reported that marital and sexual stresses do influence the psychological health of infertile couples during IVF treatment(251). Couple congruence about their infertility stress is an important factor that determines marital adjustment between couples(252).

While men seemed to cope better than women with infertility and IVF, there was significant negative impact of failed IVF on the emotional health and stress levels of both male and female partners. The main areas that were affected were the domains of personal strain, sexuality, confidence in treatment and couple concordance in men, while women scored lower in personal strain, social support, confidence in treatment, financial strain and couple concordance. Three domains were similarly affected in both partners namely personal strain, confidence in treatment and couple concordance. Men had more distress from sexual dysfunction while women had a greater impact of lack of social support. Both EM-INFERT and FPI questionnaires highlighted the fact that women’s emotional distress was more linked to social support. This is consistent with previous studies, which have reported that women are more likely to access social support than men (51, 142). Partner relationship was still strong in both men and women despite negative result. This is similar to other studies where marital relationship actually gets stronger in cases of failed IVF(253-256) (53, 255, 256). In pregnant couples, the emotional health of men improved significantly while this change was not observed in the female partners. The main areas of improvement were the domains of personal strain, financial stress and need for privacy. Similar to men, women also had lower financial stress after positive pregnancy test, but instead of personal strain and privacy, they showed an improvement in the social support domain. The main difference between men and women was that overall emotional health did not change after positive pregnancy despite an improvement in couple of factors. These results indicate the need for psychological support in both men and women especially after a failed IVF cycle.

We then assessed the emotional health and its domains among men and women based on who has the reproductive impairment. In our study 80% of couples had either male or female cause of infertility. The number of couples with female cause of infertility were similar to those with male cause of infertility (Male cause 39% vs. Female cause 41.3 %.p=NS). Men with male cause of infertility had lower emotional health than men with female cause of infertility. Similar women with male factor infertility had higher emotional health than those with a female factor infertility. In women this was mainly due to factors of guilt and blame and confidence in treatment. Women are more inclined to blame themselves for childlessness when it is not a male factor. Similar feelings of guilt is present in men too along with distress due to lack of privacy. This is not consistent with published literature where marital and sexual satisfaction were the factors linked to the diagnosis of infertility. In our study these domains did not alter depending the diagnosis of infertility. Nachtigall *et al* that gender infertility diagnosis did not make any difference to the distress level in women, but there was a significant change in male distress depending on whether there was a male factor infertility (257). Men have responded positively to group counselling during IVF especially in male factor infertility(258).

On the other hand Holter *et al* felt men were in generally well adjusted to infertility and IVF irrespective of the gender infertility diagnosis(259). Our results were also not consistent with other studies where the response to infertility is not affected by the gender specific diagnosis (134, 250, 260). In our study also such differences between male and female distress were not observed using the FPI instrument.

**Strengths and Weakness**

The study describes the gender difference and similarities in infertility related distress. Men had lower distress due to infertility at the start of the cycle, but as the treatment progressed they were also affected by the IVF treatment and its outcome. The main strength of this study is that we are able to identify the different domains of emotional health that show a significant difference between men and women. This will help us to understand how to minimise distress effectively for men and women.

One of the weakness of this study is the social desirability bias which might be more relevant for infertile men than women. There may be a tendency for the infertile men to present themselves more favourably(261). Lalos *et al* and Harrison *et al* found that infertile men had higher lie scores than their partners(235, 262). This may also be due to the fact that women are being more open about expressing their distress(263)

**7.5 Conclusion**

In summary this study shows that some gender differences do exist in psychological response to infertility. Women reacted more to infertility and IVF as compared to men. In our study men were were less distressed as compared to women at the start of the cycle, but both men and women had significant impact of negative pregnancy result on their emotional well-being. Hence psychological intervention needs to be targeted towards infertile men as much as women. Couple based interventions can help to reduce distress as well as strengthen the partner relationship which will be enable them to cope better. It also highlights the variation in the way men and women react and cope with infertility and IVF treatment. This is important while designing targeted psychological interventions in these couples.

**Chapter 8: Influence of cause and duration of infertility on Emotional Health**

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| --- |
| Overview  3.1 Background  3.2 Method  3.3 Results  3.4 Discussion  3.5 Conclusion |

**8.1 Background**

Duration and cause of infertility is said to significantly influence the psychological distress associated with infertility (264, 265). Domar *et al* in her study of 338 infertile women concluded that those with a longer duration of infertility and with an identified cause of infertility had significantly higher depression scores(46). Patient having repeat IVF have been shown to have significantly higher levels of depression as compared to those having IVF for the first time(266). Turner *et al* in their study showed a significant drop in resilience among patients having repeat IVF(186). Anxiety and depression have been implicated in the reasons for drop out after the first failed IVF(209). Marital relationship has also been shown to deteriorate with time after failed IVF(235). The cause of infertility is also an important factor in the extent of psychological distress. Men with a male infertility are more likely to express negative feelings with regards to stigma, loss and self-esteem(257). There is also an increased sexual concern in men with male infertility as compared unexplained or female cause of infertility(145). Similarly women with female infertility had more psychological distress as compared to unexplained or male factor infertility(267). Shatford *et al* in his study observedsignificant difference in anxiety, depression and psychological functioning among the different groups of infertility(268). The aim of this part of the study was to examine the effects of infertility diagnosis and duration on the extent of psychological distress. We compared the emotional health and distress scores among the different groups of infertility to find out the effect of cause of infertility. To assess the effect of duration of infertility we compared the emotional health between patients having first cycle of IVF versus repeat cycles of IVF.

**8.2 Method**

414 women undergoing IVF participated in the study. All patients who were referred to the infertility clinic had the following investigations, based on which the cause of infertility was determined.

* Day 2 LH, FSH, Oestradiol to assess ovarian reserve
* Day 21 progesterone to confirm ovulation.
* Semen analysis to estimate the concentration and motility of sperm
* Ultrasound scan to rule any pelvic pathology
* Hysterosalpingogram to investigate tubal patency. In the presence of previous chlamydia infection or pelvic pain, diagnostic laparoscopy and dye test was performed.

The entire cohort was divided into 7 groups depending on the primary cause of infertility as follows

1. Anovulation: It was diagnosed when Day 21 progesterone was below 30nmol/land rest of the investigations were normal.
2. Tubal factor: This was confirmed if one or both tubes were not patent on HSG or laparoscopy.
3. Male factor: This was defined when the sperm concentration was below 20 million/ml and progressive motility of the sample was below 50%.
4. Endometriosis: The presence of Endometriosis on laparoscopy was required to confirm the diagnosis.
5. Low ovarian reserve: FSH level of more than12nmol/l with low antral follicle count on ultrasound scan was classified as low ovarian reserve.
6. Single/Same sex couple: Single women or same sex couples who were medically normal but needed donor sperm for conception.
7. Unexplained: When all the investigations were normal, the infertility was diagnosed as unexplained.

We compared the scores of EM-INFERT, FPI, PSS and PANAS between all the groups of infertility at all three time points i.e. at the start of the cycle (T1), at egg collection (T2), and 48 hours after the pregnancy test (T3). Shapiro-Wilk test was used to check normality of distribution. Data was confirmed to be normally distributed and hence ANOVA was used to compare emotional health and distress between all the groups of infertility at all three time points.

We also compared the emotional health and fertility associated distress between women undergoing IVF for the first time versus women with previous failed IVF cycle. Independent samples ‘t’ test was used to compare the questionnaire scores between patients undergoing first and repeat IVF. A p value of less than 0.05 was considered significant.

**Table 8.1: Demographics and pregnancy outcome among all groups of infertility**

|  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Single/same sex | 5 (1.2%) | 36(6.5)  (26,41) | 25(4.3)  (21.5,29.9) | 2.7(0.5) | (2,3) | 3 | 1 | 2(40%) | 2 (40.0%) | 0(0%) | 0(0%) |
| Poor ovarian reserve | 29 (7%) | 38.6(3.3)  (37.1,40) | 23.8(3.5)  (22.3,25.4) | 2.7 (1.0) | (2.2,3.1) | 11 | 4 | 6 (20.7%) | 2 (6.9%) | 2 (6.9%) | 4 (13.8%) |
| Unexplained | 69 (16.7 %) | 34.8(3.6)  (33.9,35.7) | 23.8(3.6)  (22.9,24.8) | 3.3(1.4) | (3.0,3.7) | 22 | 7 | 24 (34.8%) | 15 (21.7%) | 1 (1.4%) | 9 (13.0%) |
| Endometriosis | 32 (7.7%) | 33.6(4.1)  (32.1,35.2) | 23.6(3.3)  (22.4,24.9) | 2.9(0.8) | (2.6,3.2) | 16 | 3 | 9 (28.1%) | 6 (18.8%) | 1 (3.1%) | 3 (9.4%) |
| Tubal factor | 83 (20%) | 33.5(4.3)  (32.5,34.5) | 25.7(3.7)  (24.8,26.3) | 3.4(2.1) | (2.9,3.9) | 46 | 16 | 22 (26.5%) | 17(20.5%) | 7 (8.4%) | 6 (7.2%) |
| Male factor | 160 (38.6%) | 32.9(4.4)  (32.1,33.7) | 24.7(3.5)  (24,25.4) | 2.9(1.5) | (2.6,3.2) | 61 | 16 | 49 (30.6%) | 43 (26.9%) | 9 (5.6%) | 6 (3.8%) |
| Anovulation | 36 (8.7%) | 32.6(3.2)  (31.2,33.9) | 25.9(3.8)  (24.3,27.5) | 2.9(0.8) | (2.5,3.2) | 12 | 3 | 18 (50%) | 13(36.1%) | 1 (2.8%) | 39 (8.3%) |
|  | Number of patients (% of total) | Mean age (SD)  (95% CI) | Mean BMI (SD)  (95% CI) | Mean years of infertility (SD) | (95% CI) | Number of patients who had previous IVF | Number of patients who had previous livebirth | Clinical pregnancy | Live births | Biochemical pregnancy | Miscarriage |

**Table 8.2: Emotional health/Distress at the start of the cycle between all groups of infertility (n=414)**

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| ANOVA test of comparison of means |  | p=0.414 | p=0.660 | p=0.143 | p=0.928 | **p=0.013** | **p=0.000** | p=0.988 | p=0.547 | p=0.974 | p=0.242 |  | p=0.574 | p=0.178 | p=0.343 | p=0.770 | p=0.754 | p=0.886 | p=0.325 | p=0.155 | p=0.508 |
| Single/same sex n=5 |  | 43.75(35.9) | 70(30) | 65(37.4) | 78.8(25.9) | **63.3(20.9)** | **63.8(33.7)** | 47.5(34.6) | 63.3(28) | 75(25) | 59.9(29) |  | 29.6(14.4) | 22.2(12.7) | 20(10.2) | 25.4(11.5) | 41.2(11.4) | 138.4(56.6) | 17.2(10.9) | 30.2(9.6) | 24.4(15.9) |
| Poor ovarian reserve n=29 |  | 46.1(20.6) | 81.9(20.9) | 61.6(25.4) | 77.2(18.6) | **71(22.2)** | **55.6(25.7)** | 51(38) | 64.4(24.1) | 77.6(27.6) | 61.6(17.1) |  | 31(8.8) | 22.3(7.8) | 25.2(8.6) | 30.6(7.9) | 39.9(9.4) | 149(29) | 17(5.9) | 33.7(7.3) | 22.8(7.2) |
| Unexplained n=69 |  | 44.3(22.7) | 79.6(17.7) | 66.2(23) | 77.5(21.7) | **75.1(18.2)** | **65.9(21.9)** | 53.1(29.4) | 56.6(23) | 81.9(20.5) | 62.5(15.6) |  | 32(8) | 21.3(8.8) | 22.3(6.2) | 29.5(8.3) | 39.2(10.1) | 144.3(32.6) | 18.8(6.2) | 29.2(7.2) | 24.1(8.1) |
| Endometriosis n=32 |  | 40.6(19.4) | 74.7(20.4) | 68.9(20.5) | 76(21.1) | **70.3(18.3)** | **60.7(19.9)** | 48.4(31.3) | 56.8(25.8) | 79.7(18.9) | 59.8(16) |  | 32.8(10.4) | 22.2(7.4) | 25.2(10) | 30.3(8.8) | 41.5(9.3) | 151.9(34.6) | 17.8(6.9) | 30.7(8.1) | 24.2(8.2) |
| Tubal factor n=83 |  | 48.9(22.5) | 77(20.8) | 70.5(25.6) | 79.4(17.8) | **76(18.9)** | **57.3(27.2)** | 49.4(33.9) | 60.1(24.6) | 81.3(20.2) | 63.5(17.2) |  | 29.5(8.3) | 19.8(8.7) | 24.4(8.6) | 30.1(8) | 41.7(10) | 145(30.8) | 17.8(6.5) | 32.4(7.1) | 25.8(9) |
| Male factor n=160 |  | 49.3(22.1) | 79.4(18.7) | 74.1(24.4) | 80(19.3) | **79.5(15.6)** | **78.7(21.9)** | 48.9(33.4) | 59.3(23.5) | 80.5(21.9) | 66.7(16) |  | 30.9(8.8) | 19(8.2) | 24.2(7.3) | 29.2(8.1) | 41.2(10.1) | 144(32.1) | 18.4(6.3) | 31.5(8.1) | 24.4(8) |
| Anovulation n=36 |  | 47.1(23) | 79.5(21.4) | 71.3(27.8) | 77.4(21.3) | **80.3(16.5)** | **66.1(23.1)** | 49.3(32.8) | 65.5(23.2) | 80.6(25.2) | 64.8(17.9) |  | 30.4(9.4) | 19.1(8.1) | 25.2(8.2) | 30.8(6.9) | 39.9(9.1) | 144.4(30.8) | 15.7(6.1) | 32(9.1) | 22.3(8.8) |
|  | EM-INFERT | Personal strain | Partner relationship | Sexuality | Social support | Confidence in treatment | Guilt and blame | Financial strain | Need for privacy | Couple concordance | Total EM-INFERT | FPI | Social concern | Sexual concern | Relationship concern | Rejection of childfree lifestyle | Parenthood need | Global stress | Total positive affect | Perceived stress affect | Total negative affect |

**Table 8.3: Emotional health/Distress at egg collection between all groups of infertility (n=282)**

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| ANOVA test of comparison of means |  | p=0.749 | p=0.836 | p=0.157 | p=0.950 | p=0.250 | **p=0.000** | p=0.980 | p=0.531 | p=0.324 | p=0.556 |  | p=0.422 | p=0.177 | p=0.613 | p=0.710 | p=0.899 | p=0.956 | p=0.899 | p=0.405 | p=0.975 |
| Single/same sex n=5 |  | 44.6(31.4) | 81(27) | 66(33.1) | 75(33.9) | 73.3(23.9) | **60(37.7)** | 52.5(28.5) | 76.7(26) | 72.5(22.4) | 62.8(28.2) |  | 32(12.2) | 20.2(11.5) | 21(8) | 25.6(11.8) | 42.4(12.4) | 141.2(51.4) | 18(10.4) | 26.2(10.1) | 26.4(14.6) |
| Poor ovarian reserve n=17 |  | 45.7(23.6) | 83.5(18.8) | 55.6(26.5) | 77.2(16.8) | 74.5(14.3) | **59.2(23)** | 47.8(39.3) | 66.2(22.7) | 81.6(22.6) | 61.8(15.4) |  | 29.6(9.1) | 25.2(9.1) | 24.1(8.2) | 27.6(8.9) | 40.5(11.1) | 146.9(34.1) | 17.9(6.7) | 29.5(10.1) | 24.5(6.1) |
| Unexplained n=48 |  | 45.6(25) | 81.3(17.1) | 66.1(25.1) | 73.1(20.9) | 73.5(22.3) | **68.6(22.6)** | 52.3(27.6) | 54.9(24.4) | 77.6(22.5) | 62.7(17.3) |  | 33.2(9.3) | 21.1(9.4) | 24(6.8) | 28.2(8.3) | 39.9(9.8) | 145.8(33.8) | 19(5.9) | 29.4(8.1) | 25.6(7.9) |
| Endometriosis n=22 |  | 42.2(21.8) | 76.8(21.5) | 72.5(19.6) | 74.7(23.7) | 70.5(16.8) | **65.3(21.9)** | 51.1(29.9) | 57.6(27.9) | 79(18.7) | 61.4(17.4) |  | 31.4(10.6) | 21.4(6.8) | 24.7(8.2) | 29.3(8) | 42(9.5) | 148.7(33.8) | 20.2(7.8) | 29.7(7.9) | 26.8(10.3) |
| Tubal factor n=51 |  | 48.4(24.9) | 80.4(20.8) | 72.3(29.2) | 75.7(22.2) | 76.6(19.9) | **60.9(28)** | 49.5(34.9) | 59.8(25.1) | 76.7(20.3) | 63.8(19.1) |  | 29.2(10) | 18.2(9.3) | 23.2(8.2) | 28.5(8.2) | 40.9(10.7) | 140.1(35.9) | 17.9(7.2) | 32.8(7.3) | 24.6(9.4) |
| Male factor n=118 |  | 50.5(22.8) | 80.9(18) | 74.1(25.9) | 77.6(22.3) | 79.7(16.7) | **80.2(21.1)** | 54(32.9) | 60.3(25.9) | 79.9(21.5) | 67.5(17.4) |  | 29.8(9.6) | 19.2(9.6) | 23.6(7.7) | 28.8(8.1) | 42.2(9.5) | 143.7(34.1) | 18.6(6.7) | 30.7(8.8) | 25.2(8.7) |
| Anovulation n=21 |  | 50(24.7) | 75.5(23.5) | 70.5(29.1) | 75.6(24.1) | 79(17.2) | **63.4(22.2)** | 50(35.3) | 60.3(31) | 67.3(26.3) | 63.4(20.2) |  | 29.2(10.6) | 19(10.2) | 26.9(9.5) | 31.4(6.9) | 41(10.9) | 147.6(35.8) | 18.9(6.5) | 30.9(9.8) | 25.7(9.3) |
|  | EM-INFERT | Personal strain | Partner relationship | Sexuality | Social support | Confidence in treatment | **Guilt and blame** | Financial strain | Need for privacy | Couple concordance | Total EM-INFERT | FPI | Social concern | Sexual concern | Relationship concern | Rejection of childfree lifestyle | Parenthood need | Global stress | Total positive affect | Perceived stress affect | Total negative affect |

**Table 8.4: Emotional health/Distress after pregnancy test between all groups of infertility (n= 181)**

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| ANOVA test of comparison of means |  | p=0.460 | p=0.332 | p=0.249 | p=0.705 | p=0.357 | **p=0.032** | p=0.740 | p=0.763 | p=0.958 | p=0.609 |  | p=0.717 | p=0.146 | p=0.277 | p=0.788 | p=0.931 | p=0.743 | p=0.826 | p=0.287 | p=0.845 |
| Single/same sex n=3 |  | 55.6(45.3) | 85(26) | 76.7(40.4) | 70.8(50.5) | 80.6(26.8) | **70.8(45.2)** | 70.8(40.2) | 58.3(28.9) | 66.7(36.1) | 68.3(39.2) |  | 27(17.3) | 17(15.6) | 20.7(8.1) | 23.7(21.1) | 38.7(16.9) | 127(78.8) | 14(12.2) | 32.7(7.5) | 22.7(16.1) |
| Poor ovarian reserve n=12 |  | 40.2(28.3) | 78.8(22.1) | 52.3(27.7) | 68.3(23.4) | 70.5(26.9) | **55.8(23.6)** | 59.6(39.6) | 65.4(26.3) | 79.8(19.5) | 58(20.7) |  | 32.9(8.9) | 26.8(9.4) | 24.9(8.9) | 29(10.1) | 40.8(13.6) | 154.4(43.4) | 20.4(8) | 28.2(9.5) | 29.2(8.5) |
| Unexplained n=30 |  | 42.9(23.9) | 76.7(19.7) | 61.9(25.9) | 73.8(21.9) | 64.8(27.2) | **67.9(19.8)** | 53.1(26.6) | 56.3(22.6) | 74(23.4) | 59.8(17.4) |  | 32.4(8.8) | 22.4(9.6) | 24.1(7.4) | 29.8(9.3) | 39.7(9.6) | 149.6(35.2) | 20.8(6.6) | 26.4(9.1) | 31.3(17.9) |
| Endometriosis n=15 |  | 34.1(19.8) | 65.9(24.6) | 65(19.9) | 66.5(27.1) | 72.1(16.4) | **64.3(23.2)** | 45.6(32.5) | 52.9(22) | 77.9(24.8) | 55.2(16.1) |  | 34.6(10.8) | 24.1(7) | 27.6(9.4) | 30.2(8.1) | 41.6(11.4) | 158.2(35.5) | 20.2(7.8) | 25.4(8) | 27.5(10.5) |
| Tubal factor n=31 |  | 46.7(28.8) | 79.5(22.9) | 69.1(30.6) | 77.7(24.4) | 69(26.5) | **59.4(35.6)** | 46.1(35.1) | 62(20.6) | 76.2(23.4) | 62.2(22.8) |  | 29.8(11.7) | 20.9(11.9) | 22.5(8.5) | 28.1(9.2) | 42.5(12.3) | 143.9(43.8) | 19.2(8.3) | 31.7(10) | 29(12.2) |
| Male factor n=79 |  | 47.7(23.4) | 79.8(20.3) | 71.4(28) | 72.2(23.3) | 74.8(21.9) | **75.8(24.5)** | 50.8(33.9) | 56.7(25.3) | 76.4(22.2) | 64.2(18.8) |  | 32.1(9.9) | 19.4(9.3) | 23.5(7.2) | 28.2(8.2) | 42(9.1) | 145.6(34.2) | 20(7.4) | 29.1(10.5) | 29.2(14.1) |
| Anovulation n=11 |  | 44.8(23) | 77.9(13.9) | 62.9(23.7) | 78.6(22.4) | 79.2(11.5) | **67.7(20.4)** | 45.8(32.1) | 56.3(26.1) | 72.9(21.2) | 61.8(13.8) |  | 30.5(10.6) | 21.9(7.9) | 26.7(4.9) | 30.8(6.8) | 41.6(9.5) | 151.5(26.2) | 19.1(7) | 27.2(9.3) | 25.3(6.1) |
|  | EM-INFERT | Personal strain | Partner relationship | Sexuality | Social support | Confidence in treatment | **Guilt and blame** | Financial strain | Need for privacy | Couple concordance | Total EM-INFERT | FPI | Social concern | Sexual concern | Relationship concern | Rejection of childfree lifestyle | Parenthood need | Global stress | Total positive affect | Perceived stress affect | Total negative affect |

**Figure 8.1: Impact of IVF on Emotional health as per the cause of infertility**

**8.3 Results**

Table 8.1 describes the demographic details and outcome of IVF in all groups of infertility. Male factor infertility had the highest number of patients (38.6%) and single/same sex couple group had the least (1.2%). Anovulatory group had the lowest mean age and the group with poor ovarian reserve had the highest mean age (32.2 vs. 38.6 p=0). Clinical pregnancy was also highest in the anovulatory group (50%) and lowest in the group with poor ovarian reserve (20%). Tables 8.2,8.3 and 8.4 compares the scores from EM-INFERT, FPI, PSS and PANAS in patients with different causes of infertility at start of the treatment cycle, at egg collection and after the pregnancy test. While the overall EM-INFERT and FPI scores between all the groups were similar at all three time points, there were differences noted in the individual domains between the groups. The distress due to feelings of guilt and blame was significantly different among the different groups at all three time points (p=0). Patients with poor ovarian reserve had lowest score for this domain followed by the group with tubal factor. Patients with male factor infertility had the least feelings of guilt or blame. Confidence in treatment was also different at the start of the cycle among the various groups(p=0.013). Single and same sex couples had the least confidence in treatment at the start of the cycle, while anovulatory group had the highest score in that domain.

The impact of IVF cycle on the emotional health as per the cause of infertility has been illustrated in Figure8.1. Patients with endometriosis start with the lowest emotional health among all groups, which drops even further after the pregnancy test. Patients with poor ovarian reserve also follow a similar pattern of fluctuation in emotional health during IVF. In contrast single women and those in same sex relationship although have very low emotional health at the start of the cycle, it improves significantly during the treatment cycle. Women with male factor infertility have the highest emotional health throughout the treatment cycle. From the figure, it is evident that emotional health more or less stays same or slightly better in the first half of the cycle in almost all groups of infertility. But invariably emotional health drops at the end of the treatment cycle after the pregnancy test in almost all the groups. The only exception being single women and those in same sex relationship who do not follow this pattern.

The second part of the study involved comparison between women having first time IVF and patients having repeat cycles. Out of 414 women, 171(41.3) had undergone previous IVF, while 243 women (58.7) were having IVF for the first time. Table 8.5 describes their demographic parameters and pregnancy outcome. The mean duration of infertility was significantly longer in patients having repeat IVF. Both groups were similar in terms of age, BMI, number of follicles and number of eggs. Table 8.6 describes the comparison of emotional health and fertility distress in these two groups. Both the groups of patients did not have any significant differences in overall emotional health or global fertility related distress at all three time points. However partner relationship deteriorated significantly after the pregnancy test in patients with repeat IVF. None of the other domains of EM-INFERT or FPI showed any significant differences between the two groups of patients.

**Table 8.5: Demographic details and pregnancy outcome in first time IVF and repeat IVF**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | First time IVF | Repeat IVF | Mean difference (95% CI) |  |
| Number of patients | 243 (58.7) | 171 (41.3%) |  |  |
| Mean age (SD) | 33.4 (4.8) | 34.3 (4) | -0.87 (-1.7,0.01) | p=0.054 |
| Mean BMI (SD) | 25.1 (3.8) | 24.3 (3.4) | 0.76 (-0.33,1.56) | p=0.060 |
| **Mean years of infertility(SD)** | **2.8 (1.6)** | **3.4 (1.5)** | **-0.55(-0.88,-0.22)** | **p=0.001** |
| **Previous children** | **17 (7%)** | **33 (19.3%)** |  |  |
| Number of follicles(SD) | 10 (4.3) | 9.7 (4.2) | 0.25(-0.6,1.11) | p=0.561 |
| Mean number of eggs(SD) | 8.9 (4.6) | 8.9 (4.6) | -0.01 (-0.94,0.91) | p=0.977 |
| Clinical pregnancy | 85 (35%) | 45 (26.3%) |  |  |
| Live births | 65 (26.7%) | 33(19.3 %) |  |  |
| Biochemical pregnancy | 12(5%) | 9(5.3%) |  |  |
| Miscarriage | 18 (7.4%) | 13 (7.6 %) |  |  |

**Table 8.6 : Comparison of emotional health between first IVF vs repeat IVF**

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| After pregnancy test | Independent samples’ ‘t’ test |  | p= 0.528 | **p= 0.037** | p= 0.633 | p= 0.965 | p= 0.354 | p= 0.378 | p= 0.139 | p= 0.325 | p= 0.589 | p= 0.366 | p= 0.886 | p= 0.869 | p= 0.078 | p= 0.424 | p= 0.341 | p= 0.347 | p= 0.106 | p= 0.677 | p= 0.944 |
| Mean Difference (95%CI |  | 2.29(-0.87,9.46) | **6.38 (0.39,12.37)** | -1.93(-9.87,6.02) | 0.15(-6.74,7.05) | 3.18(-3.56,9.92) | 3.42(-4.2,11.03) | 7.12(-0.33,16.57) | 3.43(-3.43,10.3) | 1.79(-4.73,8.3) | 2.54(-3,8.08) | 0.21 (-2.73,3.16) | -0.24 (-3.06,2.59) | -1.99(-4.21,0.22) | -1.02(-3.53,1.49) | -1.44(-4.42,1.54) | 5.12(-15.83,5.59) | -1.77(-3.92,0.38) | 0.61(-2.28,3.5) | -0.14(-4.11,3.83) |
| Repeat IVF |  | 42.7(22.9) | **72.7(24.8)** | 68.1(27.3) | 71.4(24.3) | 70.3(23.2) | 64.4(27.7) | 47(35.1) | 56.5(23.9) | 76.8(20.7) | 59.7(18.8) | 32.8(10.6) | 21.8(9.5) | 25.5(8.8) | 29.5(7.6) | 42(9.7) | 151.9(35.5) | 20.9(7.5) | 27.8(10.2) | 29(9.6) |
| First IVF |  | 45.3(26.1) | **80.7(18.1)** | 67(27.8) | 73(23.6) | 73.7(23.7) | 70.7(24.5) | 53.6(31.6) | 59.4(24.2) | 76.2(23.1) | 62.9(19.5) | 32.3(9.8) | 20.9(9.7) | 23.2(7.1) | 28.5(9.5) | 41.4(10.8) | 146.4(37.8) | 19.3(7.3) | 28.5(9.4) | 29.4(15.8) |
| At egg collection | Independent samples’ ‘t’ test |  | p= 0.259 | p= 0.169 | p= 0.716 | p= 0.71 | p= 0.248 | p= 0.242 | p= 0.23 | p= 0.652 | p= 0.973 | p= 0.289 | p= 0.712 | p= 0.832 | p= 0.068 | p= 0.112 | p= 0.556 | p= 0.396 | p= 0.072 | p= 0.316 | p= 0.115 |
| Mean Difference (95%CI |  | 3.27(-2.42,8.97) | 3.22(-1.38,7.82) | -1.18(-7.56,5.2) | 1(-4.3,6.3) | 2.61(-1.83,7.04) | 3.51(-2.38,9.41) | 4.75(-3.02,12.53) | 1.42(-4.79,7.64) | 0.09(-5.14,5.33) | 2.33(-1.98,6.64) | 0.44 (-1.92,2.8) | -0.25 (-2.53,2.03) | -1.75(-3.63,0.13) | -1.57(-3.51,0.37) | -0.72(-3.11,1.68) | -3.6(-11.94,4.74) | -1.48(-3.1,0.13) | 1.06(-1.02,3.14) | -1. 72 (-3.86,0.42) |
| Repeat IVF |  | 46.2(23.1) | 78.3(22.1) | 71.4(25.3) | 72.6(23.5) | 75.3(19.4) | 68.6(26.0) | 49.0(341) | 58.8(25.7) | 77.8(21.4) | 63.4(17.8) | 30.1(10) | 20.0(9.4) | 24.9(7.9) | 30.3(8.3) | 41.8(10.6) | 146.4(35.2) | 19.5(6.8) | 30.0(8.0) | 26.3(9.8) |
| First IVF |  | 49.4(24.1 | 81.6(17.9) | 70.2(27.3) | 76.3(21.2) | 77.9(17.8) | 72.0(23.6) | 53.8(31.2) | 60.2(26.0) | 77.9(22.1) | 65.7(18.05) | 30.5(9.6) | 19.7(9.3) | 23.2(7.7) | 28.1(8.0) | 41.0(9.8) | 142.8(34.0) | 18.0(6.6) | 31.0(8.8) | 24.6(7.9) |
| At the start of the cycle | Independent samples’ ‘t’ test |  | p=0.171 | p=0.086 | p=0.946 | p=0.746 | p=0.211 | p=0.091 | p=0.353 | p=0.940 | p=0.750 | p=0.206 | p= 0.501 | p= 0.99 | p= 0.764 | p= 0.219 | p= 0.813 | p= 0.926 | p= 0.437 | p= 0.300 | p= 0.617 |
| Mean Difference (95%CI |  | 3.05 (-1.32, 7.42) | 3.36(-0.48, 7.2) | -0.16(-5.04, 4.71) | 0.69(-3.17, 4.57) | 2.23 (-1.26,5.73) | 4.21(-0.68,9.12) | 3.05(-3.39,9.5) | 0.17(-4.52, 4.88) | -0.69(-4.98, 3.59) | 2.1(-1.16, 5.37) | 0.6 (-1.15,2.34) | 0.01 (-1.65,1.67) | -0.24 (-1.79,1.32) | -1 (-2.59,0.59) | 0.23 (-1.71,2.18) | -0.3 (-6.59,5.99) | -0.5 (-1.77,0.76) | 0.84 (-0.75,2.42) | -0.43 (-2.12,1.26) |
| Repeat IVF |  | 45.4(22.0) | 76.7(20.2) | 70.4(23) | 78.2(20.2) | 75.3(17.2) | 65.5(24.5) | 48.0(35) | 59.7(22.9) | 80.9(21.1) | 62.9(15.9) | 30.5(9.1) | 20(8.0) | 24.2(8.2) | 30.3(8.1) | 40.6(9.8) | 145.3(32.4) | 18.2(6.2) | 30.9(7.5) | 24.5(8.7) |
| First IVF |  | 48.4(22.4) | 80.0 (19.5) | 70.3(25.6) | 78.8(19.6) | 77.5.1(17.7) | 69.7(23.8) | 51(31.7) | 59.8(24.6) | 80.2(22) | 65.0(17.1) | 31.4(8.6) | 20(8.7) | 24.0(7.6) | 29.3(7.9) | 40.8(9.8) | 145.0(31.7) | 17.7(6.5) | 31.7(8.0) | 24.1(8.1) |
|  |  | EM-INFERT | Personal strain | Partner relationship | Sexuality | Social support | Confidence in treatment | Guilt and blame | Financial strain | Need for privacy | Couple concordance | Total EM-INFERT | Social concern | Sexual concern | Relationship concern | Rejection of child free life | Need for parenthood | Global stress | Perceived stress | Positive Affect | Negative Affect |

**8.4 Discussion:** The results from this study show that patients with poor ovarian reserve experience significant distress due to feelings of guilt over the childlessness. Low ovarian reserve is indicative of ovarian aging and occurs physologically in the mid-forties but sometimes can earlier. Women with low ovarian reserve are more likely to attribute the conception failure to themselves(269) which are often associated with negative feelings of inadequacy, incompetence, guilt, and hopelessness. These eventually can lead to depression. Demyttenaere *et al* reported that women with female cause of infertility were more likely to be express depressive symptomatology, which was associated with lower pregnancy rates (77, 267). On the other hand in the same study women with male factor infertility tended to express anger towards their partners. Similar observations were made by Vieyra *et al* also(269). They concluded that guilt about their own fertility problems increased their depression, while anger about their partners’ fertility problem decreased their depression. Patients with tubal factor infertility also had very similar scores to those with poor ovarian reserve. In contrast women with male factor infertility had the highest score for guilt and blame through all three time points. Patients with unexplained infertility had similar questionnaire scores to the rest of the groups of infertility. This is similar to the results reported by Lee *et al* who reported that women with unexplained or male infertility had lower guilt, higher sef-esteem health than those with a female cause of infertility. This suggests that the cause of infertility is a significant risk factor in women with poor emotional health during IVF.

The comparison between first time IVF and repeat IVF showed similar psychological profile at the start of the cycle. The mean duration of infertility among the repeat IVF patients was significantly longer than the first time IVF patients. However the emotional health at midpoint of treatment was significantly lower in the patients having repeat cycles as compared to the patients having IVF for the first time. This suggests that these patients are more affected by the treatment process due to previous repeated failed cycles while patients having their first cycle are more optimistic. This difference in emotional health does not persist after the pregnancy test. Studies have reported increased anxiety and depression in patients with long standing infertility and failed IVF(58, 79).

In patients with repeat IVF, the domain of partner relationship is significantly affected both during treatment and after pregnancy outcome as seen by the significantly lower EM-INFERT scores in this domain. Similar results were also noted with FPI scores. This is consistent with the study by Salvatore *et al* where veterans showed show a decreased desire for sexual proximity with their partner(270). In the short term the marital relationship actually imrpoves among infertile couples(223) but long standing infertility can cause marital discord. The incidence of seperation and divorce have been shown to be higher in infertile couples who have remained childless. (271, 272).In the study by Kjaer *et al* , women who did not succeed to conceive with IVF had three times higher of divorce 12 years later.

**8.5 Conclusion:**

The emotional well-being of patients undergoing IVF is linked to the cause of infertility. The attributes of self-blame for the failed IVF can lead to low self-esteem, role failure and if long-standing, may lead to clinical depression. Hence prior assessment and anticipation will enable interventions at the right stage so as to avoid worseining of their emotional health. The impact on marital relationship attributed to the duration of infertility does need to be addressed. With appropriate interventions during and after a failed cycle, it may be possible to improve the partner relationship leading to less breakdown of marriage. Both cause and duration of infertility are both important predictors of stress associated with infertility.

**Chapter 9: Summary & Future work**

|  |
| --- |
| Overview  3.1 Background  3.2 Impact of Emotional Health on IVF outcome  3.3 Effect of IVF on Emotional Health  3.4 Gender based comparison  3.5 Impact of cause and duration of infertility  3.6 Limitations of the study  3.7 Psychological interventions in infertility  3.8 Future work |

**9.1 Background:**

In this chapter I have summarised the results from the study, discussed psychological interventions in infertility and IVF and direction of future research

Infertility is a profoundly distressing experience that affects 1 in 7 heterosexual couples in the UK. Even with the advanced development of assisted reproductive technology, the success rate of IVF still remains around 30-35%. Our study was a prospective well-powered study designed to examine mainly the impact of pre-treatment emotional health on IVF outcome and to see whether we can predict the success of IVF from the pre-treatment emotional health scores. Various psychological variables that have been used to measure stress during IVF included state and trait anxiety (STAI), depression (BDI), stress (PSS), optimism and coping (CART), and fertility associated distress (FPI). In our study we measured emotional health, which has been used for the first time in the context of infertility and IVF. Emotional health is defined as a state of overall psychological wellbeing which can be affected by the individual variables of anxiety, depression and stress. Hence it is a more comprehensive and accurate psychological variable. It reflects effect of infertility on self, on relationships and life plans.

Our study results indicate no significant impact of emotional health on the IVF outcome and hence we cannot predict the success of IVF from the pre-treatment emotional health. However, the study has shown that process of IVF significantly affects emotional health of men and women especially when there is a negative result. With the help of EM-INFERT we have identified couples who have poor emotional health at the start IVF which worsens during the treatment process. This study will enable us to objectively assess these couples and offer additional psychosocial care or interventions. The measurement of emotional health in nine domains further helps us to tailor specific intervention based on the needs of the patient.

**Table 9.1: Summary of the results from the study**

|  |  |
| --- | --- |
| Impact of Emotional Health on IVF outcome | Pre-treatment emotional health in women does not affect pregnancy outcome after IVF.  Pre-treatment emotional health cannot be used to predict pregnancy outcome after IVF |
| Impact of IVF treatment on Emotional health | Emotional health remained stable in the first half of the treatment cycle until egg collection.  Emotional health deteriorated significantly in the second half of the treatment cycle for the non-pregnant women.  The pregnant women women had a slight improved in their emotional health due to less financial worries |
| Gender based comparison | Women had lower emotional health than men through all stages of IVF cycle  Men with a male cause of infertility and women with a female cause of infertility had significantly lower emotional health.  Emotional health of men dropped significantly after a negative pregnancy result |
| Emotional Impact of cause of infertility | Overall emotional health was similar throughout IVF in all groups of infertility.  Domain of guilt and blame was significantly different depending on the cause of infertility.  Patients with endometriosis and poor ovarian reserve had the lowest emotional health in comparison with male factor infertility |
| Emotional Impact of duration of infertility | Overall emotional health was similar between patients with first IVF vs. repeat IVF.  But partner relationship was significantly affceted in those having repeat cycles of IVF |

**9.2** **Impact of Emotional Health on IVF outcome**

This is the main hypothesis that we set out to investigate in our study. Our systematic review concluded that there was insufficient evidence to correlate emotional distress characterised by anxiety and depression with pregnancy rates after assisted reproduction. There were more consistent results when fertility specific tools were used. However these studies were few and had small number of patients. Our study was designed to examine the emotional health just prior to the start of the IVF cycle and correlate it with the success rate at the end of that cycle. We used four questionnaires at the start of the cycle, EM-INFERT, FPI, PSS and PANAS. Based on the EM-INFERT scores the entre cohort of 414 couples was divided into three tertiles. These tertiles were similar in demographic and biomedical variables. Our study was based on the hypothesis that higher emotional health corresponded to better pregnancy rates. To prove this we needed to show that pregnancy rates in the top tertile were significantly better than bottom tertile. Our results showed that pregnancy rates in the topmost tertile was higher than that of the lowest tertile, but the difference was not statistically significant (27.9% vs. 31.1% p=0.597). While pregnancy is the bottom tertile was lowest, the middle tertile had the highest pregnancy rate indicating that the relationship between emotional health and IVF outcome was not linear.

We also analysed and compared the domain scores between the three tertiles. They were consistent with the total EM-INFERT scores. The global stress and domain scores from FPI were also similar to EM-INFERT in all the three tertiles as was the negative affect score from PANAS and perceived stress score from PSS-10.

**9.3 Effect of IVF on Emotional health**

This is the second part of the study which investigates the impact of IVF on the emotional health. We assessed the emotional health of couples at the pre-treatment stage, mid-cycle and after the results. The intention of this was to examine the effect of IVF on the emotional health of patients. We know that infertility has a huge impact on psychological functioning of individuals. At the start of the cycle, patients are often quite anxious, a bit worried and optimistic at the same about the treatment. In the first part of the study we investigated the effect of pre-treatment stress on IVF outcome. In this part of the study we explored the impact of IVF on the emotional health of the patients by comparing the scores between all three time points.

In our study, overall emotional health (EM-INFERT score) had not significantly altered between the pre-treatment stage and midpoint of the cycle i.e after oocyte recovery. Patients starting the IVF cycle felt more socially isolation in the first phase of ovarian stimulation as indicated by lower scores in the domain of social support. In this phase marital harmony also diminished (couple concordance) yet partner relationship remained stable. The overall stress scores from FPI remained stable, but patients felt more desire for parenthood during this phase.

In the second half of the IVF cycle, (luteal phase) emotional health in most of the domains dropped significantly. This difference was more pronounced in those who did not conceive. Contrary to the first part of the cycle, marital harmony remained unaffected in this phase of treatment. The FPI also showed increased stress levels in all domains except for concern about partner relationship. In pregnant patients the emotional health improved but this was not statistically significant (63.3 versus 64.4;p=0.1) except for the domain of financial strain (52.1 versus 56.1;p=0.04).

Our results show that emotional health tends to relatively stable in the first part of the IVF cycle but gets significantly lowered in the luteal phase while awaiting the results of the treatment. A negative result further enhances this emotional distress while positive result improves the financial strain faced by the patients.

**9.4** **Gender based comparison**

This is the third part of the study where we explored the differences in emotional health between men and women. The diagnosis of infertility can also have a major impact on the emotional health of men too. In our study we found that women had lower emotional health than men through all stages of infertility treatment. The overall EM-INFERT scores and all except one domain (confidence in treatment) were significantly higher in men. This might reflect a gender- specific response to infertility and not necessarily a lack of emotion. In our study 80% of couples had either male or female cause of infertility. The number of couples with female cause of infertility were similar to those with male cause of infertility (Male cause 39% vs. Female cause 41.3 %.p=NS). Similarly men with male cause of infertility had lower emotional health than men with a female cause of infertility. Women with female cause of infertility had more distress than those with male factor infertility. The principal domain that was affected here was guilt and blame. Women with female factor infertility felt guiltier and blamed themselves for the childlessness. Similar results were noted in the men too.

Although there were considerable differences in the emotional response of men and women during IVF, both had significant drop in the emotional health following a negative pregnancy test. This study describes gender differences and similarities in the psychological response to infertility. While’s men’s reaction to infertility and coping styles may differ from women, they too experience a significant impact of negative IVF. This also highlights the importance of having couple based interventions during IVF.

**9.5** **Emotional Impact of cause and duration of infertility**

This part of the study examined the effect of cause and duration of infertility on the emotional health of patients. Overall the emotional health was similar in all the groups of infertility at all times. But the domain of guilt and differed significantly depending on the cause of infertility. Women with female factor and unexplained infertility had more feelings of guilt and blame as compared to those with male factor infertility. Women with. Thus cause of infertility is a significant risk factor in women with poor emotional health during IVF.

Several studies in the past have examined the effect of duration of infertility on the stress level. In our study first time IVF patients had lower mean duration of infertility as compared to those having repeat cycles. Hence we compared the emotional health between patients having first time IVF and repeat IVF to understand the impact of duration of infertility on emotional distress.

We found patients having first time IVF and repeat cycle of IVF had similar emotional health and fertility related stress. However relationship with the partner was consistently lower in women having repeat cycle of IVF at all three time points and was significantly lower after the pregnancy test. However couple concordance scores were stable. This suggests marital relationship is significantly affected in patients who have had previous unsuccessful IVF. This group of patients would benefit with targeted interventions. Thus emotional health profile of patients with different causes and duration of infertility is useful to identify those who will benefit with psychological interventions.

**9.6 Limitations of the study:**

The study took longer than expected time to complete due to low participation of patients. Although we had a sample size of 414 women for testing the main hypothesis which was a good sample size, the completion of questionnaires 2 and 3 dropped significantly. One of the reasons cited for non-completion of the second and third questionnaire was that patients were too worried and stressed about the treatment progress and outcome. Women who were approached and declined to participate cited stress as a significant factor in non-participation. This means that the sample was biased in that it did not include women who had poor emotional health and the results may be not be accurate. Another factor was that 2/3rd of the couples who participated were having their first cycle of IVF which is usually a time of optimism and positive emotions. However couples undergoing repeated cycles of IVF are more stressed as they have already undergone a failed cycle. The anxieties regarding the outcome and financial strain will be more pronounced in these couples. Hence the results of the study could be skewed due to the fact that fewer couples with repeat IVF cycles were recruited.

**9.7** **Psychological interventions in infertility**

There is clear evidence that infertility and assisted reproduction have a negative influence on an individual’s psychosocial functioning. In these couples psychological interventions have been known to reduce the emotional distress(273). The code of practice by Human Fertility and Embryology Authority (HFEA) has stipulated that all patients undergoing assisted reproduction must be offered counselling. Recently European Society of Reproduction and Embryology (EHSRE) published guidelines regarding psychosocial care in infertility and patients undergoing assisted reproduction(274). Our study has identified patients at risk for developing significant fertility specific distress during IVF. The results from our study can be used to screen such patients at the start of their IVF treatment and offer psychosocial interventions to them alongside medical care. Using the EM-INFERT tool, we can tailor the psychological interventions to the specific needs of the patient and stage of their treatment. They can not only improve the psychological well-being but also may increase pregnancy rates. So far four studies have reviewed the effects of psychological intervention on emotional well-being and pregnancy rates. The first study published in 2003 concluded that interventions appeared to improve anxiety and fertility-related distress but no clear benefit was seen on pregnancy rates(211). The second review published in 2005 studied the efficacy of group versus individual interventions and concluded that both were equally effective in reducing psychological distress and increasing pregnancy rates(275). The third review published in 2009 included only controlled studies and found no beneficial effect on interventions on emotional distress but increased pregnancy rates for infertile couples not undergoing IVF(276). A more recent meta-analysis published in 2015 concluded that anxiety and depression improved with psychological intervention but fertility-related distress did not get better(277). The authors inferred that this could be due to lack of sensitivity of the infertility related distress measures used. Emotional health measured by EM-INFERT is a comprehensive fertility specific measure that could be an ideal instrument to study the efficacy of psychological interventions on infertile couples. The authors also observed that reduction in the anxiety achieved with interventions could improve the chances of pregnancy.

There are various types and formats of interventions that have described in literature. The various types of interventions include cognitive behaviour therapy (CBT)(278), mind body intervention (MBI)(279), art therapy(280), expressive writing intervention(281), stress management(282, 283) and various types of counselling(283). The various formats of intervention include group format, individual format, couple interventions and online format. The emotional response to infertility and IVF can be varied. The psychological well-being also fluctuates during fertility treatment depending on the stage and progress of treatment. Hence it is important to target interventions to the various types and levels of psychological distress. This forms the basis for future research in this field

**9.8 Future work**

The results of study have helped not only to explore the effects of distress on IVF outcome but also help to identify patients with poor psychological well-being prior to undergoing IVF. Overall it has been established that infertility and IVF is associated with considerable psychological distress. Addressing the specific infertility related distress could make their IVF journey a better experience and lead to less dropout rates. There has been evidence to suggest that interventions during IVF have improved the emotional well-being of patients(284). There has already been early evidence to suggest that this may even lead to increased pregnancy rates(277). The results of this study can also help to design psychological interventions tailored to the individual needs of the patients undergoing IVF. Future work in this area should involve a study to assess the efficacy of psychological interventions in couples undergoing IVF. The fluctuations in the emotional health as reported in our study can be used to target the interventions in such a manner so as to optimise the effects on distress levels and pregnancy rates.

**References**

1. NICE. Fertility. 2013.

2. Zegers-Hochschild F, Adamson GD, de Mouzon J, Ishihara O, Mansour R, Nygren K, et al. International Committee for Monitoring Assisted Reproductive Technology (ICMART) and the World Health Organization (WHO) revised glossary of ART terminology, 2009. Fertility and Sterility. 2009;92(5):1520-4.

3. Larsen U. Research on infertility: which definition should we use? Fertility and Sterility. 2005;83(4):846-52.

4. Larsen U, Menken J. Measuring sterility from incomplete birth histories. Demography. 1989;26(2):185-201.

5. Gurunath S, Pandian Z, Anderson RA, Bhattacharya S. Defining infertility-a systematic review of prevalence studies. Human Reproduction Update. 2011;17(5):575-88.

6. Mascarenhas MN, Flaxman SR, Boerma T, Vanderpoel S, Stevens GA. National, Regional, and Global Trends in Infertility Prevalence Since 1990: A Systematic Analysis of 277 Health Surveys. Plos Medicine. 2012;9(12).

7. Evers JLH. Female subfertility. Lancet. 2002;360(9327):151-9.

8. WHO. World report on disability. In: Bank W, editor. 2011.

9. ART Factsheet 2014 [press release]. 2014.

10. www.nhs.uk. Causes of infertility 2017 [

11. Balen A. Infertility in practice. 4th Edition ed: CRC Press Taylor & Francis group; 2008.

12. Menken J, Trussell J, Larsen U. Age and infertility. Science. 1986;233(4771):1389-94.

13. Crosignani PG, Rubin B. Male-sterility and subfertility - guidelines for management. Human Reproduction. 1994;9(7):1260-4.

14. Greil AL, Porter KL, Leitko TA. Sex and Intimacy Among Infertile Couples. Journal of Psychology & Human Sexuality. 1990;2(2):117-38.

15. Dokras A, Baredziak L, Blaine J, Syrop C, VanVoorhis BJ, Sparks A. Obstetric outcomes after in vitro fertilization in obese and morbidly obese women. Obstetrics and Gynecology. 2006;108(1):61-9.

16. Hammoud AO, Gibson M, Peterson CM, Hamilton BD, Carrell DT. Obesity and male reproductive potential. Journal of Andrology. 2006;27(5):619-26.

17. Oboni J-B, Marques-Vidal P, Bastardot F, Vollenweider P, Waeber G. Impact of smoking on fertility and age of menopause: a population-based assessment. Bmj Open. 2016;6(11).

18. Kovac JR, Khanna A, Lipshultz LI. The effects of cigarette smoking on male fertility. Postgraduate Medicine. 2015;127(3):338-41.

19. Collins JA, Van Steirteghem A. Overall prognosis with current treatment of infertility. Human Reproduction Update. 2004;10(4):309-16.

20. Ferraretti A, Goossens V, Bhattacharya S, Castilla JA, de Mouzon J, Korsak V, et al. Assisted reproductive technology in Europe, 2010: results generated from European registers by ESHRE. Preliminary results. Human Reproduction. 2013;28:38-9.

21. Van Voorhis B. Outcomes from assisted reproductive technology. Obstetrics and Gynecology. 2006;107(1):183-200.

22. HFEA. IVF-Chances of success. 2010.

23. Greil AL, Slauson-Blevins K, McQuillan J. The experience of infertility: a review of recent literature. Sociology of Health & Illness. 2010;32(1):140-62.

24. A.D. Domar MMS. Emotional aspects of infertility. Infertility: A Comprehensive Text. Appleton & Lange, Stamford1997. p. 29-44.

25. Selye H. Stress and distress. Comprehensive therapy. 1975;1(8).

26. Cohen SE, Kessler RCE, Gordon LUE. Measuring stress: A guide for health and social scientists: New York, NY, US: Oxford University Press.; 1975.

27. D.A. G. A biopsychosocial theory of infertility. *The Family Journal: Counseling and Therapy for Couples and Families*. 2001;9:151-8.

28. Menning BE. The emotional needs of infertile couples. Fertility and Sterility. 1980;34(4):313-9.

29. Kubler-Ross E. On death and dying. Bulletin of the American College of Surgeons. 1975;60(6):15-7.

30. Blenner JL. Passage through infertility treatment: a stage theory. Image--the journal of nursing scholarship. 1990;22(3):153-8.

31. Berg BJ, Wilson JF. Psychological functioning across stages of treatment for infertility. Journal of Behavioral Medicine. 1991;14(1):11-26.

32. Freeman EW, Rickels K, Tausig J, Boxer A, Mastroianni L, Tureck RW. Emotional and psychosocial factors in follow-up of women after ivf-et treatment - A pilot investigation. Acta Obstetricia Et Gynecologica Scandinavica. 1987;66(6):517-21.

33. Mahlstedt PP, Macduff S, Bernstein J. Emotional factors and the invitro fertilization and embryo transfer process. Journal of in Vitro Fertilization and Embryo Transfer. 1987;4(4):232-6.

34. Bergart AM. The experience of women in unsuccessful infertility treatment: What do patients need when medical intervention fails? Social Work in Health Care. 2000;30(4):45-69.

35. Greil AL, Leitko TA, Porter KL. INFERTILITY: His and Hers. Gender & Society. 1988;2(2):172-99.

36. Olshansky EF. Infertility and its influence on women's career identities. Health care for women international. 1987;8(2-3):185-96.

37. Imeson M, McMurray A. Couples' experiences of infertility: A phenomenological study. Journal of Advanced Nursing. 1996;24(5):1014-22.

38. Becker G, Nachtigall RD. Eager for medicalization - the social production of infertility as a disease. Sociology of Health & Illness. 1992;14(4):456-71.

39. Williams ME. Toward Greater Understanding of the Psychological Effects of Infertility on Women. Psychotherapy in Private Practice. 1997;16(3):7-26.

40. Levin JB, Sher TG, Theodos V. The effect of intracouple coping concordance on psychological and marital distress in infertility patients. Journal of Clinical Psychology in Medical Settings. 1997;4(4):361-72.

41. Downey J, Yingling S, McKinney M, Husami N, Jewelewicz R, Maidman J. Mood disorders, psychiatric-symptoms, and distress in women presenting for infertility evaluation. Fertility and Sterility. 1989;52(3):425-32.

42. Connolly KJ, Edelmann RJ, Cooke ID, Robson J. The impact of infertility on psychological functioning. Journal of Psychosomatic Research. 1992;36(5):459-68.

43. Cook R, Parsons J, Mason B, Golombok S. Emotional, marital and sexual functioning in patients embarking upon IVF and AID treatment for infertility. Journal of Reproductive and Infant Psychology. 1989;7(2):87-93.

44. Band DA, Edelmann RJ, Avery S, Brinsden PR. Correlates of psychological distress in relation to male infertility. British Journal of Health Psychology. 1998;3:245-56.

45. King RB. Subfecundity and anxiety in a nationally representative sample. Social Science & Medicine. 2003;56(4):739-51.

46. Domar AD, Seibel M, Broome A, Friedman R, Zuttermeister PC. THE Prevalence and predictability of depression in infertile women. Fertility and Sterility. 1992;58(6):1158-63.

47. Beaurepaire J, Jones M, Thiering P, Saunders D, Tennant C. Psychosocial adjustment to infertility and its treatment - male and female responses at different stages of ivf et treatment. Journal of Psychosomatic Research. 1994;38(3):229-40.

48. Locke HJ, Wallace KM. Short Marital-Adjustment and Prediction Tests: Their Reliability and Validity. Marriage and Family Living. 1959;21(3):251-5.

49. Hammarberg K, Astbury J, Baker HWG. Women's experience of IVF: a follow-up study. Human Reproduction. 2001;16(2):374-83.

50. Leiblum SR, Aviv A, Hamer R. Life after infertility treatment: a long-term investigation of marital and sexual function. Human Reproduction. 1998;13(12):3569-74.

51. Berg BJ, Wilson JF, Weingartner PJ. Psychological sequelae of infertility treatment - the role of gender and sex-role identification. Social Science & Medicine. 1991;33(9):1071-80.

52. Callan VJ. The Personal and Marital Adjustment of Mothers and of Voluntarily and Involuntarily Childless Wives. Journal of Marriage and Family. 1987;49(4):847-56.

53. Leiblum SR, Kemmann E, Lane MK. The psychological concomitants of invitro fertilization. Journal of Psychosomatic Obstetrics and Gynecology. 1987;6(3):165-78.

54. Slade P, Emery J, Lieberman BA. A prospective, longitudinal study of emotions and relationships in in-vitro fertilization treatment. Human Reproduction. 1997;12(1):183-90.

55. Downey J, McKinney M. The psychiatric status of women presenting for infertility evaluation. American Journal of Orthopsychiatry. 1992;62(2):196-205.

56. Edelmann RJ, Connolly KJ, Bartlett H. Coping strategies and psychological adjustment of couples presenting for IVF. Journal of Psychosomatic Research. 1994;38(4):355-64.

57. Kedem P, Mikulincer M, Nathanson YE, Bartoov B. Psychological-aspects of male-infertility. British Journal of Medical Psychology. 1990;63:73-80.

58. Johansson M, Adolfsson A, Berg M, Francis J, Hogstrom L, Janson PO, et al. Quality of life for couples 4-5.5 years after unsuccessful IVF treatment. Acta Obstetricia Et Gynecologica Scandinavica. 2009;88(3):291-300.

59. Schenker J. Stress and human-reproduction. European Journal of Obstetrics Gynecology and Reproductive Biology. 1992;44(1):19-.

60. Lynch CD, Sundaram R, Maisog JM, Sweeney AM, Louis GMB. Preconception stress increases the risk of infertility: results from a couple-based prospective cohort studyuthe LIFE study. Human Reproduction. 2014;29(5):1067-75.

61. Rivier C, Rivier J, Vale W. Stress-induced inhibition of reproductive functions - role of endogenous corticotropin-releasing factor. Science. 1986;231(4738):607-9.

62. Berga SL, Daniels TL, Giles DE. Women with functional hypothalamic amenorrhea but not other forms of anovulation display amplified cortisol concentrations. Fertility and Sterility. 1997;67(6):1024-30.

63. Wasser SK. Psychosocial stress and infertility - cause or effect. Human Nature-an Interdisciplinary Biosocial Perspective. 1994;5(3):293-306.

64. Gallinelli A, Roncaglia R, Matteo ML, Ciaccio I, Volpe A, Facchinetti F. Immunological changes and stress are associated with different implantation rates in patients undergoing in vitro fertilization-embryo transfer. Fertility and Sterility. 2001;76(1):85-91.

65. Kondoh E, Okamoto T, Higuchi T, Tatsumi K, Baba T, Murphy SK, et al. Stress affects uterine receptivity through an ovarian-independent pathway. Human Reproduction. 2009;24(4):945-53.

66. Collodel G, Moretti E, Fontani V, Rinaldi S, Aravagli L, Sarago G, et al. Effect of emotional stress on sperm quality. Indian Journal of Medical Research. 2008;128(3):254-61.

67. Harrison KL, Callan VJ, Hennessey JF. Stress and semen quality in an invitro fertilization program. Fertility and Sterility. 1987;48(4):633-6.

68. Stoleru S, Teglas JP, Fermanian J, Spira A. Psychological-factors in the etiology of infertility - a prospective cohort study. Human Reproduction. 1993;8(7):1039-46.

69. Demyttenaere K, Nijs P, Evers-Kiebooms G, Koninckx PR. Coping and the ineffectiveness of coping influence the outcome of in vitro fertilization through stress responses. Psychoneuroendocrinology. 1992;17(6):655-65.

70. Edelmann RJ, Golombok S. Stress and reproductive failure. Journal of Reproductive and Infant Psychology. 1989;7(2):79-86.

71. Demyttenaere K, Nijs P, Steeno O, Koninckx P, Everskiebooms G. Anxiety and conception rates in donor insemination. Journal of Psychosomatic Obstetrics and Gynecology. 1988;8(3):175-81.

72. Lapane KL, Zierler S, Lasater TM, Stein M, Barbour MM, Hume AL. IS A History of depressive symptoms associated with an increased risk of infertility in women. Psychosomatic Medicine. 1995;57(6):509-13.

73. Pook M, Krause W, Rohrle B. Coping with infertility: distress and changes in sperm quality. Human Reproduction. 1999;14(6):1487-92.

74. Clarke RN, Klock SC, Geoghegan A, Travassos DE. Relationship between psychological stress and semen quality among in-vitro fertilization patients. Human Reproduction. 1999;14(3):753-8.

75. Harlow CR, Fahy UM, Talbot WM, Wardle PG, Hull MGR. Stress and stress-related hormones during in-vitro fertilization treatment. Human Reproduction. 1996;11(2):274-9.

76. Visser AP, Haan G, Zalmstra H, Wouters I. Psychosocial-aspects of in-vitro fertilization. Journal of Psychosomatic Obstetrics and Gynecology. 1994;15(1):35-43.

77. Demyttenaere K, Bonte L, Gheldof M, Vervaeke M, Meuleman C, Vanderschuerem D, et al. Coping style and depression level influence outcome in in vitro fertilization. Fertility and Sterility. 1998;69(6):1026-33.

78. Merari D, Feldberg D, Elizur A, Goldman J, Modan B. Psychological and hormonal changes in the course of invitro fertilization. Journal of Assisted Reproduction and Genetics. 1992;9(2):161-9.

79. Verhaak CM, Smeenk JMJ, Evers AWM, Kremer JAM, Kraaimaat FW, Braat DDM. Women's emotional adjustment to IVF: a systematic review of 25 years of research. Human Reproduction Update. 2007;13(1):27-36.

80. Ferin M. Stress and the reproductive cycle. Journal of Clinical Endocrinology & Metabolism. 1999;84(6):1768-74.

81. Sanders KA, Bruce NW. Psychosocial stress and treatment outcome following assisted reproductive technology. Human Reproduction. 1999;14(6):1656-62.

82. Stoleru S, Cornet D, Vaugeois P, Fermanian J, Magnin F, Zerah S, et al. The influence of psychological factors on the outcome of the fertilization step of in vitro fertilization. Journal of Psychosomatic Obstetrics and Gynecology. 1997;18(3):189-202.

83. Lintsen AME, Verhaak CM, Eijkemans MJC, Smeenk JMJ, Braat DDM. Anxiety and depression have no influence on the cancellation and pregnancy rates of a first IVF or ICSI treatment. Human Reproduction. 2009;24(5):1092-8.

84. Verhaak CM, Smeenk JMJ, Eugster A, van Minnen A, Kremer JAM, Kraaimaat FW. Stress and marital satisfaction among women before and after their first cycle of in vitro fertilization and intracytoplasmic sperm injection. Fertility and Sterility. 2001;76(3):525-31.

85. Boivin J, Griffiths E, Venetis CA. Emotional distress in infertile women and failure of assisted reproductive technologies: meta-analysis of prospective psychosocial studies. British Medical Journal. 2011;342.

86. Matthiesen SMS, Frederiksen Y, Ingerslev HJ, Zachariae R. Stress, distress and outcome of assisted reproductive technology (ART): a meta-analysis. Human Reproduction. 2011;26(10):2763-76.

87. Olivius C, Friden B, Borg G, Bergh C. Psychological aspects of discontinuation of in vitro fertilization treatment. Fertility and Sterility. 2004;81(2):276-.

88. Strauss B, Hepp U, Staeding G, Mettler L. Psychological characteristics of infertile couples: Can they predict pregnancy and treatment persistence? Journal of Community & Applied Social Psychology. 1998;8(4):289-301.

89. Hammarberg K, Astbury J, Baker H. Women's experience of IVF: a follow-up study. Hum Reprod. 2001;16(2):374-83.

90. Smeenk JMJ, Verhaak CM, Stolwijk AM, Kremer JAM, Braat DDM. Reasons for dropout in an in vitro fertilization/intracytoplasmic sperm injection program. Fertility and Sterility. 2004;81(2):262-8.

91. Cousineau TM, Domar AD. Psychological impact of infertility. Best Practice & Research in Clinical Obstetrics & Gynaecology. 2007;21(2):293-308.

92. Domar AD, Backman KL, Friscia D, Orav J, Nikolovski J. The relationship between stress and ivf outcome. Fertility and Sterility. 2010;94(4):S66-S.

93. Hosaka T, Matsubayashi H, Sugiyama Y. Effect of a psychiatric group intervention on emotions, natural-killer cell activity, and pregnancy rate in infertile Japanese women. Psychosomatics. 2003;44(2):134-5.

94. Frederiksen Y, Farver-Vestergaard I, Skovgård NG, Ingerslev HJ, Zachariae R. Efficacy of psychosocial interventions for psychological and pregnancy outcomes in infertile women and men: a systematic review and meta-analysis. BMJ Open. 2015;5(1).

95. Smeenk JMJ, Verhaak CM, Eugster A, van Minnen A, Zielhuis GA, Braat DDM. The effect of anxiety and depression on the outcome of in-vitro fertilization. Human Reproduction. 2001;16(7):1420-3.

96. Anderheim L, Holter H, Bergh C, Moller A. Does psychological stress affect the outcome of in vitro fertilization? Human Reproduction. 2005;20(10):2969-75.

97. Gourounti K, Anagnostopoulos F, Vaslamatzis G. The Relation of Psychological Stress to Pregnancy Outcome Among Women Undergoing In-Vitro Fertilization and Intracytoplasmic Sperm Injection. Women & Health. 2011;51(4):321-39.

98. Greil AL. Infertility and psychological distress: A critical review of the literature. Social Science & Medicine. 1997;45(11):1679-704.

99. Ebbesen SM, Zachariae R, Frederiksen Y. Metaanalysis of the effect of depression on in-vitro fertilization (ivf) treatment outcome. International Journal of Behavioral Medicine. 2010;17:281-2.

100. Spielberger CD, Gorsuch RL, R.E. aL. *Manual for the State-Trait Anxiety Inventory (form Y)*. Palo Alto, CA: Consulting Psychologists Press; 1970.

101. Seligman L, Moore BM. Diagnosis of mood disorders. Journal of Counseling and Development. 1995;74(1):65-9.

102. Klonoff-Cohen H, Chu E, Natarajan L, Sieber W. A prospective study of stress among women undergoing in vitro fertilization or gamete intrafallopian transfer. Fertility and Sterility. 2001;76(4):675-87.

103. Nouri K, Litschauer B, Huber JC, Buerkle B, Tiringer D, Tempfer CB. Saliva cortisol levels and subjective stress are not associated with number of oocytes after controlled ovarian hyperstimulation in patients undergoing in vitro fertilization. Fertility and Sterility. 2011;96(1):69-72.

104. Ebbesen SMS, Zachariae R, Mehlsen MY, Thomsen D, Hojgaard A, Ottosen L, et al. Stressful life events are associated with a poor in-vitro fertilization (IVF) outcome: a prospective study. Human Reproduction. 2009;24(9):2173-82.

105. Boivin J, Takefman JE. Stress level across stages of in-vitro fertilization in subsequently pregnant and nonpregnant women. Fertility and Sterility. 1995;64(4):802-10.

106. Kee BS, Jung BJ, Lee SH. A study on psychological strain in IVF patients. Journal of Assisted Reproduction and Genetics. 2000;17(8):445-8.

107. Smeenk JMJ, Eugster A, Verhaak CM, Vingerhoets AJJM, Van Minnen A, Sweep F, et al. Biochemical and questionnaire-based assessment of stress in IVF/ICSI. Human Reproduction. 2001;16:81-2.

108. Guinard A, Bachelot A, Stoleru S, de Mouzon J. Are stress and anxiety prognostic factors for IVF outcome? Human Reproduction. 2003;18:47-.

109. Eugster A, Vingerhoets A, van Heck GL, Merkus J. The effect of episodic anxiety on an in vitro fertilization and intracytoplasmic sperm injection treatment outcome: A pilot study. Journal of Psychosomatic Obstetrics and Gynecology. 2004;25(1):57-65.

110. Klonoff-Cohen H, Natarajan L. The Concerns During Assisted Reproductive Technologies (CART) scale and pregnancy outcomes. Fertility and Sterility. 2004;81(4).

111. Lancastle D, Boivin J. Dispositional optimism, trait anxiety, and coping: Unique or shared effects on biological response to fertility treatment? Health Psychology. 2005;24(2):171-8.

112. Lee A, Duckworth AL, Elkind-Hirsch KE, Seligman ME, Scott RT, Jr. Negative emotion predicts poor outcome in poor prognosis IVF patients. Fertility and Sterility. 2006;86:S55-S6.

113. Cooper BC, Gerber JR, McGettrick AL, Johnson JV. Perceived infertility-related stress correlates with in vitro fertilization outcome. Fertility and Sterility. 2007;88(3):714-7.

114. de Klerk C, Hunfeld JAM, Heijnen EMEW, Eijkemans MJC, Fauser BCJM, Passchier J, et al. Low negative affect prior to treatment is associated with a decreased chance of live birth from a first IVF cycle. Human Reproduction. 2008;23(1):112-6.

115. Sohrabvand F, Abedinia N, Pirjani R, Jafarabadi M. Effect of anxiety and depression on ART outcome. Iranian Journal of Reproductive Medicine. 2008;6(2):89-94.

116. Lintsen AM, Verhaak CM, Eijkemans MJ, Smeenk JM, Braat DD. Anxiety and depression have no influence on the cancellation and pregnancy rates of a first IVF or ICSI treatment. Hum Reprod. 24. England2009. p. 1092-8.

117. Gurhan N, Akyuz A, Atici D, Kisa S. Association of depression and anxiety with oocyte and sperm numbers and pregnancy outcomes during in vitro fertilization treatment. Psychol Rep. 2009;104(3):796-806.

118. Hunter RK, Traub ML, Knochenhauer ES. Stress at the initiation of fertility treatment affects ivf outcomes. Fertility and Sterility. 2010;94(4):S224-S.

119. Turner K, Reynolds-May MF, Zitek EM, Tisdale RL, Carlisle AB, Westphal LM. Stress and anxiety scores in first and repeat ivf cycles. Fertility and Sterility. 2010;94(4):S224-S.

120. Li X-H, Ma Y-G, Geng L-H, Qin L, Hu H, Li S-W. Baseline psychological stress and ovarian norepinephrine levels negatively affect the outcome of in vitro fertilisation. Gynecological Endocrinology. 2011;27(3):139-43.

121. Pasch LA, Gregorich SE, Katz PK, Millstein SG, Nachtigall RD, Bleil ME, et al. Psychological distress and in vitro fertilization outcome. Fertility and Sterility. 2012;98(2):459-64.

122. An Y, Sun Z, Li L, Zhang Y, Ji H. Relationship between psychological stress and reproductive outcome in women undergoing in vitro fertilization treatment: Psychological and neurohormonal assessment. J Assist Reprod Genet. 2013;30(1):35-41.

123. Harlow CR, Fahy UM, Talbot WM, Wardle PG, Hull MG. Stress and stress-related hormones during in-vitro fertilization treatment. Hum Reprod. 1996;11(2):274-9.

124. Gourounti K, Anagnostopoulos F, Paparisteidis N, Bolaris S, Kiriakaki M, Lykeridou K, et al. The impact of psychological stress on pregnancy outcome among women undergoing in-vitro fertilization. Human Reproduction. 2011;26:I79-I.

125. Dunkel-Schetter C, Lobel M. Psychological Reactions to Infertility. In: Stanton AL, Dunkel-Schetter C, editors. Infertility: Perspectives from Stress and Coping Research. Boston, MA: Springer US; 1991. p. 29-57.

126. Berg BJ. A researchers guide to investigating the psychological sequelae of infertility - methodological considerations. Journal of Psychosomatic Obstetrics and Gynecology. 1994;15(3):147-56.

127. Clarke A, Dawson R. Evaluation research : An Introduction to principles,methods and practice. London: Sage publications Limited; 1999.

128. Jenkinson C, McGee M. *Health status measurement: A brief but critical introduction*. Abingdon: Radcliffe Medical Press.; 1998.

129. Streiner D, Norman G. Health Measurement Scales: A practical guide to their development and use: OUP Oxford; 1985.

130. Rust J, Golombok S. Modern Psychometrics: The Science of Psychological Assessment: Psychology Press, 1999; 1999.

131. Barrett P, Kline P. The observation to variable ratio in factor analysis. Personality Study in Group Behavior. 1981;1:23–33.

132. Kline P. A Psychometrics Primer: Free Association, 2000; 2000. 179 p.

133. Cronbach LJ. Coefficient alpha and the internal structure of tests. Psychometrika. 1951;16(3):297-334.

134. Bernstein J, Potts N, Mattox JH. Assessment of psychological dysfunction associated with infertility. Journal of obstetric, gynecologic, and neonatal nursing : JOGNN / NAACOG. 1985;14(6 Suppl):63s-6s.

135. Shu-Hsin L. Effects of using a nursing crisis intervention program on psychosocial responses and coping strategies of infertile women during in vitro fertilization. The journal of nursing research : JNR. 2003;11(3):197-208.

136. Lee TY, Sun GH, Chao SC, Chen CC. Development of the Coping Scale for Infertile Couples. Archives of Andrology. 2000;45(3):149-54.

137. van Balen F, Bos HMW. Infertility, culture, and psychology in worldwide perspective. Journal of Reproductive and Infant Psychology. 2004;22(4):245-7.

138. Vanbalen F, Trimboskemper TCM. Factors influencing the well-being of long-term infertile couples. Journal of Psychosomatic Obstetrics and Gynecology. 1994;15(3):157-64.

139. Ulbrich PM, Coyle AT, Llabre MM. Involuntary childlessness and marital adjustment - his and hers. Journal of Sex & Marital Therapy. 1990;16(3):147-58.

140. Derogatis LR, Cleary PA. Confirmation of dimensional structure of scl-90 - study in construct-validation. Journal of Clinical Psychology. 1977;33(4):981-9.

141. Collins A, Freeman EW, Boxer AS, Tureck R. Perceptions of infertility and treatment stress in females as compared with males entering invitro fertilization treatment. Fertility and Sterility. 1992;57(2):350-6.

142. Hjelmstedt A, Andersson L, Skoog-Svanberg A, Bergh T, Boivin J, Collins A. Gender differences in psychological reactions to infertility among couples seeking IVF- and ICSI-treatment. Acta Obstetricia Et Gynecologica Scandinavica. 1999;78(1):42-8.

143. Boivin J, Shoog-Svanberg A, Andersson L, Hjelmstedt A, Bergh T, Collins A. Distress level in men undergoing intracytoplasmic sperm injection versus in-vitro fertilization. Human Reproduction. 1998;13(5):1403-6.

144. Keye WR. Psychosexual responses to infertility. Clinical Obstetrics and Gynecology. 1984;27(3):760-6.

145. Newton CR, Sherrard W, Glavac I. The fertility problem inventory: measuring perceived infertility-related stress. Fertility and Sterility. 1999;72(1).

146. Beck AT, Steer RA, Garbin MG. Psychometric properties of the beck depression inventory - 25 years of evaluation. Clinical Psychology Review. 1988;8(1):77-100.

147. Spanier GB. Measuring dyadic adjustment - new scales for assessing quality of marriage and similar dyads. Journal of Marriage and the Family. 1976;38(1):15-28.

148. Moura-Ramos M, Gameiro S, Canavarro MC, Soares I. Assessing infertility stress: re-examining the factor structure of the Fertility Problem Inventory. Human Reproduction. 2012;27(2):496-505.

149. Nouri K, Litschauer B, Huber JC, Buerkle B, Tiringer D, Tempfer CB. Saliva cortisol levels and subjective stress are not associated with number of oocytes after controlled ovarian hyperstimulation in patients undergoing in vitro fertilization. Fertil Steril. 96. United States: 2011 American Society for Reproductive Medicine. Published by Elsevier Inc; 2011. p. 69-72.

150. Faramarzi M, Pasha H, Esmailzadeh S, Kheirkhah F, Heidary S, Afshar Z. The effect of the cognitive behavioral therapy and pharmacotherapy on infertility stress: a randomized controlled trial. International journal of fertility & sterility. 2013;7(3):199-206.

151. Peng T, Coates R, Merriman G, Zhao Y, Maycock B. Testing the psychometric properties of Mandarin version of the fertility problem inventory (M-FPI) in an infertile Chinese sample. Journal of Psychosomatic Obstetrics and Gynecology. 2011;32(4):173-81.

152. Peterson BD, Newton CR, Feingold T. Anxiety and sexual stress in men and women undergoing infertility treatment. Fertility and Sterility. 2007;88(4):911-4.

153. Slade P, O'Neill C, Simpson AJ, Lashen H. The relationship between perceived stigma, disclosure patterns support and distress in new attendees at an infertility clinic. Human Reproduction. 2007;22(8):2309-17.

154. Donarelli Z, Lo Coco G, Gullo S, Marino A, Volpes A, Allegra A. The role of attachment style, state-anxiety and partneris concerns in predicting infertility-related stress in couples undergoing their first IVF treatment. Human Reproduction. 2011;26:I261-I.

155. Pook M, Rohrle B, Tuschen-Caffier B, Krause W. Why do infertile males use psychological couple counselling? Patient Education and Counseling. 2001;42(3):239-45.

156. Pook M, Tuschen-Caffier B, Krause W. Is infertility a risk factor for impaired male fertility? Human Reproduction. 2004;19(4):954-9.

157. Pook M, Krause W. The impact of treatment experiences on the course of infertility distress in male patients. Human Reproduction. 2005;20(3):825-8.

158. Saito Y, Matsuo H. Trial development of the Cognitive Appraisal Scale for Infertility (CASI) (version 1). Fertility and Sterility. 2009;91(6):2596-601.

159. Craig S. A medical model for infertility counselling. Australian family physician. 1990;19(4):491-2, 5-6, 9-500.

160. Fukuda K, Kobayashi S. A study on a self-rating depression scale (author's transl). Seishin shinkeigaku zasshi = Psychiatria et neurologia Japonica. 1973;75(10):673-9.

161. Farmer GA, Magill PJ, Shaw-Smith R, McVeigh JE, Kennedy SH, Jenkinson C. The development and initial psychometric testing of the ermotional health in infertility questionnaire (EHIQ). Human Reproduction. 2007;22:I87-I8.

162. Verhaak CM, Lintsen BM, Kraaimaat FW, Kremer JA, Braat DD. Who is at risk of developing emotional problems after in vitro fertilization (IVF): Pre treatment identification of risk groups. Fertility and Sterility. 2006;86:S3-S.

163. Spielberger C, Gorsuch R, Lushene R, Vagg P, Jacobs G. Manual for the State-Trait Anxiety Inventory. Palo Alto, CA: Consulting Psychologists Press, Inc; 1983.

164. Beck AT, Guth D, Steer RA, Ball R. Screening for major depression disorders in medical inpatients with the Beck Depression Inventory for Primary Care. Behaviour Research and Therapy. 1997;35(8):785-91.

165. Evers AWM, Kraaimaat FW, van Lankveld W, Jongen PJH, Jacobs JWG, Bijlsma JWJ. Beyond unfavorable thinking: The illness cognition questionnaire for chronic diseases. Journal of Consulting and Clinical Psychology. 2001;69(6):1026-36.

166. Verhaak CM, Smeenk JMJ, van Minnen A, Kremer JAM, Kraaimaat FW. A longitudinal, prospective study on emotional adjustment before, during and after consecutive fertility treatment cycles. Human Reproduction. 2005;20(8):2253-60.

167. van Dam-Baggen R, Kraaimaat F. Assessing social anxiety: The Inventory of Interpersonal Situations (IIS). European Journal of Psychological Assessment. 1999;15(1):25-38.

168. Glover L, Hunter M, Richards JM, Katz M, Abel PD. Development of the fertility adjustment scale. Fertility and Sterility. 1999;72(4):623-8.

169. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. Acta Psychiatrica Scandinavica. 1983;67(6):361-70.

170. Salter-Ling N, Hunter M, Glover L. Donor insemination: exploring the experience of treatment and intention to tell. Journal of Reproductive and Infant Psychology. 2001;19(3):175-86.

171. Mahajan NN, Turnbull DA, Davies MJ, Jindal UN, Briggs NE, Taplin JE. Changes in affect and state anxiety across an in vitro fertilization/intracytoplasmic sperm injection cycle. Fertility and Sterility. 2010;93(2):517-26.

172. Davis DC, Dearman CN. Coping strategies of infertile women. Journal of obstetric, gynecologic, and neonatal nursing : JOGNN / NAACOG. 1991;20(3):221-8.

173. Cohen S, Kamarck T, Mermelstein R. A global measure of perceived stress. Journal of Health and Social Behavior. 1983;24(4).

174. Jalowiec A, Murphy SP, Powers MJ. Psychometric assessment of the jalowiec coping scale. Nursing Research. 1984;33(3):157-61.

175. Jordan C, Revenson TA. Gender differences in coping with infertility: A meta-analysis. Journal of Behavioral Medicine. 1999;22(4):341-58.

176. Schmidt L, Holstein BE, Boivin J, Tjornhoj-Thomsen T, Blaabjerg J, Hald F, et al. High ratings of satisfaction with fertility treatment are common: findings from the Copenhagen Multi-centre Psychosocial Infertility (COMPI) Research Programme. Human Reproduction. 2003;18(12):2638-46.

177. Ware JE, Kosinski M, Gandek B, Aaronson NK, Apolone G, Bech P, et al. The factor structure of the SF-36 Health Survey in 10 countries: Results from the IQOLA Project. Journal of Clinical Epidemiology. 1998;51(11):1159-65.

178. Folkman S, Lazarus RS. Manual for the Ways of Coping Questionnaire. Palo Alto, CA: Consulting Psychologists Press.; 1988.

179. Abbey A, Andrews FM, Halman LJ. Genders role in responses to infertility. Psychology of Women Quarterly. 1991;15(2):295-316.

180. Daniluk JC. Infertility - intrapersonal and interpersonal impact. Fertility and Sterility. 1988;49(6):982-90.

181. Benazon N, Wright J, Sabourin S. Stress, sexual satisfaction, and marital adjustment in infertile couples. Journal of Sex & Marital Therapy. 1992;18(4):273-84.

182. Sundby J, Olsen A, Schei B. Quality of care for infertility patients - an evaluation of a plan for a hospital investigation. Scandinavian Journal of Social Medicine. 1994;22(2):139-44.

183. Cousineau TM, Green TC, Corsini EA, Barnard T, Seibring AR, Domar AD. Development and validation of the Infertility self-efficacy scale. Fertility and Sterility. 2006;85(6):1684-96.

184. Arslan-Ozkan I, Okumus H, Buldukoglu K. A randomized controlled trial of the effects of nursing care based on Watson's Theory of Human Caring on distress, self-efficacy and adjustment in infertile women. Journal of Advanced Nursing. 2014;70(8):1801-12.

185. Pasha H, Faramarzi M, Esmailzadeh S, Kheirkhah F, Salmalian H. Comparison of pharmacological and nonpharmacological treatment strategies in promotion of infertility self-efficacy scale in infertile women: A randomized controlled trial. Iranian Journal of Reproductive Medicine. 2013;11(6):495-502.

186. Turner K, Reynolds-May MF, Zitek EM, Tisdale RL, Carlisle AB, Westphal LM. Stress and Anxiety Scores in First and Repeat IVF Cycles: A Pilot Study. Plos One. 2013;8(5).

187. Galhardo A, Cunha M, Pinto-Gouveia J. Measuring self-efficacy to deal with infertility: Psychometric properties and confirmatory factor analysis of the portuguese version of the infertility self-efficacy scale. Research in Nursing & Health. 2013;36(1):65-74.

188. Pinto-Gouveia J, Galhardo A, Cunha M, Matos M. Protective emotional regulation processes towards adjustment in infertile patients. Human Fertility. 2012;15(1):27-34.

189. Kovarova P, Smith CA, Turnbull DA. An exploratory study of the effect of acupuncture on self-efficacy for women seeking fertility support. Explore-the Journal of Science and Healing. 2010;6(5):330-4.

190. Klonoff-Cohen H, Natarajan L, Klonoff E. Validation of a new scale for measuring concerns of women undergoing assisted reproductive technologies (CART). Journal of Health Psychology. 2007;12(2):352-6.

191. Gameiro S, Canavarro MC, Boivin J. Patient centred care in infertility health care: Direct and indirect associations with wellbeing during treatment. Patient Education and Counseling. 2013;93(3):646-54.

192. Pedro J, Canavarro MC, Boivin J, Gameiro S. Positive experiences of patient-centred care are associated with intentions to comply with fertility treatment: findings from the validation of the Portuguese version of the PCQ-Infertility tool. Human Reproduction. 2013;28(9):2462-72.

193. Boivin J, Takefman J, Braverman A. The Fertility Quality of Life (FertiQoL) tool: development and general psychometric properties. Fertility and Sterility. 2011;96(2):409-U79.

194. Sut HK, Kaplan PB. Quality of life in women with infertility via the FertiQoL and the Hospital Anxiety and Depression Scales. Nursing & Health Sciences. 2015;17(1):84-9.

195. Smith NK, Madeira J, Millard HR. Sexual Function and Fertility Quality of Life in Women Using In Vitro Fertilization. Journal of Sexual Medicine. 2015;12(4):985-93.

196. Cserepes RE, Koroesi T, Bugan A. Characteristics of infertility specific quality of life in Hungarian couples. Orvosi Hetilap. 2014;155(20):783-8.

197. Karabulut A, Ozkan S, Oguz N. Predictors of fertility quality of life (FertiQoL) in infertile women: analysis of confounding factors. European Journal of Obstetrics & Gynecology and Reproductive Biology. 2013;170(1):193-7.

198. Heredia M, Tenias JM, Rocio R, Amparo F, Calleja MA, Valenzuela JC. Quality of life and predictive factors in patients undergoing assisted reproduction techniques. European Journal of Obstetrics & Gynecology and Reproductive Biology. 2013;167(2):176-80.

199. Huppelschoten AG, van Duijnhoven NTL, Hermens RPMG, Verhaak C, Kremer JAM, Nelen WLDM. Improving patient-centeredness of fertility care using a multifaceted approach: study protocol for a randomized controlled trial. Trials. 2012;13.

200. Verhaak CM, Aarts JWM, Boivin J, Kremer JAM, van Empel IWH. Measuring quality of life in infertility using the FertiQoL questionnaire. Human Reproduction. 2010;25:I16-I7.

201. Valsangkar S, Bodhare T, Bele S, Sai S. An evaluation of the effect of infertility on marital, sexual satisfaction indices and health-related quality of life in women. Journal of human reproductive sciences. 2011;4(2):80-5.

202. Romera N, Llacer J, Aula M, Canevelli S, Ten J, Bernabeu R. Assessment quality of life in cross-border patients using the new tool "fertiqol". Human Reproduction. 2010;25:I77-I8.

203. Preamble to the Constitution of the World Health Organization as adopted by the International Health Conference, New York, 19 June - 22 July 1946; signed on 22 July 1946 by the representatives of 61 States., (1946).

204. Watson D, Clark LA, Tellegen A. Development and validation of brief measures of positive and negative affect - the panas scales. Journal of Personality and Social Psychology. 1988;54(6).

205. Boivin J, Lancastle D. Medical waiting periods: imminence, emotions and coping. Women's health (London, England). 2010;6(1):59-69.

206. Schmidt L. Social and psychological consequences of infertility and assisted reproduction - what are the research priorities? Human Fertility. 2009;12(1):14-20.

207. Eugster A, Vingerhoets A. Psychological aspects of in vitro fertilization: a review. Social Science & Medicine. 1999;48(5):575-89.

208. Hashemi S, Simbar M, Ramezani-Tehrani F, Shams J, Majd HA. Anxiety and success of in vitro fertilization. Eur J Obstet Gynecol Reprod Biol. 164. Ireland: 2012 Elsevier Ireland Ltd; 2012. p. 60-4.

209. Olivius C, Friden B, Borg G, Bergh C. Why do couples discontinue in vitro fertilization treatment? A cohort study. Fertility and Sterility. 2004;81(2):258-61.

210. Verberg MFG, Eijkemans MJC, Heijnen EMEW, Broekmans FJ, de Klerk C, Fauser BCJM, et al. Why do couples drop-out from IVF treatment? A prospective cohort study. Human Reproduction. 2008;23(9):2050-5.

211. Boivin J. A review of psychosocial interventions in infertility. Social Science & Medicine. 2003;57(12):2325-41.

212. Verhaak CM, Lintsen AME, Evers AWM, Braat DDM. Who is at risk of emotional problems and how do you know? Screening of women going for IVF treatment. Human Reproduction. 2010;25(5):1234-40.

213. Cooper BC, Gerber JR, McGettrick AL, Johnsom JV. Perceived infertility-related stress correlates with in vitro fertilization outcome. Fertility and Sterility. 2005;84:S232-S.

214. Domar AD, Zuttermeister PC, Friedman R. The psychological impact of infertility - a comparison with patients with other medical conditions. Journal of Psychosomatic Obstetrics and Gynecology. 1993;14:45-52.

215. Reading AE, Chang LC, Kerin JF. Psychological state and coping styles across an IVF treatment cycle. Journal of Reproductive and Infant Psychology. 1989;7(2):95-103.

216. vanBalen F, Naaktgeboren N, TrimbosKemper TCM. In-vitro fertilization: The experience of treatment, pregnancy and delivery. Human Reproduction. 1996;11(1):95-8.

217. Ardenti R, Campari C, Agazzi L, La Sala GB. Anxiety and perceptive functioning of infertile women during in-vitro fertilization: exploratory survey of an Italian sample. Human Reproduction. 1999;14(12):3126-32.

218. Brod M, Verhaak CM, Wiebinga CJ, Gerris J, Hoomans EHM. Improving clinical understanding of the effect of ovarian stimulation on women's lives. Reproductive Biomedicine Online. 2009;18(3):391-400.

219. Huisman D, Raymakers X, Hoomans EHM. Understanding the burden of ovarian stimulation: fertility expert and patient perceptions. Reproductive Biomedicine Online. 2009;19:5-10.

220. Miall CE. The stigma of involuntary childlessness. Social Problems. 1986;33(4):268-82.

221. Sabatelli RM, Meth RL, Gavazzi SM. Factors mediating the adjustment to involuntary childlessness. Family Relations. 1988;37(3):338-43.

222. Bhatti LI, Fikree FF, Khan A. The quest of infertile women in squatter settlements of Karachi, Pakistan: a qualitative study. Social Science & Medicine. 1999;49(5):637-49.

223. Holter H, Anderheim L, Bergh C, Moller A. First IVF treatment-short-term impact on psychological well-being and the marital relationship. Human Reproduction. 2006;21(12):3295-302.

224. Connolly KJ, Edelmann RJ, Bartlett H, Cooke ID, Lenton E, Pike S. AN Evaluation of counseling for couples undergoing treatment for in-vitro fertilization. Human Reproduction. 1993;8(8):1332-8.

225. Dudok De Wit AC, Snoek FJ, De Moree S, Schats R, Goverde A. Coping with IVF: Perceived support during and after treatment: A retrospective study. Human Reproduction (Oxford). 1992;7(SUPPL. 2):205-.

226. Yong P, Martin C, Thong J. A comparison of psychological functioning in women at different stages of in vitro fertilization treatment using the mean affect adjective check list. Journal of Assisted Reproduction and Genetics. 2000;17(10):553-6.

227. de Klerk C, Heijnen E, Macklon NS, Duivenvoorden HJ, Fauser B, Passchier J, et al. The psychological impact of mild ovarian stimulation combined with single embryo transfer compared with conventional IVF. Human Reproduction. 2006;21(3):721-7.

228. Skiadas CC, Terry K, De Pari M, Geoghegan A, Lubetsky L, Levy S, et al. Does emotional support during the luteal phase decrease the stress of in vitro fertilization? Fertility and Sterility. 2011;96(6):1467-72.

229. Domar AD, Smith K, Conboy L, Iannone M, Alper M. A prospective investigation into the reasons why insured United States patients drop out of in vitro fertilization treatment. Fertility and Sterility. 2010;94(4):1457-9.

230. Eisenberg ML, Smith JF, Millstein SG, Nachtigall RD, Adler NE, Pasch LA, et al. Predictors of not pursuing infertility treatment after an infertility diagnosis: examination of a prospective US cohort. Fertility and Sterility. 2010;94(6):2369-71.

231. Mazure CM, Greenfeld DA. Psychological studies of invitro fertilization embryo transfer participants. Journal of in Vitro Fertilization and Embryo Transfer. 1989;6(4):242-56.

232. Halman LJ, Andrews FM, Abbey A. Gender differences and perceptions about childbearing among infertile couples. Journal of obstetric, gynecologic, and neonatal nursing : JOGNN / NAACOG. 1994;23(7):593-600.

233. Wright J, Bissonnette F, Duchesne C, Benoit J, Sabourin S, Girard Y. Psychosocial distress and infertility - men and women respond differently. Fertility and Sterility. 1991;55(1):100-8.

234. Newton CR, Hearn MT, Yuzpe AA. Psychological-assessment and follow-up after invitro fertilization - assessing the impact of failure. Fertility and Sterility. 1990;54(5):879-86.

235. Lalos A, Lalos O, Jacobsson L, Vonschoultz B. The psychosocial impact of infertility 2 years after completed surgical-treatment. Acta Obstetricia Et Gynecologica Scandinavica. 1985;64(7):599-604.

236. Fenster L, Katz DF, Wyrobek AJ, Pieper C, Rempel DM, Oman D, et al. Effects of psychological stress on human semen quality. Journal of Andrology. 1997;18(2):194-202.

237. Hjollund NHI, Bonde JPE, Henriksen TB, Giwercmam A, Olsen J, Danish First Pregnancy P. Reproductive effects of male psychologic stress. Epidemiology. 2004;15(1):21-7.

238. Dooley M, Dineen T, Sarma K, Nolan A. The psychological impact of infertility and fertility treatment on the male partner. Human Fertility. 2014;17(3):203-9.

239. King JA, Rosal MC, Ma YS, Reed GW. Association of stress, hostility and plasma testosterone levels. Neuroendocrinology Letters. 2005;26(4):355-60

240. Klimek M, Pabian W, Tomaszewska B, Kolodziejczyk J. Levels of plasma ACTH in men from infertile couples. Neuroendocrinology Letters. 2005;26(4):347-50.

241. Eskiocak S, Gozen AS, Kilic AS, Mollat S. Association between mental stress & some antioxidant enzymes of seminal plasma. Indian Journal of Medical Research. 2005;122(6):491-6.

242. Eskiocak S, Gozen AS, Taskiran A, Kilic AS, Eskiocak M, Gulen S. Effect of psychological stress on the L-arginine-nitric oxide pathway and semen quality. Brazilian Journal of Medical and Biological Research. 2006;39(5):581-8.

243. Karlidere T, Bozkurt A, Yetkin S, Doruk A, Suetcigil L, Oezmenler KN, et al. Is there gender difference in infertile couples with no axis one psychiatric disorder in context of emotional symptoms, social support and sexual function? Turk Psikiyatri Dergisi. 2007;18(4):311-22.

244. Khademi A, Alleyassin A, Amini M, Ghaemi M. Evaluation of sexual dysfunction prevalence in infertile couples. Journal of Sexual Medicine. 2008;5(6):1402-10.

245. Bartolo A, Reis S, Monteiro S, Leite R, Montenegro N. Psychological Adjustment of Infertile Men Undergoing Fertility Treatments: An Association With Sperm Parameters. Archives of Psychiatric Nursing. 2016;30(5):521-6.

246. Vellani E, Colasante A, Mamazza L, Minasi MG, Greco E, Bevilacqua A. Association of state and trait anxiety to semen quality of in vitro fertilization patients: a controlled study. Fertility and Sterility. 2013;99(6):1565-+.

247. Bongso TA, Ng SC, Mok H, Lim MN, Teo HL, Wong PC, et al. Effect of sperm motility on human invitro fertilization. Archives of Andrology. 1989;22(3):185-90.

248. Kruger TF, Menkveld R, Stander FSH, Lombard CJ, Vandermerwe JP, Vanzyl JA, et al. Sperm morphological features as a prognostic factor in invitro fertilization. Fertility and Sterility. 1986;46(6):1118-22.

249. Donnelly ET, Lewis SEM, McNally JA, Thompson W. In vitro fertilization and pregnancy rates: the influence of sperm motility and morphology on IVF outcome. Fertility and Sterility. 1998;70(2):305-14.

250. McEwan KL, Costello CG, Taylor PJ. Adjustment to infertility. Journal of Abnormal Psychology. 1987;96(2):108-16.

251. Tuzer V, Tuncel A, Goka S, Bulut SD, Yuksel FV, Atan A, et al. Marital adjustment and emotional symptoms in infertile couples: gender differences. Turkish Journal of Medical Sciences. 2010;40(2):229-37.

252. Peterson BD, Newton CR, Rosen KH. Examining congruence between partners' perceived infertility-related stress and its relationship to marital adjustment and depression in infertile couples. Family Process. 2003;42(1):59-70.

253. Peterson BD, Pirritano M, Block JM, Schmidt L. Marital benefit and coping strategies in men and women undergoing unsuccessful fertility treatments over a 5-year period. Fertility and Sterility. 2011;95(5):1759-U295.

254. Schmidt L, Holstein B, Christensen U, Boivin J. Does infertility cause marital benefit? An epidemiological study of 2250 women and men in fertility treatment. Patient education and counseling. 2005;59(3):244-51.

255. Dennerstein L, Morse C. Psychological issues in ivF. Clinics in Obstetrics and Gynaecology. 1985;12(4):835-46.

256. Hearn MT, Yuzpe AA, Brown SE, Casper RF. Psychological characteristics of invitro fertilization participants. American Journal of Obstetrics and Gynecology. 1987;156(2):269-74.

257. Nachtigall RD, Becker G, Wozny M. The effects of gender-specific diagnosis on mens and womens response to infertility. Fertility and Sterility. 1992;57(1):113-21.

258. Furman I, Parra L, Fuentes A, Devoto L. Men's participation in psychologic counseling services offered during in vitro fertilization treatments. Fertility and Sterility. 2010;94(4):1460-4.

259. Holter H, Anderheim L, Bergh C, Moeller A. The psychological influence of gender infertility diagnoses among men about to start IVF or ICSI treatment using their own sperm. Human Reproduction. 2007;22(9):2559-65.

260. Morrow KA, Thoreson RW, Penney LL. Predictors of psychological distress among infertility clinic patients. Journal of Consulting and Clinical Psychology. 1995;63(1):163-7.

261. Berg BJ, Wilson JF. Psychiatric morbidity in the infertile population - a reconceptualization. Fertility and Sterility. 1990;53(4):654-61.

262. Harrison RF, Omoore RR, Omoore AM. Stress and fertility - some modalities of investigation and treatment in couples with unexplained infertility in dublin. International Journal of Fertility. 1986;31(2):153-9.

263. Phillips DL, Segal BE. Sexual status and psychiatric symptoms. American Sociological Review. 1969;34(1):58-72.

264. Connolly KJ, Edelmann RJ, Cooke ID. Distress and marital problems associated with infertility. Journal of Reproductive and Infant Psychology. 1987;5(1):49-57.

265. Reading AE. Decision-making and invitro fertilization - the influence of emotional state. Journal of Psychosomatic Obstetrics and Gynecology. 1989;10(2):107-12.

266. Thiering P, Beaurepaire J, Jones M, Saunders D, et al. Mood state as a predictor of treatment outcome after in vitro fertilization/embryo transfer technology (IVF/ET). Journal of Psychosomatic Research. 1993;37(5):481-91.

267. Lee TY, Sun GH, Chao SC. The effect of an infertility diagnosis on the distress, marital and sexual satisfaction between husbands and wives in Taiwan. Human Reproduction. 2001;16(8):1762-7.

268. Shatford LA, Hearn MT, Yuzpe AA, Brown SE, Casper RF. Psychological correlates of differential infertility diagnosis in an invitro fertilization program. American Journal of Obstetrics and Gynecology. 1988;158(5):1099-107.

269. Vieyra MA, Tennen H, Affleck G, Allen G, McCann L. The effects of gender and measurement strategy on causal attributions for infertility. Basic and Applied Social Psychology. 1990;11(2):219-32.

270. Salvatore P, Gariboldi S, Offidani A, Coppola F, Amore M, Maggini C. Psychopathology, personality, and marital relationship in patients undergoing in vitro fertilization procedures. Fertility and Sterility. 2001;75(6):1119-25.

271. Ferreira M, Sanchez ET, Gatimel N, Fajau C, Lesourd F, Bujan L, et al. Parenthood and separation in couples 6 years after their first infertility consultation. European Journal of Obstetrics & Gynecology and Reproductive Biology. 2016;198:7-11.

272. Kjaer T, Albieri V, Jensen A, Kjaer SK, Johansen C, Dalton SO. Divorce or end of cohabitation among Danish women evaluated for fertility problems. Acta Obstetricia Et Gynecologica Scandinavica. 2014;93(3):269-76.

273. Domar AD, Clapp D, Slawsby E, Kessel B, Orav J, Freizinger M. The impact of group psychological interventions on distress in infertile women. Health Psychology. 2000;19(6):568-75.

274. Gameiro S, Boivin J, Dancet E, de Klerk C, Emery M, Lewis-Jones C, et al. ESHRE guideline: routine psychosocial care in infertility and medically assisted reproduction-a guide for fertility staff. Human Reproduction. 2015;30(11):2476-85.

275. de Liz TM, Strauss B. Differential efficacy of group and individual/couple psychotherapy with infertile patients. Human Reproduction. 2005;20(5):1324-32

276. Hammerli K, Znoj H, Barth J. Psychological Interventions for Infertile Couples: Does Gender Matter? Geburtshilfe Und Frauenheilkunde. 2011;71(10):838-46.

277. Frederiksen Y, Farver-Vestergaard I, Skovgard NG, Ingerslev HJ, Zachariae R. Efficacy of psychosocial interventions for psychological and pregnancy outcomes in infertile women and men: a systematic review and meta-analysis. Bmj Open. 2015;5(1).

278. Tuschen-Caffier B, Florin I, Krause W, Pook M. Cognitive-behavioral therapy for idiopathic infertile couples. Psychotherapy and Psychosomatics. 1999;68(1):15-21.

279. Domar AD, Rooney KL, Wiegand B, Orav EJ, Alper MM, Berger BM, et al. Impact of a group mind/body intervention on pregnancy rates in IVF patients. Fertility and Sterility. 2011;95(7):2269-73.

280. Hughes EG, da Silva AM. A pilot study assessing art therapy as a mental health intervention for subfertile women. Human Reproduction. 2011;26(3):611-5

281. Matthiesen S, Klonoff-Cohen H, Zachariae R, Jensen-Johansen MB, Nielsen BK, Frederiksen Y, et al. The effect of an expressive writing intervention (EWI) on stress in infertile couples undergoing assisted reproductive technology (ART) treatment: A randomized controlled pilot study. British Journal of Health Psychology. 2012;17:362-78.

282. Schmidt L, Holstein BE, Christensen U, Boivin J. Communication and coping as predictors of fertility problem stress: cohort study of 816 participants who did not achieve a delivery after 12 months of fertility treatment. Human Reproduction. 2005;20(11):3248-56.

283. de Klerk C, Hunfeld JAM, Duivenvoorden HJ, den Outer MA, Fauser B, Passchier J, et al. Effectiveness of a psychosocial counselling intervention for first-time IVF couples: a randomized controlled trial. Human Reproduction. 2005;20(5):1333-8.

284. Ockhuijsen H, van den Hoogen A, Eijkemans M, Macklon N, Boivin J. The impact of a self-administered coping intervention on emotional well-being in women awaiting the outcome of IVF treatment: a randomized controlled trial. Human Reproduction. 2014;29(7):1459-70.

**Appendix 1: Abstracts from the study**

**Abstract submitted to ESHRE conference in London 2013**

Title: Investigation of the impact of emotional health on pregnancy rates after assisted conception

Authors: Tamhankar, V. Jones, GL. Magill, P. Skull, J. Ledger, W.

Study Question: Does emotional health as assessed by Emotional Health in Infertility Questionnaire (EM-INFERT) have an effect on the outcome of in-vitro fertilization (IVF) treatment.

Summary Answer: EM-INFERT scores before and during IVF treatment had no significant impact on the outcome of IVF and post treatment EM-INFERT scores reduced significantly in patients who did not conceive.

What is known already: Studies examining the relationship between stress and IVF have been inconsistent. Most used generic questionnaires not designed for infertility and addressed concepts such as anxiety and depression that do not characterise the emotional health of infertile couples. Some studies used infertility-specific questionnaires that had limitations in their construction methods. EM-INFERT is a comprehensive, validated infertility-specific instrument with well-defined construction methods that can be used accurately to measure emotional health in nine domains in infertile couples.

Study design, size, duration: 335 patients having IVF from June 2011 to December 2012 were approached for this prospective longitudinal cohort study. 300 patients consented for the study and were asked to complete EM-INFERT questionnaire pre-treatment, during treatment and after the pregnancy result. 33 patients could not complete their IVF cycle for medical reasons.

Methods: Emotional health was assessed in nine domains: personal strain, partner relationship, sexuality, social support, confidence in treatment, guilt and blame, financial strain, need for parenthood and couple concordance. The mean EM-INFERT scores were compared between the pregnant and non-pregnant patients before, during and after IVF cycle.

Main results and the role of chance: EM-INFERT scores in 267 couples were analysed at the start of ovarian stimulation. All couples completed the pre-treatment questionnaires; while 124 patients completed all three sets of questionnaires. The overall pregnancy rate from the treatment cycle was 33.7%. The EM-INFERT scores, pre-treatment and during treatment, in all its domains were higher in the pregnant patients than the non-pregnant cohort (pre-treatment scores: 65.6 vs. 63.6, p=0.3; during treatment scores: 67.5 vs. 64.7, p= 0.2), but the difference was not statistically significant. EM-INFERT scores declined significantly after the pregnancy result in the patients who did not conceive (pre-treatment score: 65.4 to post-treatment score: 61.1, p=0.001). This was distinct from the patients who conceived (pre-treatment score: 63.3 to post-treatment score: 64.8, p=0.3).

Limitations: 35 couples cited stress as the reason for declining to participate in the study. Their EM-INFERT scores are unknown and the study cohort may have a bias towards higher pre-treatment EM-INFERT scores.

Wider implications of the findings: In this large cohort study, we used an accurate comprehensive instrument to measure infertility-specific emotional health. In contrast to previous studies, which measured only depression or anxiety, EM-INFERT measured specific factors that concern infertile couples and still found no relationship between emotional health and IVF outcome. Our study also shows that failed IVF treatment has significant impact on emotional health and these patients may benefit with psychological interventions.

Study funding/competing interest(s): Part funding received from Sheffield Teaching Hospitals NHS Trust Small Grants Scheme. No competing interests to declare.

Trial registration number: Not a randomised control trial. Regional Ethics Committee reference number: 10/H1308/46.

**Abstract submitted to BFS conference in Sheffield 2014**

Gender differences in emotional distress among infertile couples undergoing IVF treatment.

Authors: Tamhankar, V. Jones, GL. Magill, P. Skull, J. Ledger, W.

**Introduction:** It is generally believed that infertility evokes more psychological distress for women than for men. Women tend to be more anxious, likely to get more depressed and seek support more readily. It is important to understand the gender differences in emotional impact of infertility and IVF so as to tailor appropriate psychological interventions. The aim of this study was to compare the psychological distress across various domains between infertile men and women seeking IVF treatment.

**Methods:** Emotional health in infertile couples was assessed using validated infertility specific questionnaires. Couples completed the questionnaires at three times during their IVF cycle: at the start of the ovarian stimulation, oocyte recovery and 48 hours after the pregnancy result. Questionnaire scores were compared between men and women at all three time points and across various domains. Further comparisons were also made between male and female causes of infertility.

**Results:** A total of 267 women and 251 men participated in the study. Overall, men had higher emotional health scores than women undergoing IVF (73 vs. 64.2; p<0.05). Despite this, men had significantly higher negative impact of IVF on their marital relationship as compared to women (p=0.01). Female cause of infertility evoked significantly higher guilt and blame in women (p=0.005).There was no such effect in men with male cause of infertility. Both men and women experienced significant emotional distress following a negative result (p<0.05).

**Conclusion:** This study has shown that women experience greater infertility-related distress as compared to men and thereby need more psychological support during their IVF treatment. It also highlights the variation in the way men and women react and cope with infertility and IVF treatment. This is important while designing targeted psychological interventions in these couples.

**Abstract submitted to ESHRE conference in in Helsinki 2016**

Title: Can pre-treatment emotional health predict pregnancy rates after IVF?

Authors: Tamhankar, V. Jones, GL. Jacques, R. Magill, P. Metwally M. Skull, J. Ledger, W.

Study Question: Can pre-treatment emotional health predict pregnancy rates after in-vitro fertilization (IVF) treatment.

Summary Answer: Pre-treatment emotional health does not predict pregnancy rates after IVF.

What is known already: The emotional burden of infertility is increasingly becoming a significant priority. Studies on psychological interventions suggest a link between emotional health improvement and IVF outcome. The evidence from existing literature demonstrates higher levels of anxiety and depression in IVF patients, but the effect this has on the conception rates is inconclusive. Existing studies have methodological limitations due to use of generic tools to assess emotional health which cannot capture the complex nature of fertility specific distress. There is a need for large cohort study to examine this relationship using a fertility specific tool.

Study design, size, duration: The aim of this study is to investigate if emotional health of patients can be used to predict IVF outcome. The study was designed by recruiting a prospective cohort of 414 women undergoing IVF between June 2011 till February 2015. The treatment cycle of 35 women were cancelled at different stages due to medical reasons. 379 patients completed the treatment cycle. An intention to treat analysis was performed

Methods: Women undergoing IVF were asked to complete a set of patient-reported outcomes at the start of the cycle which included Emotional Health in Infertility Questionnaire(EM-INFERT) , Perceived Stress Scale, Positive and Negative Affect and Fertility Problem Inventory. Clinical pregnancy rates and live birth rates were compared between women with low, average and high emotional health. We then used logistic regression to see if pre-treatment emotional health can predict the probability of pregnancy.

Main results and the role of chance: 414 women undergoing IVF were divided into three tertiles according to their emotional health profile: poor emotional health (EM-INFERT 13.13-56.88; n=140), average emotional health (EM-INFERT 57.5-71.88; n=139) and high emotional health (72.5-97.50; n=135). The three groups were similar with regards to female age, BMI, previous live births and proportion of patients having their first IVF. The overall pregnancy rate is this study group was 31.4%. Clinical pregnancy in patients with low emotional health was statistically similar to patients with high emotional health. (27.9% vs. 31.1% p=0.597). The clinical pregnancy rate was lowest (27.9%) in women with poor emotional health, but the highest pregnancy rates were found in women with average emotional health (36.2%). This difference was not statistically significant (27.9% vs.36.2 % p=0.199). Logistic regression showed that EM-INFERT scores did not predict the clinical pregnancy in this study group.

Limitations: Some patients who declined to participate, cited stress about the treatment outcome as the main reason. This indicates selection bias as some patients with poor emotional health have not been included. About 60% of patients were recruited during first cycle of IVF which is usually a time of optimism and positive emotions.

Wider implications of the findings: Our study has helped to identify a group of patients with poor emotional health at the start of IVF, who are at risk of significant psychological distress following a failed cycle. Psychological interventions may be indicated in this group and help reduce dropout rates.

Study funding/competing interest(s): Part funding received from Sheffield Teaching Hospitals NHS Trust Small Grants Scheme. No competing interests to declare.

Trial registration number: Not a randomised control trial. Regional Ethics Committee reference number: 10/H1308/46.

**Appendix 2: Patient Information Sheet**



**Patient Introduction Sheet**

Dear …………………..

Research project number **10/H1308/46**

**Title:** Emotional health and pregnancy rates following assisted conception techniques.

We are writing to you to ask for your help with a research study being carried out at the University of Sheffield. The aim of the study is to try and understand whether distress has any effect on the success of IVF treatment. Please find enclosed a research information leaflet which explains this study in some detail.

The research will involve completing four questionnaires on a total of three occasions before, during and after IVF treatment. We would be grateful if you would read the enclosed patient information sheet. If you are happy to participate please would you complete the enclosed consent form and return it to the research team in Sheffield in the pre-paid envelope provided.

Please do not hesitate to contact me should you require any further information.

With kind regards

Yours sincerely

**Patrick Magill**



**Patient Information Sheet**

Researchers: **Dr Vidya Tamhankar**

Dr Georgina Jones

Dr Patrick Magill

**Title:** Emotional health and pregnancy rates following assisted conception techniques.**.**

**An invitation to take part**

We would like to invite you to take part in our study. Before you decide, it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information and, if you wish, discuss it with friends, relatives or your GP. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part. If you would like further information please contact **Dr Vidya Tamhankar on 07954 333862** or Dr Patrick Magill on 07980 256908.

**What is the purpose of the study?**

The purpose of this study is to find out whether distress felt by couples with infertility can affect the chances of success of IVF.

Infertility has long been known to be stressful. Many couples describe infertility as having very wide effects across their lives, involving family, work and plans for the future. This stress can lead to distress (sometimes called low emotional health) and researchers have suspected for a long time an effect on the chances of becoming pregnant. Researchers in Oxford have developed a new questionnaire (called the Emotional Health in Infertility Questionnaire or EM-INFERT) to measure emotional health. We plan to use this to see whether the scores from the questionnaire affect the chance of pregnancy after IVF.

**What will I have to do if I take part?**

If you do decide to take part, we would ask both you and your partner to complete the EM-INFERT and three other questionnaires on three occasions – at the start of your IVF cycle, on the day of egg collection and two days after the result of your pregnancy test. The Emotional Health in Infertility Questionnaire (EM-INFERT) has 40 questions designed to measure emotional strain in couples with infertility. The areas covered include personal strain, social support, confidence in treatment and the need for privacy. It should take approximately 15 minutes to complete. The Fertility Problem Inventory (FPI) was designed to measure the stress that can result from infertility. It has 46 questions which cover areas such as social concern, sexual concern and the need for parenthood. It should take approximately 10 to 15 minutes to complete.

The Perceived Stress Scale (PSS) is a measure of how stressful situations in your life appear to be. It has 10 questions and should take about one minute to complete. Finally the Positive and Negative Affect Schedule (PANAS) is designed to measure both positive feelings (for example: interested, enthusiastic, inspired and attentive) and negative feelings (for example: distressed, upset and nervous). It has 20 questions in total and should take around 5 minutes to complete.

We would ask you to leave the first two sets of completed questionnaires at the IVF Clinic during one of your routine visits and to post the final set to **Dr Vidya Tamhankar.**

We would also ask for other information such as your ages, the cause of infertility, for how long it has lasted and how many previous treatments you have had. With your permission we would check your notes for other information that might affect the chances of pregnancy following IVF.

You **do not** need to attend clinic more often than usual.

You **would not** need to have any extra physical examinations or investigations.

You **would not** need to take any additional medicines.

The scores from the four questionnaires will be analysed and compared to see how well these agree with each other and to see whether low scores, which indicate a lot of stress, tend to be associated with less successful IVF treatment. A summary of the results of the research will be sent to you if you would be interested to see these.

**Why me?**

We hope that approximately 450 couples with infertility who are having IVF in Sheffield will take part in this research. As a lot of factors can affect whether IVF is successful or not, we need to involve a large number of couples with infertility to see if emotional health is one of the deciding factors or not. We are contacting you because we understand that you are waiting for IVF. If you do decide to take part, your information and completed questionnaires would be very valuable to our work.

**What about confidentiality?**

All reasonable steps will be taken to ensure confidentiality. If you decide to take part, your name will be kept on the paper copy of your consent form. It will be linked with a unique study number and all other documents will be identified only by your number. Your name will not be entered into a computer database for the purposes of this research. All the information which is collected about you during the course of the research will be kept strictly confidential. When the results are published, no names will be used, and it will not be possible to identify anyone who has taken part.

**Would I be examined?**

No. Taking part **would not** include any type of physical examination. Equally, it **would not** include any type of investigation such as blood tests or X-rays, or any consumption of tablets or medicines.

**What are the possible risks of taking part?**

There should be no risks of taking part in this study.

**Do I have to take part?**

No. Taking part is voluntary. If you would prefer not to take part, you do not have to give a reason. Your doctor would not be upset and your IVF treatment would not be affected in any way.

If you agree to take part, but later change your mind, you may withdraw at any time. This would not affect your care in any way. However, with your permission we would still wish to retain your data (if the interview had already been carried out) in the analysis of this research.

**What will happen to the results of the research study?**

The results will help us better understand how distress, or low emotional health, affects the changes of pregnancy after IVF. The results will be written up in a report at the end of the research and we hope that they will also be published in a scientific journal. The results will also be a great help in the next stage of the research which will be to find out what can be done to help couples who find infertility very stressful and whether any forms of assistance can help to increase pregnancy rates.

We would like to emphasise that it will not be possible to identify you from any report of this study.

If you would like a copy of the research report we will send this to you.

**Who is organising and funding the research?**

Dr Georgina Jones (Sheffield University) is organising the research in collaboration with Dr. Patrick Magill from Oxford University.

**What if I wish to complain about the way in which this study has been conducted?**

If you have any cause to complain about any aspect of the way in which you have been approached or treated during the course of this study, the normal National Health Service complaints mechanisms are available to you and are not compromised in any way because you have taken part in a research study.

If you have any complaints or concerns please contact the project co-ordinator

Dr. Georgina Jones Tel: 0114 2220806 of 2268515 Sheffield University

Otherwise you can use the normal University complaints procedure and contact the following person:

Dr. D. Fletcher Tel: 0114 2221100 Research Consultative Unit,

Sheffield University

Otherwise you can use the normal hospital complaints procedure and contact the following person:  
Professor C. Welsh Tel: 0114 2712923 Royal Hallamshire Hospital,

Sheffield

**What do I do now?**

Now that you have read the information sheet, we would like our researcher **(Dr Vidya Tamhankar)** to telephone you about the study. If you are happy to be telephoned please would you sign the consent form. She will then contact you about the study within the next few days and if you are happy to participate, arrange a time that would be convenient for you to be interviewed.

However, if you would like to discuss this information with your family, friends, GP or you would like to contact me to discuss this study further, please do. My contact details are at the top of the sheet. Please leave your details and I will get back to you.

If you do not wish to take part, your clinical care will not be affected in any way.

Thank you.

**Patrick Magill**

University of Sheffield

**Appendix 3: Consent form**



**Re: Patient Consent Form (Telephone Contact)**

**Emotional health and pregnancy rates following assisted conception techniques.**

Please read the following. If you are happy to discuss this study with the researcher **(Dr Vidya Tamhankar)** please would you complete your name and contact details at the bottom of the page and return it in the pre-paid envelope enclosed. Thank you very much for your time.

1. I have read and understood the patient information sheet and am happy to be telephoned in the first instance about this study.

2. I understand that I am under no obligation to take part in this research.

3. I understand that I am free to withdraw from the study at any time.

4. I understand that all the information that is collected will be kept strictly confidential.

Name………………………………………………………

Address…………………………………….……………...

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Postcode…………………………………………………..

Telephone Number………………………………………..

Best time of day/evening to call ? ……………………….



**Patient Consent Form (Completing questionnaires)**

**Emotional health and pregnancy rates following assisted conception techniques.**

Please read the following. If you are happy to take part in this research please would you sign the form and complete your details at the bottom of the page. Thank you.

1. I have read and understood the patient information sheet and am happy to participate and be interviewed in this study.

2. I understand that I am under no obligation to take part in this research.

3. I understand that I am free to withdraw from the study at any time, without giving reason, and without my future care being affected.

4. I understand that all the information that is collected will be kept strictly confidential.

5. I understand that relevant sections of my medical notes and data collected during the study, may be looked at by individuals involved in the research, from regulatory authorities or from the NHS Trust, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records.

Signed …………………………………………………… Date………………

Name………………………………………………………

Address…………………………………….……………...

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Postcode…………………..

**Appendix 4: Ethics approval**

**NRES Committee Yorkshire & The Humber - Sheffield**

Yorkshire and the Humber REC Office

First Floor, Millside

Mill Pond Lane

Meanwood

Leeds

LS6 4RA

Tel: 0113 30 50126

03 May 2011

Professor William Ledger

Academic Unit of Reproductive Med

Level4, Jessop Wing, Tree Root Walk

Sheffield

S10 2SF

Dear Professor Ledger

|  |  |
| --- | --- |
| **Study title:** | **Investigation of the impact of emotional health on pregnancy rates following assisted conception** |
| **REC reference:** | **10/H1308/46** |
| **Protocol number:** | **Not applicable** |
| **Amendment number:** | **1** |
| **Amendment date:** | **14 April 2011** |

The above amendment was reviewed by the Sub-Committee in correspondence.

**Ethical opinion**

There were a number of changes in this amendment: a change of chief investigator from Professor Ledger to Dr Patrick Magill, who will be the custodian of the data; the withdrawal from the study of researchers Miss Naomi Meardon and Miss Kirsten Thompson and the appointment of Dr Vidya Tamhankar, research fellow and a member of medical staff of the Assisted Conception Unit; a change to recruitment of couples with infertility who will either be contacted by post or will be approached by the Research Fellow at consultations on the Unit; the start and finish dates of the project have been changed to reflect the delay in the project due to changes in personnel- start date is now May 2011 and end date for data collection is November 2012. There were no ethical issues with these amendments.

The members of the Committee taking part in the review gave a favourable ethical opinion of the amendment on the basis described in the notice of amendment form and supporting documentation.

**Approved documents**

The documents reviewed and approved at the meeting were:

|  |  |  |  |
| --- | --- | --- | --- |
| Document | Version | Date |  |
| IRAS Declaration signed by new CI |  | 15 April 2011 |  |
| Participant Information Sheet | 3 | 30 March 2011 |  |
| Investigator CV | Patrick Magill |  |  |
| Protocol | 2 | 30 March 2011 |  |
| Notice of Substantial Amendment (non-CTIMPs) | 1 | 14 April 2011 |  |
| Covering Letter |  | 09 April 2011 |  |
| Patient introduction sheet | 3 | 30 March 2011 |  |
| Participant Consent Form: (completing questionnaires) | 3 | 30 March 2011 |  |
| Participant Consent Form: (telephone contact) | 3 | 30 March 2011 |  |
| Investigator CV | Vidya Tamhankar | 01 March 2011 |  |

**Membership of the Committee**

The members of the Committee who took part in the review are listed on the attached sheet.

**R&D approval**

All investigators and research collaborators in the NHS should notify the R&D office for the relevant NHS care organisation of this amendment and check whether it affects R&D approval of the research*.*

**Statement of compliance**

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees (July 2001) and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

**10/H1308/46: Please quote this number on all correspondence**

Yours sincerely

**Dr Basil Sharrack**

**Chair**

E-mail: anne.ward7@nhs.net

|  |  |
| --- | --- |
| *Enclosures:* | *List of names and professions of members who took part in the review* |

**NRES Committee Yorkshire & The Humber - Sheffield**

**Attendance at Sub-Committee of the REC meeting on 02 May 2011**

|  |  |  |  |
| --- | --- | --- | --- |
| *Name* | *Profession* | *Capacity* |  |
| Dr Basil Sharrack | Chair of REC and Consultant Neurologist | Expert |  |
| Dr Ruth Stirton | Lecturer in Law | Lay Plus |  |

**Appendix 5: Questionnaires**



**Emotional health and infertility questionnaire**

**Please answer each of the questions indicating the response that applies best to how you have felt over the past four weeks. Do not spend too much time considering your answer; your immediate response is likely to be more accurate.**

**These questions ask about your overall health.**

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| --- | --- |
| In general would you say your health has been:  Please circle one number only | Excellent …………………………… 1  Very good …………………………… 2  Good ………………………………… 3  Fair ………………………………….. 4  Poor …………………………………. 5 |
|  |  |
| How much have you been bothered by  emotional problems such as feeling  anxious, depressed, irritable or  down-hearted and sad?  Please circle one number only | Not at all …………………………….. 1  Slightly ……………………………… 2  Moderately ………………………….. 3  Quite a lot …………………………… 4  Extremely …………………………… 5 |

**These questions ask you how you have felt about your fertility problem over the past four weeks. Frequently we have used the term “our fertility problem”. This relates to your problem in trying to conceive as a couple, regardless of what that problem is.**

**How true are each of the following statements for you? Please tick the box that best applies.**

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| I feel that information given by staff is sometimes inadequate. | | | | | | | | | | | | | |  |  | |  | | |  | |  | |  | |  | |  | |  | |  | |  | |  | |  |  | | |  | |
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| 2. I feel upset when people make insensitive comments about childless couples. | | | | | | | | | | | | | |  |  | |  | | |  | |  | |  | |  | |  | |  | |  | |  | |  | |  |  | | |  | |
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| **Definitely**  **true** | | | | | | | | **Mostly true** | | | | | **Not sure** | | | **Mostly untrue** | | | | | **Definitely untrue** | | | | | | |
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| 3. I get upset when family and/or friends talk about their children.. | | | | | | | | | | | | | | |  | |  | |  | | |  |  |  |  | |  |  | |  |  |  |  | | |  | |  | |
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| 4. I may have to stop treatment sooner than I would like because of the financial cost. | | | | | | | | | | | | | | |  | |  | |  | | |  |  |  |  | |  |  | |  |  |  |  | | |  | |  | |
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| 5. My life is on hold because of fertility treatment. | | | | | | | | | | | | | | |  | |  | |  | | |  |  |  |  | |  |  | |  |  |  |  | | |  | |  | |
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| 6. I find it hard to share my feelings about infertility with my family and/or friends. | | | | | | | | | | | | | | |  | |  | |  | | |  |  |  |  | |  |  | |  |  |  |  | | |  | |  | |
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| 7. I feel my partner blames me for our fertility problem. | | | | | | | | | | | | | | |  | |  | |  | | |  |  |  |  | |  |  | |  |  |  |  | | |  | |  | |
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| 8. I find it hard to cope with our fertility problem. | | | | | | | | | | | | | | |  | |  | |  | | |  |  |  |  | |  |  | |  |  |  |  | | |  | |  | |
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| 9. Trying to maintain privacy during treatment is stressful. | | | | | | | | | | | | | | |  | |  | |  | | |  |  |  |  | |  |  | |  |  |  |  | | |  | |  | |
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| 10. At times I feel we are not getting the best treatment. | | | | | | | | | | | | | | |  | |  | |  | | |  |  |  |  | |  |  | |  |  |  |  | | |  | |  | |
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| 11. I resent having to put other aspects of my life on hold because of infertility. | | | | | | | | | | | | | | |  | |  | |  | | |  |  |  |  | |  |  | |  |  |  |  | | |  | |  | |
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| 12. I find it hard to help my partner cope with our fertility problem. | | | | | | | | | | | | | | |  | |  | |  | | |  |  |  |  | |  |  | |  |  |  |  | | |  | |  | |
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| 13. I avoid seeing family and/or friends who have children. | | | | | | | | | | | | | | |  | |  | |  | | |  |  |  |  | |  |  | |  |  |  |  | | |  | |  | |
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| **Definitely**  **true** | | | | | | | | **Mostly true** | | | | | **Not sure** | | | **Mostly untrue** | | | | | **Definitely untrue** | | | | | | |
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| 14. Infertility strains my relationship with my partner. | | | | | | | | | | | | | | |  | |  | |  | | |  |  |  |  | |  |  | |  |  |  |  | | |  | |  | |
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| 15. I feel that decisions about treatment are out of my control. | | | | | | | | | | | | | | |  | |  | |  | | |  |  |  |  | |  |  | |  |  |  |  | | |  | |  | |
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| 16. I feel pressured to have sex at the ‘right time’ even when I don’t feel like it. | | | | | | | | | | | | | | |  | |  | |  | | |  |  |  |  | |  |  | |  |  |  |  | | |  | |  | |
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| 17. Infertility has taken over my life. | | | | | | | | | | | | | | |  | |  | |  | | |  |  |  |  | |  |  | |  |  |  |  | | |  | |  | |
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| 18. I feel unsupported by family and/or friends. | | | | | | | | | | | | | | |  | |  | |  | | |  |  |  |  | |  |  | |  |  |  |  | | |  | |  | |
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| 19. I feel that sex is more about conceiving than expressing our love for each other. | | | | | | | | | | | | | | |  | |  | |  | | |  |  |  |  | |  |  | |  |  |  |  | |  | | |  | |
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| 20. Fertility treatment makes me feel like a ‘thing’ rather than a person. | | | | | | | | | | | | | | |  | |  | |  | | |  |  |  |  | |  |  | |  |  |  |  | | |  | |  | |
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| 21. I find it difficult to talk to my partner about our fertility problem without one of us getting upset or angry. | | | | | | | | | | | | | | |  | |  | |  | | |  |  |  |  | |  |  | |  |  |  |  | | |  | |  | |
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| 22. I find it painful when family members and/or friends become pregnant. | | | | | | | | | | | | | | |  | |  | |  | | |  |  |  |  | |  |  | |  |  |  |  | | |  | |  | |
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| 23. I will feel incomplete as a person if I cannot have my own child. | | | | | | | | | | | | | | |  | |  | |  | | |  |  |  |  | |  |  | |  |  |  |  | | |  | |  | |
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| 24. Sometimes I think that infertility could lead to us separating. | | | | | | | | | | | | | | |  | |  | |  | | |  |  |  |  | |  |  | |  |  |  |  | | |  | |  | |
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| 25. Infertility makes me feel I have lost control of my life. | | | | | | | | | | | | | | |  | |  | |  | | |  |  |  |  | |  |  | |  |  |  |  | | |  | |  | |
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| **Definitely**  **true** | | | | | | | | **Mostly true** | | | | | **Not sure** | | | **Mostly untrue** | | | | | **Definitely untrue** | | | | | | |
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| 26. I disagree with my partner about how much money to spend on treatment. | | | | | | | | | | | | | | |  | |  | |  | | |  |  |  |  | |  |  | |  |  |  |  | |  | |  | |
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| 27. I avoid places where there might be pregnant women or children. | | | | | | | | | | | | | | |  | |  | |  | | |  |  |  |  | |  |  | |  |  |  |  | |  | |  | |
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| 28. I feel my partner is obsessed with trying to have children. | | | | | | | | | | | | | | |  | |  | |  | | |  |  |  |  | |  |  | |  |  |  |  | |  | |  | |
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| 29. Sex is less enjoyable now that I know about our fertility problem. | | | | | | | | | | | | | | |  | |  | |  | | |  |  |  |  | |  |  | |  |  |  |  | |  | |  | |
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| 30. I blame myself for our fertility problem. | | | | | | | | | | | | | | |  | |  | |  | | |  |  |  |  | |  |  | |  |  |  |  | |  | |  | |
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| 31. I feel my partner is not as committed to having children as I am. | | | | | | | | | | | | | | |  | |  | |  | | |  |  |  |  | |  |  | |  |  |  |  | |  | |  | |
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| 32. I find it hard to agree with my partner whether to tell family and/or friends about our fertility problem. | | | | | | | | | | | | | | |  | |  | |  | | |  |  |  |  | |  |  | |  |  |  |  | |  | |  | |
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| 33. I am exhausted by the emotional roller coaster of infertility. | | | | | | | | | | | | | | |  | |  | |  | | |  |  |  |  | |  |  | |  |  |  |  | |  | |  | |
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| 34. I find trying to balance fertility treatment with my other commitments stressful. | | | | | | | | | | | | | | |  | |  | |  | | |  |  |  |  | |  |  | |  |  |  |  | |  | |  | |
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| 35. I feel less sexually attractive since discovering our fertility problem. | | | | | | | | | | | | | | |  | |  | |  | | |  |  |  |  | |  |  | |  |  |  |  | |  | |  | |
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| 36. I feel angry that I may not be able to have a / another child. | | | | | | | | | | | | | | |  | |  | |  | | |  |  |  |  | |  |  | |  |  |  |  | |  | |  | |
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| **Definitely**  **true** | | | | | | | | **Mostly true** | | | | | **Not sure** | | | **Mostly untrue** | | | | | **Definitely untrue** | | | | | | |
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| 37. Each birthday without a / another child is more upsetting. | | | | | | | | | | | | | | |  | |  | |  | | |  |  |  |  | |  |  | |  |  |  |  | |  | |  | |
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| 38. I feel guilty that my past actions may have affected my fertility. | | | | | | | | | | | | | | |  | |  | |  | | |  |  |  |  | |  |  | |  |  |  |  | |  | |  | |
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| 39. Having a fertility problem makes me feel inadequate. | | | | | | | | | | | | | | |  | |  | |  | | |  |  |  |  | |  |  | |  |  |  |  | |  | |  | |
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| 40. Finding the money for treatment is a constant worry. | | | | | | | | | | | | | | |  | |  | |  | | |  |  |  |  | |  |  | |  |  |  |  | |  | |  | |
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If you would like to add anything further please do so here.

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Thank you for your help.

**Fertility Problem Inventory**

**Instruction for completing the questionnaire**

The following statements express different opinions about a fertility problem. Please place a number on the line to the left of each statement to show how much you agree or disagree with it.

Please answer every item. Use the following response categories:

6 = strongly agree

5 = moderately agree

4 = slightly agree

3 = slightly disagree

2 = moderately disagree

1 = strongly disagree

1. \_\_\_ Couples without a child are just as happy as those with children.

2. \_\_\_ Pregnancy and childbirth are the two most important events in a couple's relationship.

3. \_\_\_ I find I've lost my enjoyment of sex because of the fertility problem.

4. \_\_\_ I feel just as attractive to my partner as before.

5. \_\_\_ For me, being a parent is a more important goal than having a satisfying career.

6. \_\_\_ My marriage needs a child (or another child).

7. \_\_\_ I don't feel any different from other members of my sex.

8. \_\_\_ It's hard to feel like a true adult until you have a child.

9. \_\_\_ It doesn't bother me when I'm asked questions about children.

10. \_\_\_ A future without a child (or another child) would frighten me.

11. \_\_\_ I can't show my partner how I feel because it will make him/her feel upset.

12. \_\_\_ Family don't seem to treat us any differently.

13. \_\_\_ I feel like I've failed at sex.

14. \_\_\_ The holidays are especially difficult for me.

6 = strongly agree

5 = moderately agree

4 = slightly agree

3 = slightly disagree

2 = moderately disagree

1 = strongly disagree

15. \_\_\_ I could see a number of advantages if we didn't have a child (or another child).

16. \_\_\_ My partner doesn't understand the way the fertility problem affects me.

17. \_\_\_ During sex, all I can think about is wanting a child (or another child).

18. \_\_\_ My partner and I work well together handling questions about our infertility.

19. \_\_\_ I feel empty because of our fertility problem.

20. \_\_\_ I could visualize a happy life together, without a child (or another child).

21. \_\_\_ It bothers me that my partner reacts differently to the problem.

22. \_\_\_ Having sex is difficult because I don't want another disappointment.

23. \_\_\_ Having a child (or another child) is not the major focus of my life.

24. \_\_\_ My partner is quite disappointed with me.

25. \_\_\_ At times, I seriously wonder if I want a child (or another child).

26. \_\_\_ My partner and I could talk more openly with each other about our fertility problem.

27. \_\_\_ Family get-togethers are especially difficult for me.

28. \_\_\_ Not having a child (or another child) would allow me time to do other satisfying things.

29. \_\_\_ I have often felt that I was born to be a parent.

30. \_\_\_ I can't help comparing myself with friends who have children.

31. \_\_\_ Having a child (or another child) is not necessary for my happiness.

32. \_\_\_ If we miss a critical day to have sex, I can feel quite angry.

6 = strongly agree

5 = moderately agree

4 = slightly agree

3 = slightly disagree

2 = moderately disagree

1 = strongly disagree

33. \_\_\_ I couldn't imagine us ever separating because of this.

34. \_\_\_ As long as I can remember, I've wanted to be a parent.

35. \_\_\_ I still have lots in common with friends who have children.

36. \_\_\_ When we try to talk about our fertility problem, it seems to lead to an argument.

37. \_\_\_ Sometimes I feel so much pressure, that having sex becomes difficult.

38. \_\_\_ We could have a long, happy relationship without a child (or another child).

39. \_\_\_ I find it hard to spend time with friends who have young children.

40. \_\_\_ When I see families with children I feel left out.

41. \_\_\_ There is a certain freedom without children that appeals to me.

42. \_\_\_ I will do just about anything to have a child (or another child).

43. \_\_\_ I feel like friends or family are leaving us behind.

44. \_\_\_ It doesn't bother me when others talk about their children.

45. \_\_\_ Because of infertility, I worry that my partner and I are drifting apart.

46. \_\_\_ When we talk about our fertility problem, my partner seems comforted by my comments.

**Perceived Stress Scale**

 Instructions: The questions in this scale ask you about your feelings and thoughts during the last month.  In each case, please circle how often you felt or thought a certain way.   
   
1. In the last month, how often have you been upset because of something that happened unexpectedly?

  0=never 1=almost never 2=sometimes 3=fairly often 4=very often   
  
2. In the last month, how often have you felt that you were unable to control the important things in your life?

  0=never 1=almost never 2=sometimes 3=fairly often 4=very often

3. In the last month, how often have you felt nervous and "stressed"?

0=never 1=almost never 2=sometimes 3=fairly often 4=very often

4. In the last month, how often have you felt confident about your ability to handle your personal problems?

0=never 1=almost never 2=sometimes 3=fairly often 4=very often

5. In the last month, how often have you felt that things were going your way?

0=never 1=almost never 2=sometimes 3=fairly often 4=very often

6. In the last month, how often have you found that you could not cope with all the things that you had to do?

0=never 1=almost never 2=sometimes 3=fairly often 4=very often

7. In the last month, how often have you been able to control irritations in your life?

0=never 1=almost never 2=sometimes 3=fairly often 4=very often

8. In the last month, how often have you felt that you were on top of things?

0=never 1=almost never 2=sometimes 3=fairly often 4=very often

9. In the last month, how often have you been angered because of things that were outside of your control?

0=never 1=almost never 2=sometimes 3=fairly often 4=very often

10. In the last month, how often have you felt difficulties were piling up so high that you could not overcome them?

0=never 1=almost never 2=sometimes 3=fairly often 4=very often

**PANAS**

Directions

This scale consists of a number of words that describe different feelings and emotions. Read each item and then circle the appropriate answer next to that word. Indicate to what extent you have felt this way during the past week.

Use the following scale to record your answers.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| (1) = Very slightly or not at all | (2) = A little | (3) = Moderately | (4) = Quite a bit | (5) = Extremely |

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| --- | --- | --- | --- | --- | --- |
|  | **Very slightly or not at all** | A little | **Moderately** | **Quite a bit** | Extremely |
| 1. Interested | 1 | 2 | 3 | 4 | 5 |
| 1. Distressed | 1 | 2 | 3 | 4 | 5 |
| 1. Excited | 1 | 2 | 3 | 4 | 5 |
| 1. Upset | 1 | 2 | 3 | 4 | 5 |
| 1. Strong | 1 | 2 | 3 | 4 | 5 |
| 1. Guilty | 1 | 2 | 3 | 4 | 5 |
| 1. Scared | 1 | 2 | 3 | 4 | 5 |
| 1. Hostile | 1 | 2 | 3 | 4 | 5 |
| 1. Enthusiastic | 1 | 2 | 3 | 4 | 5 |
| 1. Proud | 1 | 2 | 3 | 4 | 5 |
| 1. Irritable | 1 | 2 | 3 | 4 | 5 |
| 1. Alert | 1 | 2 | 3 | 4 | 5 |
| 1. Ashamed | 1 | 2 | 3 | 4 | 5 |
| 1. Inspired | 1 | 2 | 3 | 4 | 5 |
| 1. Nervous | 1 | 2 | 3 | 4 | 5 |
| 1. Determined | 1 | 2 | 3 | 4 | 5 |
| 1. Attentive | 1 | 2 | 3 | 4 | 5 |
| 1. Jittery | 1 | 2 | 3 | 4 | 5 |
| 1. Active | 1 | 2 | 3 | 4 | 5 |
| 1. Afraid | 1 | 2 | 3 | 4 | 5 |

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