The Diagnosis and Management of Ectopic Pregnancy

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I would like to thank, sincerely, Jimmy Walker for his support and inspiration. His guidance has been pivotal in helping me produce this thesis. I would also like to thank Anne Walker, who has lived through the production of yet another thesis.

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...and Richard, Meadhbh, Eric and Aelffled; this is a family achievement.

Abstract

The increase in the number of women in whom a diagnosis of ectopic pregnancy is made presents challenges to the gynaecologist. It is important to follow diagnostic protocols to ensure that cases are not missed. But because diagnostic tools, such as the use of serum hCG estimations, improves pick-up, clinicians need to be aware that surgery is not the only effective way of managing ectopic pregnancy and women can be offered management choices.

Diagnosis of ectopic pregnancy is made by considering the clinical situation in conjunction with the ultrasound and biochemical (hCG or progesterone) findings. There is no test that conclusively proves that an ectopic pregnancy is present. Fetal fibronectin is explored as a possible diagnostic test as part of this thesis. Whilst there are appears to be some differences in the levels in different situations in early pregnancy, the assay, which detects the FDC-6 epitope of the fetal form of fibronectin and is in widespread use in later pregnancy, is fundamentally flawed, as it is not specific to the fetal form of fibronectin and detectable levels can be found in the cervixes of non-pregnant women, as the presence of blood leads to a positive result. It is not possible to show whether or not fetal fibronectin is a useful tool in the diagnosis of ectopic pregnancy with the available assay.

A series of questionnaires were used to assess the availability of Early Pregnancy Units and women's experiences of the diagnostic and management of ectopic pregnancy. I demonstrated that women can weigh different choices, where the choices offer complex advantages and disadvantages, and value involvement of management decisions.

An audit of the use of hCG estimations within St. James's University Hospital was used as a basis of a protocol for the management of ectopic pregnancy.

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List of Abbreviations

APS	antiphospholipid syndrome
BPV	bleeding per vagina
BV	bacterial vaginosis
CI	confidence interval
d.f.	degrees of freedom
EPAS	Early Pregnancy Assessment Service
EP	ectopic pregnancy
EPT	Ectopic Pregnancy Trust
EPU	Early Pregnancy Unit
FCU	Fertility Control Unit
fFN	fetal fibronectin
FH	fetal heart
GP	General Practitioner
hCG	human chorionic gonadotrophin
βhCG	beta human chorionic gonadotrophin

IUD	intrauterine contraceptive device
2nd IS	second international standard
3rd IS	third international standard
IVF	in-vitro fertilization
IVF-ET	in-vitro fertilisation and embryo transfer
KCl	potassium chloride
lmp	last menstrual period
LR	likelihood ratio
mxt	methotrexate
NPV	negative predictive value
OR	odds ratio
PCR	polymerase chain reaction
PG	prostaglandin
PID	pelvic inflammatory disease
PPV	positive predictive value
preg	pregnancies
RCOG	Royal College of Obstetricians and Gynaecologists

RMC	Recurrent Miscarriage Clinic
ROCET	Radical or Conservative Ectopic Trial
RR	relative risk
v	versus
+ve	positive
-ve	negative

Chapter 1 - Introduction

1.1 Ectopic Pregnancy

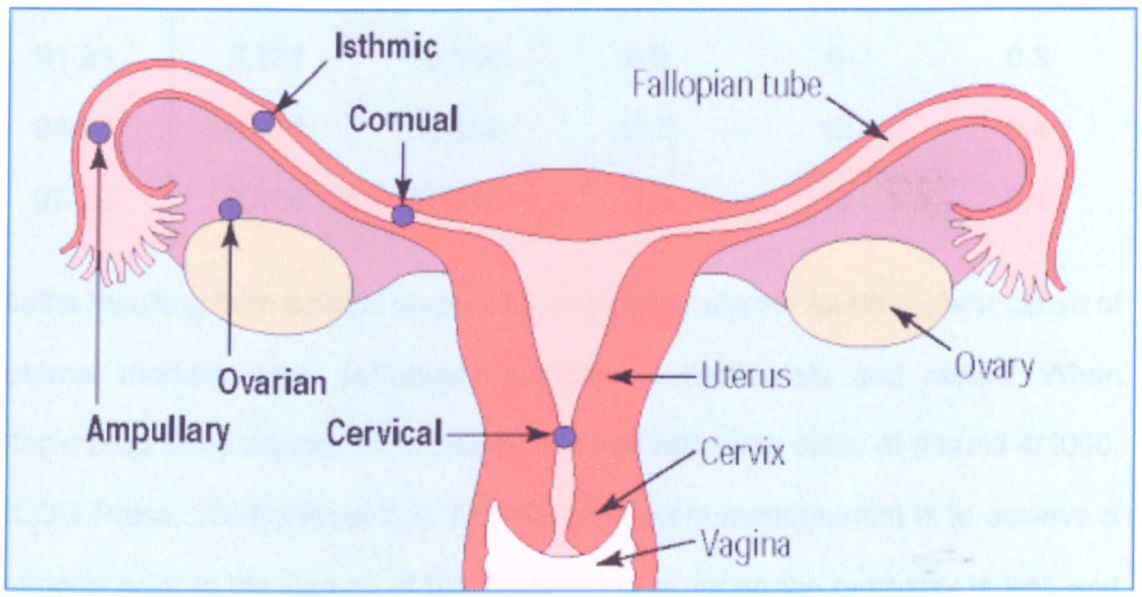


Figure 1.1 Sites of ectopic pregnancy (Tay, Moore, Walker, 2000)

An ectopic pregnancy is one that implants outwith the uterine cavity. The vast majority occur in the Fallopian tube, mostly in the ampullary region, some in the ovary and cervix and rarely in the abdominal cavity. The reason that ectopic pregnancy is important is that is carries significant morbidity and mortality. If the ectopic pregnancy erodes through the Fallopian tube, there is damage to the tube itself and potential rupture of the adjacent blood vessels, which can lead to severe maternal illness and death. The numbers of women that die of this condition has stayed relatively static over the last 12 years (Table 1.1)

Table 1.1 "Why Women Die" figures from the maternal mortality reports 1988-99. The numbers for ectopic pregnancies are estimated.

	Preg 1000	Ectopic	Ectopics /1000 preg	Deaths	Deaths /1000 ectopic
88-90	2,886	24,775	9.6	15	0.5
91-93	3,137	30,160	9.6	9	0.3
94-96	2,914	33,550	11.5	12	0.4
97-99	2,873	31,946	11.1	13	0.4

Deaths resulting from ectopic pregnancy now contribute the fourth highest cause of maternal mortality after pulmonary embolus, preeclampsia and sepsis. When ectopic pregnancy occurs, the mortality rate has remained static at around 4/1000. (RCOG Press, 2001) (Table 1.1) The aim of modern management is to achieve a diagnosis prior to the rupture of the Fallopian tube, when the morbidity is less and the treatment less invasive.

1.2 Incidence of Ectopic Pregnancy

The incidence of ectopic pregnancy has risen steadily in recent decades. Although recently some countries are now seeing a fall, the incidence is still much greater than in the 1960's and 70's. The reasons for this increase are multifactorial, but it is partly as the result of an improvement in diagnosis of the condition following the introduction of high-resolution ultrasound scans and serum hCG estimations for diagnostic purposes. However, the background upward trend has largely been

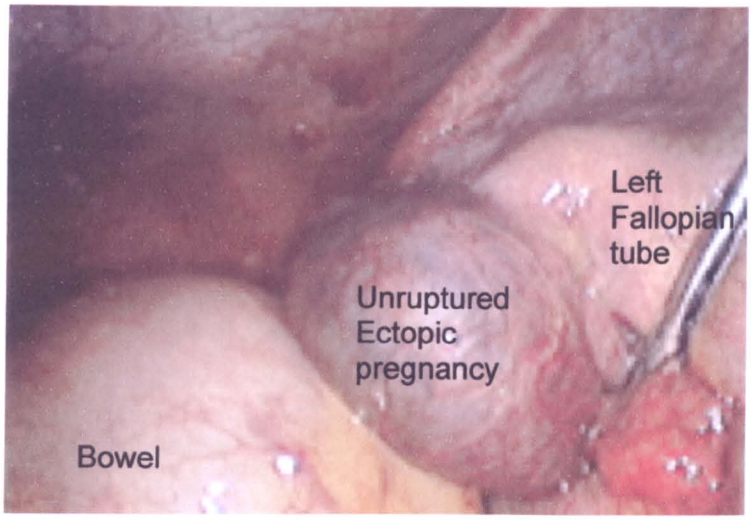


Figure 1.2 An unruptured ectopic pregnancy in the left fallopian tube.

blamed on the changes in sexual practices, and the wide availability of reliable contraception, resulting in an increase in exposure to infective agents such as *Chlamydia trachomatis*. Although this is partly related to the acute disease, it is more probably linked to the tubal damage that may result. Indeed, in the countries in which a decline in the incidence of ectopic pregnancy is being observed, this fall has been attributed to the implementation of programmes aimed at preventing chlamydial disease. Since there is a lag period of around 10 years between the widespread introduction of such programmes and the observed reduction, the effect of tubal damage resulting from chlamydial infections would appear to be long term. Studies of the changes in the incidence of ectopic pregnancy in different countries are discussed below.

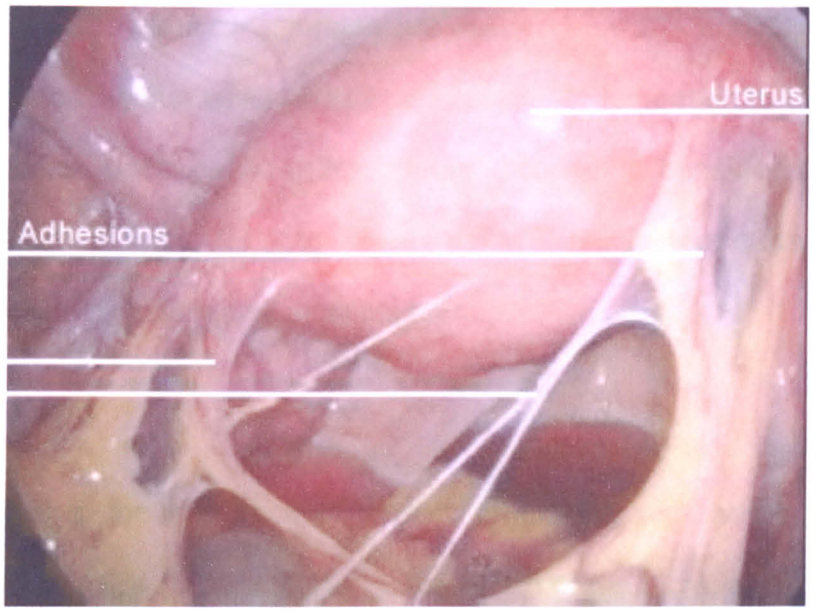


Figure 1.3 Adhesions seen at laparoscopy, probably caused by previous infection with *Chlamydia Trachomatis*.

1.2.1 Canada

The reported incidence of ectopic pregnancy in Southern Canada in 1998 was 15.7 per 1,000 reported pregnancies (Orr and Brown, 1998). In Keewatin, in the arctic territories of Canada, the incidence of ectopic pregnancy was lower at 9.6 per 1,000 reported pregnancies. The fertility rate is higher in the northern regions of Canada, and the spacing between pregnancies less. Perhaps the delay in becoming pregnant after the onset of sexual activity, that results from the separation of sexual activity from reproduction, might mean that tubal damage occurs before pregnancy is achieved in cultures where fertility rates are lower and spacing between pregnancies greater. It is interesting that the rates of gonorrhoea

and chlamydia in the Northern Canada are respectively 27- and 22-fold those found in Southern Canada, which would be expected to increase the incidence of ectopic pregnancy, since pelvic inflammatory disease is considered such an important aetiological factor for ectopic pregnancy. Other factors such as age at pregnancy and genetic differences may play a role.

1.2.2 Finland

A large increase in the incidence of ectopic pregnancy was noted in Finland between 1967 and 1984 (Mäkinen, 1987), the zenith of the increase was found in 1987 and since then the incidence has decreased (Mäkinen, 1996). These data showed a population-based incidence of 159 per 100,000 women in 1984, 176 per 100,000 women in 1988 and 155 per 100,000 women in 1994. Although these figures use a different denominator, they show the same recent decline in the incidence of ectopic pregnancy found in Sweden, described below. Mäkinen *et al.* (1998) postulated that the peak of the incidence of ectopic pregnancy was a result of the large cohort of "baby-boomers" reaching the peak of their fertility leading to distortion of the figures.

1.2.3 France

Coste *et al.* (2000[8]) analysed data from the Auvergne ectopic pregnancy register. They observed a global decline in the incidence of ectopic pregnancy between 1992 and 1997. To determine the reasons behind this decline, they divided the cases of ectopic pregnancy into a group that was caused by reproductive failure

and another group that was caused by contraceptive failure. Consistently, 3/4s of cases secondary to contraceptive failure were in women using intra-uterine devices (IUDs). Over the period studied, there was a decline in the use of IUDs and an increase in the use of contraceptive pills in France, this lead to a decrease in the number of ectopic pregnancies secondary to contraceptive failure, resulting in a reduction in the total number of ectopic pregnancies. The number of ectopic pregnancies resulting from reproductive failure remained constant.

1.2.4 India

A lower incidence is reported in India, although here too, the incidence is rising. In the fifteen-year period between 1959 and 1973, the incidence was 2.7 per 1,000 pregnancies. In the five years between 1988 and 1993 the incidence was 6.3 per 1,000 pregnancies (Arora *et al.*, 1998). This may reflect a lower incidence in this population where sexual relations outside of marriage are less common, but it might also show that in an environment where there is not universal free health care that many ectopic pregnancies resolve without requiring medical intervention.

1.2.5 Ireland

The incidence of ectopic pregnancy at the National Maternity Hospital doubled from 1995 to 1996 (4.8 to 8.3 per 1,000 pregnancies, respectively). This coincided with the introduction of serum hCG testing and a protocol for the diagnosis of ectopic pregnancy (Ong and Wingfield, 1999). There was no increase in the incidence of ruptured ectopic pregnancy or blood transfusion in these two years,

and indeed these were required no more frequently than in 1986 when the incidence of ectopic pregnancy in the same unit was 1.8 per 1,000 pregnancies. The authors suggested that there was not so much an increase in incidence of ectopic pregnancy than an increase in its diagnosis.

1.2.6 Norway

Skjeldestad *et al.*, (1997[a]) noted a four-fold increase in the incidence of ectopic pregnancy in a stable Norwegian population between 1970 and 1993. Storeide *et al.* (1997) observed a different Norwegian population over a similar time – 1976 and 1993. They again noticed an increase in the incidence of ectopic pregnancy. This increase was greater in older women; in women of less than 30 years the rate per 1,000 reported pregnancies increased by 25% from 9.4 to 11.8; in women of more than 35 years of age the rate per 1,000 reported pregnancies increased by 98% from 20.7 to 40.9. Compared with the 15 to 19 year old age group, the over 35's had an eight-fold increase in the risk of ectopic pregnancy. This was explained as an "accumulation of risk factors" in the older age group.

1.2.7 Sweden

In Sweden there has been a widespread implementation of a screening programme for chlamydia. This has lead to a decrease in the incidence of new chlamydial infections between 1985 and 1995. As a result, the incidence of ectopic pregnancy has fallen by 45% (Egger *et al.*, 1998).

1.2.8 United States

The incidence of ectopic pregnancy has been seen to increase in recent decades:

Table 1.2. Incidence of ectopic pregnancy in the United States*Rubin *et al.*, 1983; **Centers for Disease Control, 1993; ***Rajkhowa *et al.*, 2000

Year	Incidence - US	(UK figures for comparison)
1970	4.5 per 1,000 pregnancies*	3.51 per 1,000 pregnancies***
1978	9.4 per 1,000 pregnancies*	5.59 per 1,000 pregnancies***
1992	19.7 per 1,000 pregnancies**	12.4 per 1,000 pregnancies***

This has a knock-on effect on hospital admissions with the number of hospitalisations for ectopic pregnancies increasing from 17,800 in 1970 to 88,400 in the United States in 1989. (Anonymous, 1995[a])

1.2.8 United Kingdom

Figures for the incidence of ectopic pregnancy between 1966 and 1970 were published by Beral, (1975) and Rajkhowa *et al.*, (2000) continued this to 1996 (Figure 1.4)

This suggests that the incidence of ectopic pregnancy might have reached its peak in the UK in the early 90's, and when information from the next decade is available, it will be possible to see whether the decline seen in some other countries, is

evident in the UK as well. If the incidence has indeed peaked, this is at a lower level than in the US or Scandinavia.

Data is missing for 1986 to 1988; this represents a change in the method of collecting data. It is possible that the apparent increase in incidence might be an artefact of data collection, rather than a true rise in incidence. Data from other countries would, however, support at least some of this rise being genuine.

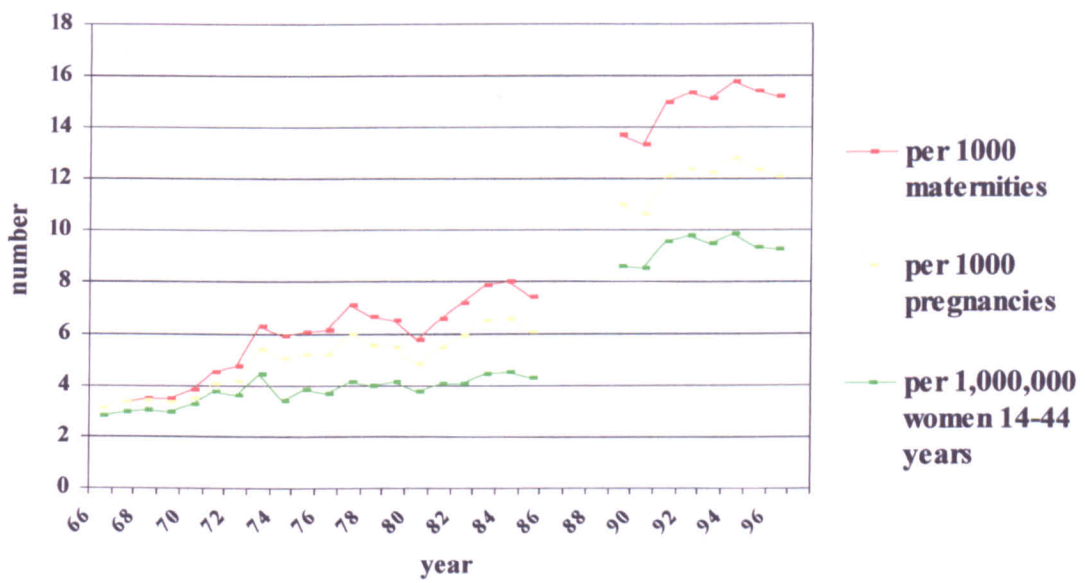


Figure 1.4. Rise in incidence of ectopic pregnancy in the UK 1966-1996.

1.3 Presentation of Ectopic Pregnancy

It can be seen that the presentation and diagnosis of ectopic pregnancy has varied with place and time. Early diagnosis is important because it can reduce morbidity, but will result in an increase in the reported incidence. However, traditionally, most

women with ectopic pregnancy have only presented when acute symptoms are apparent and so it is seen as a gynaecological emergency.

In one study, 96% of subjects presented with abdominal pain and 83% with vaginal bleeding (Aboud and Chaliha, 1998). Overcoming the failure to recognise the symptoms of ectopic pregnancy would seem to be the greatest challenge in reducing the associated mortality and morbidity. Another difficulty with the diagnosis of ectopic pregnancy arises, not so much from recognising the symptoms, but from the possibility that ectopic pregnancy can be present in asymptomatic women with apparently normal periods. A pregnancy test is simple to perform, and should be performed in any woman in whom pregnancy is a possibility, even when symptoms do not suggest a pregnancy related problem. A negative test almost certainly rules out an ectopic pregnancy.

1.4 Epidemiology

Cagnacci *et al.* (1999) found a seasonal variation in the incidence of spontaneously conceived ectopic pregnancy, the frequency being significantly higher from November to January and May to July than it was from February to April and August to October. Lemus (2000) reports that no such seasonal variation is found after assisted conception. This would suggest a changing behaviour pattern in the spontaneously conceived group.

Many risk factors for ectopic pregnancies have been implicated in its aetiology:

1.4.1. Pelvic Inflammatory Disease:

Pelvic inflammatory disease is estimated to cost the United State $4.2 billion each year (Quan, 1994). Barlow *et al.* (2001) found evidence of past or present infection with chlamydia in 50% of women presenting with ectopic pregnancy using PCR on fresh tissue specimens. Chlamydia could be found in the endometrium, ovary and Fallopian tube at the time of surgery.

Gaydos *et al.* (1998) assessed risk factors for chlamydia infection in US military recruits and found the following risk factors were independently associated with infection:

ever having had vaginal sex (OR for infection 5.9)

being 25 years of age or less (OR 3.0)

being black (OR 3.4)

having had more than one sexual partner in the last 90 days (OR 1.4)

having had a new sexual partner in the last 90 days (OR 1.3)

A Swedish Study (Egger *et al.*, 1998) looked at the incidence of both chlamydia infection and ectopic pregnancy. They found a strong and significant correlation in the 20 to 24 year old group (correlation coefficient=0.93, $p<0.001$), which was lost in the older 35-39 year old group (correlation coefficient=0.07, $p=0.8$). A further study from Sweden (Kamwendo *et al.*, 2000) found a 10-year lag between a reduction in the incidence of pelvic inflammatory disease and any resultant

decrease in the ectopic pregnancy rate. This work suggests that current infection with chlamydia is important in the aetiology of ectopic pregnancy, but the association of the risk of ectopic with this primary chlamydial infection remains with this cohort for up to ten years.

Recurrent chlamydial infections further increase the risk of ectopic pregnancy (Hillis *et al.*, 1997). Compared to women who had had a single chlamydia infection, women with two infections had an elevated risk of ectopic pregnancy, OR 2.1 (95% CI 1.3-3.4) and with three or more infections the risk rose further, OR 4.5 (95% CI 1.8-5.3).

Urbach and Cohen (1999) examined the role of previous perforation of the appendix in the aetiology of ectopic pregnancy, as infection and adhesion formation associated with the complications of appendicitis were thought to be responsible for some tubal damage. They found only four original studies. These gave risks of adverse fertility outcome, following a perforated appendix, of between 1.6 and 4.8 compared to women who had not had an appendicitis. They concluded that the trials were so poorly designed that the results were not reliable and felt a properly designed trial would be necessary to examine what role, if any, perforation of the appendix had in predisposing to ectopic pregnancy.

1.4.2. Influence of Contraceptive Practice on Incidence

This relates to methods that prevent intra-uterine pregnancies, but may have less of an effect on extra-uterine pregnancies, such as the intra-uterine contraceptive

device. This will not increase the incidence of ectopic pregnancies in the population but means there is a higher incidence of ectopic when pregnancy occurs.

Xiong *et al.* (1995) performed a meta-analysis of case-control studies of the relationship between intrauterine contraceptive devices (IUD) and ectopic pregnancy. Between 1970 and 1994, sixteen such studies were found. They found no increase in the risk of ectopic pregnancy when current IUD users were compared with non-pregnant controls (pooled OR: 1.06, 95% CI 0.91-1.24). Past IUD use only mildly increased the risk (OR 1.40, 95% CI: 1.23-1.59).

In France, figures obtained from the Auvergne Register associate 25-30% of all ectopic pregnancies with the use of IUDs (Bouyer *et al.*, 2000). This reflects the high prevalence of usage of this method of contraception in France. In the UK this figure is lower, with only 14% of ectopic pregnancies being associated with the use of IUDs (Aboud, 1997). However, women using IUDs have a lower rate of ectopic pregnancy than women who are not using any form of contraception, which means the risk of ectopic pregnancy, as well as intrauterine pregnancy, is lower in IUD users (Ory, 1981; Sivin, 1991; Rossing *et al.*, 1993; Skeldestad, 1997). But, as IUDs protect against intrauterine pregnancy more effectively than extra-uterine pregnancy, failure of this method of contraception is more likely to result in an extra-uterine pregnancy. Women using other forms of contraception that prevented ovulation or conception, such as the combined oral contraceptive or barrier methods, had a lower risk of ectopic pregnancy than non-contraceptors and users of IUDs (Rossing *et al.*, 1993).

Bouyer *et al.*, 2000[a] found that women who experienced pelvic pain or discomfort in the month following insertion of the IUD had a higher risk of ectopic pregnancy, presumably, because these were the women who got pelvic inflammatory disease as a result of coil insertion. IUDs tend to be used more in women who are approaching the end of their reproductive life. On one hand, this group has the highest incidence of ectopic pregnancy, but on the other, it might be the increased usage of IUDs for contraception that goes some way to explaining the high risk in this group.

Women who have an ectopic pregnancy with an IUD in-situ have a different long-term prognosis. Women who conceived with an IUD in-situ had a rate 69.2% of a subsequent live birth, whilst those who did not had a subsequent 38.0% live birth rate (Sandvei *et al.*, 1987). Ego *et al.*, (2001) reported a similar finding, with 81% of women IUD associated ectopics achieving on-going intra-uterine pregnancies within two years of trying to conceive, but only 67% in the group that conceived their ectopic pregnancy in the absence of an IUD. This is explained by the higher rate of a history of pelvic inflammatory disease and infertility of the group in whom an ectopic pregnancy was found in the absence of an IUD. Bernoux *et al.* (2000) found a similar pattern, with IUD users having an 87% 1-year cumulative rate of intra-uterine pregnancy after ectopic, with the cumulative rate in non-users being 60%. However, they also found a big difference in the recurrent ectopic rate; 28% of the IUD non-users had recurrent ectopic pregnancy, whilst none of the IUD users had had a further ectopic pregnancy.

Wollen *et al.* (1984) examined the endosalpinx of healthy, non-pregnant women and found that users of IUDs had only half the area of ciliated epithelium compared to tubes of other women. The significance of this is unclear in the light of later evidence suggesting a lower risk of ectopic pregnancy in IUD users than in women not using contraception.

Skjeldestad *et al.* (1997[b]) found no increase in the incidence of ectopic pregnancy in women who had undergone therapeutic termination of pregnancy. Multiple therapeutic terminations did increase the risk, although it might be expected that this group would be higher risk of sexually transmitted diseases. This finding was confirmed in a similar study by Atrash *et al.*, 1997.

1.4.3 Assisted Conception

The results form the registry of the American Society for Reproductive Medicine/Society for Assisted Reproductive Technology for 1993 (Anonymous, 1995[b]), found a rate of ectopic pregnancy of 1.2% for all IVF transfers and of 4.4% for all established cycles. Mol *et al.* (1997) found a 5.1% risk of ectopic pregnancy after IVF-ET, Strandell *et al.* (1999) found a rate of 4%. These rates are more than twice those found after natural conceptions.

Ribic-Pucelj *et al.* (1995) found the main risk factor for ectopic pregnancy after IVF-ET was a history of tubal factor infertility. This was confirmed by Strandell *et al.* (1999) and Lesny *et al.* (1999), who found the OR of having an ectopic pregnancy when tubal infertility was present was 5.41 (95% CI 1.96-14.91), but also that

ectopic pregnancy was more likely when the embryo transfer was difficult, and particularly so if there were also tubal damage present.

Aboud (1997) found 15% of women with ectopic pregnancy had a prior history of infertility.

1.4.4 Influence of Maternal Age on Incidence

The relationship between maternal age and ectopic pregnancy is frequently reported. Older women have a greater risk of any pregnancy being ectopically sited. Simms *et al.* (1997), reported that women over 40 have a 14 times greater risk of ectopic pregnancy than the under sixteens. This trend was seen in UK women as well, Rajkhowa *et al.* (2000), found the incidence of ectopic pregnancy in the 35-44 year old group to be more than double that of the 15-24 year old group. Coste *et al.* (1994) found a steep rise in the rate of ectopic pregnancy per 1000 live births after the age of 35. When they looked at the rate of ectopic pregnancy as a proportion of women of reproductive age, the rate rose steadily until 35 years, at which point it began to decline.

Sobande (2000) found that the risk of a second ectopic pregnancy increased with maternal age and with the interval between the ectopic pregnancy and the next conception. Women with a greater number of pregnancies before the ectopic pregnancy were less likely to have a second ectopic.

1.4.5. Miscarriage

Some authors have found an association with a prior history of spontaneous miscarriage (Honore, 1979; Bouyer *et al.*, 2000). Analysis of ectopic pregnancies shows them to have the same rate of karyotypic abnormality as intra-uterine pregnancy (Goddijin *et al.*, 1996; Block *et al.*, 1998; Coste *et al.*, 2000[b]).

1.4.6 Tubal Surgery

Pisarska *et al.* (1998) reported an odds ratio for ectopic pregnancy following tubal surgery of 21.0 compared to those women in whom this was not a risk factor. However, caesarean section is not associated with any increase in risk of subsequent ectopic pregnancy (Kendrick *et al.*, 1996).

1.4.7 Sterilisation and its Reversal.

Peterson *et al.* (1997) followed up women who had undergone a sterilisation procedure and found a 10-year cumulative probability of ectopic pregnancy of 7.3 per 1,000 procedures. The annual rates of ectopic pregnancy were no lower between 4 and 10 years post-procedure than they were in the first three years.

1.4.8 *In-utero* Exposure to Diethylstilboestrol (DES)

Pons *et al.* (1988) reported a 15% incidence of extra-uterine pregnancy in DES-exposed women. More recently Kaufman *et al.* (2000) reported ectopic pregnancy in 4.2% of DES-exposed women compared to 0.77% of unexposed controls.

1.4.9 Smoking

Castles *et al.* (1999) found an increased risk of ectopic pregnancy associated with smoking, with an odds ratio of 1.77 of ectopic pregnancy in smokers compared to non-smokers. Smoking also decreased the subsequent rate of intra-uterine pregnancy at two years after an ectopic pregnancy (51% in smokers, 60% in non-smokers, p= 0.07) (Ego *et al.*, 2001).

1.4.10 Vaginal Douching

Zhang *et al.* (1997), found vaginal douching to be associated with an increase in the incidence of ectopic pregnancy due to an increase in the risk of pelvic inflammatory disease.

1.4.11 Previous Ectopic Pregnancy

9.8% (Job-Spira *et al.*, 1996) or 10.2% (Ego *et al.*, 2001) of women who have one ectopic pregnancy will have further ectopics. Each time a woman has an ectopic pregnancy, her chance of a future intra-uterine pregnancy decreases. Ego *et al.* (2001) found a 58% rate of ongoing intra-uterine pregnancy in women who desired a further pregnancy within two years of a first ectopic pregnancy. If she had had two previous ectopic pregnancies, the rate was only 29% at the same point in time.

1.5 Importance of Diagnosis and Management on Morbidity and Mortality

A summary of the figures for maternal death, compiled for the Confidential Enquiries into Maternal Deaths, was shown in Table 1.1. The rates have not changed over the last 12 years. In the two most recent reports, most fatal cases are not diagnosed in either primary care or Accident and Emergency departments. The majority of women who had some sort of medical attention prior to death had reported symptoms suggestive of gastrointestinal or urinary tract disease. Early pregnancy deaths were the second leading cause of maternal death in the most recent report, and ectopic pregnancy taken in isolation was the fourth leading cause.

This is the same as is found in other countries. Ectopic pregnancy is reported as the second leading cause of maternal death in Japan (Shinagawa *et al.*, 1983). In Jamaica and Hong Kong it is the third leading cause, with a rate of 10.8 deaths related to ectopic pregnancy per 100,000 live births in Jamaica and 5.0 per 100,000 live births in Hong Kong (Walker *et al.*, 1986; Duthie *et al.*, 1989). Goldner *et al.* (1993) found ectopic pregnancy to be responsible for 13% of pregnancy related deaths in the United States. The case fatality fell from 3.55 per 1,000 ectopic pregnancies in 1970 to 0.38 per 1,000 ectopic pregnancies in 1989, which is similar to the UK.

Schneider *et al.* (1977), in his study population in the United States, found that older women were more likely to die from the complications of ectopic pregnancy. Deaths were characterised by a marked delay between onset of symptoms and both presentation and diagnosis.

Dorfman (1983) noted a doubling in the number of hospitalisations for ectopic pregnancy during the 1970's, with a mortality rate of 0.8 per 1,000 ectopic pregnancies. Black women and "other races" had 3.2 times the relative risk of dying as a result of ectopic pregnancy than white and Hispanic women. In Dorfman *et al.'s* (1984) paper they found that 85% of ectopic pregnancy related deaths were due to haemorrhage, with abdominal and interstitial pregnancies presenting later and, therefore, being more likely to result in death. They concluded that more prompt diagnosis and management might have prevented half of deaths related to ectopic pregnancy, and the woman seeking medical attention at an earlier stage might have prevented one third.

Rubin *et al.* (1983) noted a 75% reduction in the mortality from ectopic pregnancy between the year 1970 and 1978 in the United States. They, too, found that white women were less likely to die from ectopic pregnancy than non-white women. This might be because of issues of access to health care, or of language problems. The issue of language was also discussed as a barrier to diagnosis in the 1994 -1996 Confidential Enquiries (The Stationery Office, 1998). Duthie *et al.* (1989) observed a 72% decrease in the number of deaths due to ectopic pregnancy between 1961 and 1985 in the Hong Kong population.

What can be seen from data on maternal deaths related to ectopic pregnancy is that many of them might be avoided by increased awareness of the condition amongst women of childbearing age. In addition, increased awareness, and guidelines for the diagnosis and management of ectopic pregnancy, amongst the professionals who are responsible for the care of these women, is needed if the number of deaths is to be reduced to a minimum.

Whilst death resulting from ectopic pregnancy is the most important adverse outcome, it is rare. However, ectopic pregnancy is associated with long-term morbidity: infertility and recurrence of ectopic pregnancy. These issues are discussed further in following chapters.

Ectopic pregnancy remains a leading cause of maternal mortality; eight of the thirteen maternal mortalities in the 1997 to 1999 triennial report, occurring in women with ectopic pregnancy, were considered to be associated with substandard care (RCOG Press, 2001). When discussing how to improve the management of ectopic pregnancy, where and how the diagnosis of ectopic pregnancy is made needs to be considered:

1.5.1 Where the Diagnosis is Made.

Early Pregnancy Units (EPU) have evolved, firstly, from the recognition that some women required more than evacuation of their uterus when miscarriage was diagnosed (Turner *et al.,* 1991; Bradley and Hamilton-Fairley, 1998), and secondly,

from the realisation that they provided an efficient and cost effective means of dealing with common gynaecological complaints (Bigrigg and Read, 1991; Wren and Craven, 1999). Efficiency brings benefits to those providing the service: most women can be seen in normal working hours, reducing the burden upon the on-call doctors; ultrasound scanning is available at presentation; efficient use is made of theatre-time; in-patient stay is reduced, both before diagnosis and whilst awaiting treatment. But there are benefits for the patients as well; they are seen by dedicated staff who can provide ongoing support for the psychological recovery from miscarriage; the advice they receive is consistent; these units are easily accessible whether the patient is referred by her GP or the casualty officer, or she makes direct contact with the unit herself (Walker and Shillito, 1997).

The EPU was established at St. James's University Hospital in 1994. In the following year, 30% of women with pregnancies seen through this hospital experienced early pregnancy bleeding. 57% of women reporting early pregnancy bleeding to the EPU had a viable pregnancy on initial ultrasound scan. 3.4% of these women had an ectopic pregnancy that required intervention (Walker and Shillito, 1997).

EPUs are the ideal setting for patients who might potentially have an ectopic pregnancy to be reviewed and a management plan made. The patient's symptoms can be screened when the initial contact, usually by telephone, is made with the unit. Those with worrying symptoms can be fast-tracked for urgent review. Women, who have had an ectopic pregnancy in the past, can contact the unit as soon as

pregnancy is diagnosed to allow serum monitoring until the site of the current pregnancy can be established with the help of ultrasound examination. The results of ultrasound scans and serum monitoring can be reviewed by nursing and medical staff with specialist knowledge of early pregnancy complications, reducing the opportunities for the diagnosis to be missed. Once an ectopic pregnancy is diagnosed, the management options can be discussed with the patient, rather than just an automatic listing for "laparoscopy ?proceed". With the provision of protocols and guidelines for management, early pregnancy complications can be largely managed by specialist nurses with senior medical back-up, which removes the problem of management being decided by the more inexperienced junior medical staff. Within such a structure, proper training in early pregnancy complications can be offered to junior obstetricians and gynaecologists.

1.5.2 How is the Diagnosis Made.

This is not just the availability of appropriate investigations, both ward-based and surgical, but also the ability of the nursing and medical staff to interpret and act upon these results. Protocols aid in the diagnosis of early pregnancy complications giving guidelines to practitioners who have a general, rather than an expert understanding, and they also allow nurses to manage early pregnancy complications independently of doctors.

1.5.2a Clinical Findings

Ectopic pregnancy is a well known complication of early pregnancy, the first description recognisable as an ectopic pregnancy was that of Abulcasis AD936-1013, (Dimitry and Reid, 1993). The classically described symptoms are of pain, bleeding and amenorrhoea; but this presentation has not held true with time. In recent years more sensitive pregnancy tests have meant that women can confirm their pregnancy at a much earlier gestation and greater access to early pregnancy assessment means that many ectopic pregnancies are picked up in women who are, as yet, largely asymptomatic. This is proposed as one of the reasons why the incidence of ectopic pregnancy might be rising, with ectopic pregnancies that would have resolved without diagnosis now diagnosed and treated. Earlier presentation means that the classical triad of the symptoms of ectopic pregnancy is seen less frequently.

When hCG levels were tracked in asymptomatic women prior to performing an ultrasound scan, 64% of women with ectopic pregnancies and 40% with spontaneous miscarriages became symptomatic during the period of observation (Shepherd *et al.*, 1990). Reliance on symptoms alone would be misleading, as 16% of women with normal intrauterine pregnancies also reported the same symptoms and 36% of women with ectopic pregnancies reported none; patient reported symptoms are an unreliable predictor of ectopic pregnancy. In women

with symptoms suggestive of ectopic pregnancy after IVF-ET (Mol *et al.*, 1997), just over half were eventually diagnosed with ectopic pregnancies.

At the other extreme, some women present with major haemorrhage. This haemorrhage can be life-threatening. In some cases, it happens so suddenly that it is unlikely that earlier diagnosis would have been possible. In others, increased awareness amongst women of reproductive age, and better management by the doctors attending them, might have prevented a medical emergency, which, at its worst, is a cause of maternal death. A recent estimate by Bajekal *et al.* (2000) puts 8-10% of women with ectopic pregnancy presenting with signs of shock requiring immediate treatment.

Unilateral pain might be a symptom indicating tubal rupture, but tubal rupture is not always associated with major haemorrhage; some women with tubal rupture will have little in the way of active blood loss, as demonstrated by occasional cases of abdominal pregnancies reaching viability. Equally, every case of major haemorrhage is not associated with tubal rupture and large quantities of intra-abdominal blood can be seen with an intact tube. Tubal abortion is also associated with unilateral, sometimes severe, abdominal pain, and yet, tubal abortion often leads to spontaneous resolution of the ectopic pregnancy. With a low specificity for complicated ectopic pregnancy, abdominal pain and/or tenderness would not be a contraindication to medical management if there were no evidence of cardiovascular compromise. A symptomatic patient might, however, prefer surgical management, as this will lead to a more rapid resolution of her symptoms. But, if

the patient's clinical state allows, paired hCG estimations 48 hours apart might prevent unnecessary intervention for a spontaneously resolving tubal abortion.

Equally, clinical examination might not help with diagnosis. If no suspicious signs are found, this does not exclude ectopic pregnancy. There is also the danger that pelvic examination might precipitate tubal rupture and haemorrhage.

Mol *et al.* (1999[a]) felt that digital vaginal examination was unnecessary when a combination of trans-vaginal ultrasound and hCG estimations was used. They also looked at factors predictive of tubal rupture and/or active bleeding (Mol *et al.* 1999[b]). Abdominal pain was the most sensitive predictor with a sensitivity of 95%. But again, the specificity was low at 37%.

Pain that is described as moderate to severe, lateral or sharp, is more predictive of ectopic pregnancy than centralised pain. On examination, peritoneal signs, cervical excitation pain, and lateral or bilateral abdominal or pelvic tenderness increased the risk of ectopic pregnancy (Dart *et al.*, 1999). Although the authors found these factors predictive, the outcomes were so variable that they concluded no constellation of findings could confirm or exclude a diagnosis of ectopic pregnancy with a high degree of reliability.

If pelvic examination is considered unnecessary in most cases of suspected ectopic pregnancy, this will limit the opportunity to take endo-cervical swabs to screen for chlamydia in a population that is at higher risk of being infected. This problem could be overcome by using urine PCR testing for chlamydia and, as it is more

acceptable to the patient, its introduction is likely to result in more patients being tested.

1.5.2b Ultrasound

The presence of an intrauterine pregnancy largely excludes ectopic pregnancy. A fetal heart beat is always found when the mean sac diameter exceeds 18mm (Cacciatore *et al.*, 1990[a]). As a result of the public inquiry called by South Glamorgan Health Authority (Hately *et al.*, 1995) it was recommended that on trans-vaginal scan, a 20mm mean gestation sac diameter be the cut-off for diagnosing a failed pregnancy when neither yolk sac nor fetal pole was found.

Trans-vaginal ultrasound will detect a yolk sac or fetal pole up to one week earlier than trans-abdominal ultrasound (Weston, 2001). Trans-vaginal ultrasound appears to be an acceptable investigation with 88.1% of women agreeing to the examination in one study, the common reasons for refusal were fear of miscarriage or discomfort (Braithwaite and Economides, 1997). Trans-vaginal scanning may be the more comfortable option, as the bladder is not required to be full.

The presence of an intrauterine gestation sac generally excludes an ectopic pregnancy, although the level of hCG at which an intrauterine gestation sac should *always* be seen is not established (Lipscomb *et al.*, 2000). It is probably difficult to give a fail-safe level because of differences in the assay between units, and the differences in level that can be found in the same individual in one day.

There are two situations when the apparent appearance of an intrauterine sac can be misleading, firstly, in the presence of a heterotopic pregnancy, and secondly, when a pseudogestation sac is seen.

Heterotopic pregnancy is the co-existence of an intrauterine pregnancy and an ectopically sited pregnancy. It is said to occur once in every 7000 pregnancies (Mehta *et al.*, 1997) and the incidence is higher after assisted conception where more than one embryo is replaced, often in women with pre-existing tubal disease. To diagnose heterotopic pregnancy, a high index of suspicion is required. If a heterotopic pregnancy is suspected and the woman's symptoms give concern, a laparoscopy is the only means of diagnosis - hCG levels will be misleading as they are partly made up by the viable pregnancy which will give normally rising levels on serial measurement even if the ectopically placed trophoblast is non-viable. Ultrasound is likely to be unhelpful unless an adnexal mass contains a fetal heart pulsation or yolk sac. Mol *et al.* (1997[a]) found that in women who had undergone IVF-ET, the presence of an intrauterine gestation sac virtually excluded a heterotopic pregnancy if the woman was asymptomatic. In the presence of symptoms of pain and bleeding, an intrauterine gestation sac reduces the probability of a heterotopic pregnancy from 53% to 17%.

A pseudogestation sac is a fluid collection found within the endometrial cavity in ectopic pregnancies. Various ultrasound findings have been described to help differentiate the early gestation sac from the pseudogestation sac. The normal early pregnancy is eccentrically placed within the endometrium, the

pseudogestation sac central within the cavity. An intrauterine sac displays the intradecidual sign - the presence of an oval or round fluid collection within the decidua with an echogenic rim (Mehta *et al.*, 1997). The double decidual sac sign is the appearance of two concentric rings and is specific for an intrauterine pregnancy (Bradley *et al.*, 1982; Nyberg *et al.*, 1983). However, in up to a third of normal early gestations the double ring sign is not seen (Weston, 2001). Nyberg *et al.* (1988) found pseudogestation sacs in only 2 out of 26 ectopic pregnancies in their prospective study of trans-vaginal ultrasound findings in early pregnancy complications. In both cases, the pseudogestation sac was clearly within the endometrial cavity, which should have differentiated it from a true gestation sac.

Cacciatore *et al.* (1990[b]) claimed that an adnexal mass was a reliable sign of ectopic pregnancy with a specificity of 99%, an adnexal mass was not seen in only 8% of ectopic pregnancies in their series. However, in Ankum *et al.'s* (1993) experience, an ectopic pregnancy (defined as either an adnexal gestation sac, with or without a fetal pole or fetal heart pulsation or an adnexal mass with associated fluid in the Pouch of Douglas) was found with trans-vaginal ultrasound in only 56% of cases of ectopic pregnancy.

Mol *et al.* (1998[a]) looked at the predictive value of various ultrasound findings for ectopic pregnancy. They diagnosed ectopic pregnancy on the basis of ultrasound findings alone if a yolk sac, a fetal pole or fetal cardiac activity were seen within the adnexa. When an intrauterine gestation sac was not found on the initial trans-vaginal ultrasound, additional findings increased the likelihood of an ectopic

pregnancy. If an adnexal mass was found, the likelihood ratio was 3.6 for the presence of an ectopic pregnancy. Fluid in the Pouch of Douglas was a little more predictive with a likelihood ratio of 4.4. When both findings were combined, the likelihood ratio for an ectopic pregnancy increased to 9.9. However, in 3% patients where an intrauterine pregnancy was diagnosed on initial trans-vaginal ultrasound, a final diagnosis of ectopic pregnancy was made. In women with an empty uterus and the presence of additional ultrasound findings, the likelihood ratio for ectopic pregnancy increased strongly when serum hCG was >1500miu/ml (3rd IS). If no additional ultrasound findings were present, the likelihood ratio for an ectopic pregnancy increased strongly when the serum hCG was >2000miu/ml (3rd IS).

Fluid in the Pouch of Douglas can be a normal finding in early viable intrauterine pregnancies. In Nyberg *et al.'s* 1988 series, small to moderate amounts of fluid were found in 22% of women with normal intrauterine pregnancies. Adnexal masses are likewise not always abnormal. A collapsing or haemorrhagic corpus luteum cyst will be reported as such if an intra-uterine pregnancy is found, but the same finding raises suspicion of ectopic pregnancy if the uterus is empty.

The thickness of the endometrium on trans-vaginal ultrasound has been examined as a further means of differentiating between intrauterine and extra-uterine pregnancies. Spandorfer and Barnhart (1996) proposed that the endometrial stripe thickness was dependent upon the hormonal milieu, and therefore a thicker endometrial stripe would be found in normal early pregnancy and a thinner endometrial stripe in an abnormal pregnancy. Their retrospective study found that

no ectopic pregnancies were found if the endometrial stripe thickness was >13mm, no normal intrauterine pregnancies were found if it were <6mm. In all cases the hCG level was <1500miu/ml. Using receiver-operator curves, they used a cut-off of 8mm. This detected 71% of ectopic pregnancies, although it did not discriminate between ectopic pregnancy and abnormal intrauterine pregnancy and would seem to offer little advantage over other investigations for ectopic pregnancy.

Others have not supported their findings. Levgur *et al.* (2000) found that endometrial stripe thickness did not vary with gestation. They compared ectopic pregnancies with normal intrauterine pregnancies, and, whilst they found that the endometrial thickness was less in ectopic pregnancies (9.9mm +/- 5.9) than in normal pregnancies (12.6mm+/- 5.3), the range of measurements obtained was similar, 2 to 24mm in the ectopic pregnancy group and 4 to 26mm in the normal intrauterine pregnancy group.

Mehta *et al.* (1999) found endometrial thickness unhelpful in the differential diagnosis of early pregnancy problems, as there was no difference in the endometrial thickness in ectopic pregnancy (mean 9.0mm, range 2 to 20mm) and spontaneous miscarriage (mean 8.4mm, range 2 to 18mm). Endometrial thickness was assessed when an empty uterus was found and was not correlated with the level of hCG.

1.5.2c hCG

In 1976, Braunstein *et al.* used newer assays, specific to the β-subunit of hCG, to describe the pattern of serum hCG throughout pregnancy. They showed the exponential rise in levels in early first trimester, which has subsequently been exploited to differentiate normal from abnormal early pregnancy.

Kadar *et al.* (1981) proposed the concept of the discriminatory level of hCG; that is, the level of hCG when an empty uterus is likely to represent an ectopic pregnancy, rather than an early intrauterine pregnancy. This was based on the findings of trans-abdominal ultrasound and they suggested an hCG level of 6500miu/ml.

With increasing use of trans-vaginal ultrasound, where the greater magnification and the closer proximity of the transducer to the uterus improve resolution, the contents of the uterus can be determined at an earlier stage. This has lead to a reduction in the discriminatory hCG level.

Cacciatore *et al.* (1990a) found the following hCG levels with progressive changes on transvaginal ultrasound:

Table 1.3 hCG levels related to ultrasound findings

	Serum hCG (miu/ml)		Gestational age (days)	
	Mean	Range	Mean	Range
Intrauterine sac	730	432-935	31.2	30-33
Yolk sac	4310	120-7280	36.0	34-38
Fetal heart beat	12050	9280-22950	41.1	39-43

They suggested a level of 1000miu/ml as the cut-off at which the absence of a gestational sac implied an ectopic pregnancy (Cacciatore *et al.* 1990b). They used the 2nd International Standard (2nd IS) for the measurement of hCG, the 3rd International Standard (3rd IS) is now more widely used and produces values 1.5 to 2 times that of the 2nd IS (Buster and Carson 1997). They equated Cacciatore *et al.'s* cut-off level of 1000miu/ml to a level of 1800miu/ml on the 3rd IS. They also noted that multiple pregnancies had higher levels of hCG for equivalent gestations, hence they set their discriminatory zone above the level at which they felt confident that an intrauterine gestation sac should be seen.

Ankum *et al.* (1993[b]) analysed the sensitivity and specificity of various ranges of single hCG estimations in the diagnosis of ectopic pregnancy when an empty uterus is found on ultrasound scan. All ranges of hCG levels approached a sensitivity of 1.00, but the specificity was poor at low levels of hCG. Even in the range of 3000 to 4500miu/ml, (equivalent to 3rd IS) the specificity was only 0.87. In

their conclusions, they felt that an hCG of 3,000miu/ml represented the best discriminatory zone.

Unlike spontaneous conception, when assisted conception techniques are used the gestation of the pregnancy is usually accurately known. 4.5% of clinical pregnancies after IVF-ET are ectopic pregnancies (Marcus and Brindsen, 1995). Marcus *et al.* (1995) found that they could predict 90% of ectopic pregnancies by day 23 post embryo transfer, on isolated hCG results alone. However, 10% of women with ectopic pregnancies had hCG levels of <10miu/ml, and were thought not to be pregnant (it is not clear whether treatment for ectopic pregnancy was required in these cases). 22.5% of women with ectopic pregnancies, had hCG levels comparable with viable singleton pregnancies and, by the author's own admission, this demonstrated the limitation of a single hCG level.

In the series described by Mehta *et al.* (1997) of women with hCG levels >2000miu/ml (3rd IS), suspected of having an ectopic pregnancy who underwent laparoscopy, 33% were eventually found to have normal intrauterine pregnancies. On review, six of the seventeen could have been said to have a weak intradecidual sign. They suggested, to avoid unnecessary intervention, a second hCG level would be desirable and they also concluded that there were limitations to the use of hCG estimations.

The doubling rate of hCG has also been examined as a predictor of ectopic pregnancy; non-viable trophoblast, whether that is an ectopic pregnancy or a non-

viable intrauterine pregnancy, has a prolonged doubling time. Zegers-Hochschild *et al.* (1994) found that the doubling time for hCG between 11 and 23 days post-ovulation in normal pregnancy, was 1.43 days. Daya (1987), found the doubling time gradually increased throughout first trimester with the hCG levels plateauing at 9 weeks gestation. Pittaway *et al.* (1985) found a doubling time of 1.4 days between days 28 to 35 post last menstrual period (lmp), 2.7 days between 35 to 42 days post lmp and 3.3 days between days 41-49 post lmp. The hCG level in viable intrauterine pregnancies in first trimester can therefore be said to double approximately every 48 hours. Although a doubling time of greater than 48 hours will, therefore, distinguish most ectopic pregnancies, it is not reliable in isolation. As Yao and Tulandi (1997) state, 15% of normal pregnancies have an abnormal hCG rise, O'Leary *et al.* (1996) found that with normal intrauterine pregnancies, the rise in hCG will be at least 66% over 48 hours. Neither does a normal rise always exclude ectopic pregnancy, as well implanted ectopic trophoblast can result in normal levels of hCG, at least in the early stages. In Shepherd *et al.'s* (1990) series, 64% of women with asymptomatic ectopic pregnancies initially exhibited a normal doubling of hCG and 15% persisted with a normal rise.

Mol *et al.* (1998[a]) observed that an ectopic pregnancy was never observed when the hCG level fell by >50% over 48 hours, although their definition of ectopic pregnancy, in this case, did not include ectopically situated non-viable trophoblast. They found serial values of hCG more discriminatory than single values, p=0.0003 for absolute value versus absolute difference. The measurement that was of most

diagnostic value was that taken 4 days after the baseline value. Unlike ultrasound characteristics, patient characteristics of abdominal pain and vaginal bleeding had no influence on the diagnostic performance of hCG measurements.

A single hCG estimation has little value in predicting ectopic pregnancy; paired levels are also of little value without also considering the clinical presentation and ultrasound appearances.

1.5.2d Progesterone

Progesterone has similar limitations to hCG, in that it will not differentiate between an ectopic pregnancy and a non-viable intrauterine pregnancy. It has the advantage over hCG that its levels in the first nine weeks of pregnancy remain constant (O'Leary *et al.*, 1991) and so a single sample is of value. In the first trimester, hCG reflects function of the trophoblast and progesterone function of the corpus luteum. Levels of progesterone, like hCG, are lower in abnormal pregnancy when compared to normal pregnancy. But also, as with hCG, normal levels of progesterone do not exclude ectopic pregnancy, as there is substantial over-lap between levels found in extra-uterine and normal pregnancies. This explains the wide range of suggested "critical" progesterone levels to discriminate between intrauterine and extra-uterine pregnancies, with levels of progesterone ranging between 21-80nmol/l (Yeko *et al.*, 1987; Buck *et al.*, 1988; Hahlin *et al.*, 1990).

O'Leary *et al.* (1996) suggested that a combination of a single hCG and progesterone level provides better discrimination: hCG <3000miu/ml had a sensitivity of 74% and a specificity of 88%, in combination with a progesterone level of <40nmol/l, the sensitivity was 88% with a specificity of 82%. Whether this offers any advantage for the additional expense is unclear. Neither was this combination compared to the use of serial hCGs, their argument being that serial hCG estimations are not appropriate in some cardiovascularly unstable women, although an additional serum investigation at presentation in such women is unlikely to alter management anyway.

1.5.2e Diagnostic Laparoscopy

In 1989[a], Vermesh felt diagnostic laparoscopy was indicated in all cases of suspected ectopic pregnancy, unless the woman's condition merited an immediate laparotomy.

If diagnostic laparoscopy is required in every case of ectopic pregnancy, there is little to justify medical management of ectopic pregnancy as this exposes the woman to the risks of both types of management.

There have been various attempts at producing diagnostic algorithms to allow diagnosis of ectopic pregnancy without recourse to laparoscopy. An early algorithm from Ankum *et al.* (1993[a]) used daily hCG measurements and a discriminatory level of 1500miu/ml, but did not consider the rate of increase of the hCG level with

time as part of their diagnostic process. This algorithm had a sensitivity of 0.97 and specificity of 0.95, but 8.4% of patients did not complete the protocol because of signs of shock. 1% of the subjects had a diagnostic laparoscopy to confirm an ectopic pregnancy and were later found to have a viable intrauterine pregnancy. They felt that a higher discriminatory zone might have reduced the false positive rate, but were concerned that this would lead to too great a delay in diagnosis of ectopic pregnancy. Also, intrauterine pregnancies were diagnosed as ectopics because adnexal masses on ultrasound scan were misinterpreted as ectopic pregnancies.

Stovall and Ling (1993[a]) proposed that the introduction of diagnostic algorithms would lead to "the virtual elimination of diagnostic laparoscopy", earlier diagnosis of ectopic pregnancy, with fewer women experiencing tubal rupture and greater use of medical and expectant management. Their algorithm incorporated history and clinical findings, serum hCG and progesterone levels, colour flow vaginal Doppler flow sonography and endometrial curettage with a combination of medical, surgical and expectant options for management.

Mol *et al.* (1999[d]) examined algorithms again to see if their predictive value could be improved by making them flexible. This model took into account the patients risk factors for ectopic pregnancy, so that the post-test probability of ectopic pregnancy would be greatest in those women with the greatest pre-test risk factors. They concluded that incorporating probabilistic decision rules into algorithms improved the diagnosis of ectopic pregnancy.

If a miscarrying pregnancy is medically treated as an ectopic pregnancy, it is unlikely that this will lead to an adverse outcome, but it is unacceptable to medically treat a viable intrauterine pregnancy as an ectopic pregnancy.

1.5.2f Diagnostic Curettage

Lipscomb *et al.* (2000) argued that there is a greater role for diagnostic curettage in excluding non-viable intrauterine pregnancy if hCG levels are <2000miu/ml. This is not withstanding the extra expense of an additional surgical procedure and the delay whilst the curettings are analysed histologically. Pisarska *et al.* (1998) use curettage as a first line a diagnosis for non-viable pregnancies, proposing that a drop in the serum hCG level of 15% or more following a diagnostic curettage is indicative of miscarriage as opposed to ectopic pregnancy. If the presence, but not the site, of non-viable trophoblast has been determined, a single dose of methotrexate would be a possible treatment in either case, and would reduce the need for further surgical procedures.

It is obvious that, although there is a great improvement in diagnostic methods, there is still no perfect approach.

1.6 Fibronectins – is there a Role for Fetal Fibronectin in the Diagnosis of Ectopic Pregnancy?

Fibronectins are non-collagenous glycoproteins and are widely distributed throughout the body. They are present in varying forms at different sites; a soluble

form, produced in the liver, is found in the plasma, an insoluble form is found in the extra-cellular matrices. Fibronectins promote cell attachment to the substratum and are active in cell spreading and migration.

Fibronectins have been demonstrated in the villous stroma and trophoblastic basement membranes (Rukosuev, 1992) and the walls of fetal blood vessels in first trimester placentae. In late pregnancy, fibronectins are found predominantly in the walls of fetal blood vessels. (Yamada *et al.*, 1987)

Fibronectins present only in fetal and malignant invasive cells, which have invasive as well as adhesive properties, have been described. (Borsi *et al.*, 1987; Carnemolla *et al.*, 1989; Frank *et al.*, 1994) An IgG1 monoclonal antibody, FDC-6 defines a unique domain on the oncofetal form of fibronectin which is not found on the normal adult form of fibronectin. (Matsuura and Hakomori, 1985) A single glycosylation at a defined threonine residue of the III CS region of fibronectin induces conformational changes in the peptide to form the specific oncofetal epitope recognised by the FDC-6 antibody (Matsuura *et al.*, 1988). It is this FDC-6 antibody that has been used to measure levels of fetal fibronectin in following chapters.

Fetal fibronectin has already an established role in the diagnosis of later pregnancy complications. A diagnostic kit and a quantitative assay are available commercially. Its current use is discussed below, and part of this thesis seeks to explore its potential as a diagnostic aid with early pregnancy complications.

1.6.1 Fetal Fibronectin as a Predictor of Preterm Delivery

The presence of the fetal form of fibronectin in the cervico-vaginal secretions as a predictor of pre-term labour was first proposed in 1991 (Lockwood *et al.*, 1991). It was postulated that damage to the fetal membranes would release fetal fibronectin, which would then be found in the cervico-vaginal secretions. It was found that women who delivered at term rarely had concentrations of fetal fibronectin above 0.05 μg/ml between 21 and 37 weeks gestation.

Numerous studies have looked at fetal fibronectin levels in high risk subjects, (Nageote *et al.*, 1994; Bittar *et al.*, 1996; Leeson *et al.*, 1996) low risk subjects (Morrison *et al.*, 1993; Hellemans *et al.*, 1995; Goldenberg *et al.*, 1997; Crane *et al.*, 1999; Goepfert *et al.*, 2000; Heath *et al.*, 2000;) and symptomatic subjects (Goldenberg *et al.*, 1996; Malak *et al.*, 1996; Lukes *et al.*, 1997; Peaceman *et al.*, 1997; Chuileannain *et al.*, 1998; Joffe *et al.*, 1999). All have found raised levels of fetal fibronectin to be predictive of premature labour, but as one author points out, there is no evidence that use of this test leads to any reduction in spontaneous preterm birth (Goldenberg *et al.*, 1996).

An overview (Chien *et al.*, 1997) of the use of fetal fibronectin to predict preterm labour identified 32 studies addressing the issue. 17 of these studies were selected for analysis (2 were eliminated because of inappropriate study populations, 6 for lack of original data, 2 for lack of relevant outcome measures being reported and 5 because the same data was reported in more than one article).

They concluded that fetal fibronectin in the cervico-vaginal mucus has limited accuracy in predicting preterm labour as the likelihood ratios for positive and negative test results generated only minimal to moderate changes in the pretest probability of preterm birth. A negative result for fetal fibronectin would seem to have more significance than a positive. *(Tables 1.4 and 1.5)*

Table 1.4. Summarises the results of the meta-analysis of the role of fetal fibronectin in the diagnosis of preterm labour – the effect on the likelihood ratios (LR) of positive and negative results. 95% confidence intervals in brackets. Positive result >0.05μg/ml of fetal fibronectin

Group tested	Outcome	Pooled LR +ve swab	Pooled LR –ve swab
Symptomatic	Delivery <34/40	2.6 (1.8 – 3.7)	0.2 (0.1 – 0.5)
	Delivery within 1 week	5.0 (3.8 – 6.4)	0.2 (0.1 – 0.4)
Asymptomatic high risk	Delivery <37/40	2.0 (1.5 – 2.6)	0.4 (0.2 – 0.8)
	Delivery <34/40	2.4 (1.8 – 3.2)	0.6 (0.4 – 0.9)
Asymptomatic low risk	Delivery <37/40	3.2 (2.2 – 4.8)	0.8 (0.7 – 0.9)

Table 1.5. Summarises the results of the meta-analysis of the role of fetal fibronectin in the diagnosis of preterm labour – the change in the pre-test probability of having a positive or negative result for pre-term delivery. Positive result >0.05μg/ml

Group tested	Outcome	Pre-test probability	+ve result	-ve result
Symptomatic	Delivery <34/40	32.5%	55.6%	8.2%
	Delivery within 1 week	6.6%	25.8%	1.2%
Asymptomatic high risk	Delivery <37/40	31.5%	47.9%	16.6%
	Delivery <34/40	15.7%	31.0%	9.9%
Asymptomatic low risk	Delivery <37/40	25.0%	52.0%	22.0%

1.6.2 Fetal Fibronectin in Pre-Labour Rupture of the Membranes

Lockwood *et al.* also found high levels of fetal fibronectin in the amniotic fluid and in 93.8% of the cervicovaginal secretions of women with preterm rupture of the membranes (Lockwood *et al.*, 1991). As a consequence, the presence of fetal fibronectin with the cervicovaginal secretions has been explored as a means of diagnosing pre-labour rupture of the membranes in equivocal clinical situations. Although it was a sensitive indicator of preterm rupture of the membranes, with 98.2% of subjects having fetal fibronectin levels of greater than 0.05μg/ml, it was not specific with 19.4% of controls having similar levels (Eriksen *et al.*, 1992). The

latter is not surprising, as it would be expected that elevated fetal fibronectin would be found, as some subjects will deliver prematurely despite intact membranes.

If fetal fibronectin is detected when a diagnosis of pre-labour rupture of membranes is suspected, this finding does not appear to predict any difference in the outcome of the pregnancy – either in duration of the pregnancy or in complications of labour (Nisell *et al.*, 1996).

1.6.3 Fetal Fibronectin in Post-Dates Pregnancy

As the presence of fetal fibronectin in the cervicovaginal secretions is associated with preterm labour, the next logical step would seem to be to evaluate its role in the post-term pregnancy and whether it might predict those pregnancies that can be successfully induced. Lockwood *et al.* found that the presence of a positive fetal fibronectin swab between 39+0 and 39+6 weeks predicted delivery within the next ten days (Lockwood *et al.*, 1994). Garite *et al.* (1996) found that women with levels of fetal fibronectin that were greater than 0.05μg/ml took less time to induce: 21.3 hours with positive swabs and 31.1 hours with negative swabs (p=0.0001) and had a lower caesarean section rate: 15% of those with positive results and 27% of those negative results (p=0.05).

1.6.4 Fetal Fibronectin in Early Pregnancy

Since starting this study, two papers have been published on fetal fibronectin in the diagnosis of ectopic pregnancy (Ness *et al.*, 1998; Nowacek *et al.*, 1999).

Ness *et al.* compared the levels of fetal fibronectin found in women with a diagnosis of ectopic pregnancy (31 subjects) or threatened, incomplete or complete miscarriages (38 subjects) with normal early pregnancy (41 subjects). A further group consisted of those with pain or bleeding with an as yet undetermined diagnosis (45 subjects). They found that fetal fibronectin discriminated poorly between extra-uterine gestations and other early pregnancy complications, a level of 0.3μg/ml having a sensitivity of 0.94 and a specificity of 0.14. This should be considered against a background of a test being considered positive at a level of 0.05μg/ml in later pregnancy and bedside tests are designed to give positive readings at this level.

Nowacek *et al.* examined 46 subjects at high risk of ectopic pregnancy, or with signs or symptoms of ectopic pregnancy. 12 had a final diagnosis of ectopic pregnancy, 34 intrauterine pregnancies. Positive results (defined as fetal fibronectin levels of more than 0.05μg/ml) were obtained in 41.7% of cases in which the diagnosis was ectopic pregnancy and 35.3% of cases where an intra-uterine pregnancy was diagnosed.

The work on fetal fibronectin presented in this thesis will explore the predictive value of fetal fibronectin before a diagnosis can be made and study why the results are so variable.

1.7 Management of Ectopic Pregnancy

Once a diagnosis of ectopic pregnancy has been made, it becomes important to consider what treatment options are available. The optimum treatment of ectopic pregnancy will depend on the outcomes required. At one extreme, any possible case should be treated aggressively and early to avoid maternal death. However, although minimising maternal mortality is an important outcome, it is a rare outcome and overly aggressive management will increase mortality and morbidity resulting from unnecessary surgery. In both of the last Confidential Enquiries, a proportion of the deaths were caused by the surgical treatment of the ectopic pregnancies, rather than by misdiagnosis (The Stationery Office, 1998; RGOG Press, 2001). If a more considered approach to diagnosis is used, more normal and failing intra-uterine pregnancies can be differentiated from ectopic pregnancy without resorting to laparoscopy and a wider choice of management options can be offered to the woman in whom an ectopic pregnancy is confirmed. This thesis will discuss women's choices for the management of ectopic pregnancy and the short and long-term implications of these choices.

1.7.1 Evolution of the Treatment of Ectopic Pregnancy.

In 1888, Lawson Tait first described the surgical management of ectopic pregnancy, pioneering the then new concept that surgical intervention, in such cases, might be life saving. He saved the life of 38 out of 40 women with ectopic

pregnancy (Stromme, 1973). He used salpingectomy; his basic technique has remained largely unchanged.

The first conservative surgical procedure for the treatment of ectopic pregnancy, with preservation of the fallopian tube, was described in 1953, (Stromme 1953). Laparoscopic management of ectopic pregnancy was first described in 1973, (Shapiro and Adler, 1973), and the first description of conservative laparoscopic surgery was in 1980, (Bruhat *et al.*, 1980).

The first reported case of ectopic pregnancy treated with methotrexate was by Tanaka *et al.* in 1982. This was a logical progression from the use of methotrexate in the management of trophoblastic disease.

When surgery was first performed in the management of ectopic pregnancy, the aim was to preserve the woman's life. As time has gone on, there have been increasing efforts to try to reduce the morbidity associated with ectopic pregnancy. Ectopic pregnancy poses two main long-term problems: reduced subsequent fertility and an increased risk of a further ectopic pregnancy. Changes in management of ectopic pregnancy have centered around attempts to conserve the Fallopian tube in the hope that this will increase the chances of a spontaneous conception by leaving both tubes to function. The concern is that conservative methods of treating ectopic pregnancy also leave a damaged tube, increasing the risk of future tubal pregnancies in women who are already at greater risk of ectopic pregnancy.

Bouyer *et al.* (2000[b]) looked at 291 women who had attempted to conceive after an ectopic pregnancy. 66% had achieved a conception, 41% had had either a live birth or their pregnancy was ongoing at the time of survey, 15% had had a miscarriage and 10% a further ectopic pregnancy (that is 16% of women who had actually become pregnant had a further ectopic pregnancy). The 18 month cumulative spontaneous intrauterine pregnancy rates were 57% for radical surgery, 73% for conservative surgery and 80% for medical treatment. When the figures were adjusted for confounding factors (e.g. age and education), there was no significant difference in subsequent intrauterine pregnancy rates for radical or conservative surgical treatment, although a similar trend was noted. If women with a prior history of infertility were considered, radical surgery gave a significantly lower subsequent pregnancy rate than conservative surgery, if there was no such prior history, no significant difference was found.

1.7.2 Surgical – Laparoscopy v Laparotomy

In the Cochrane Library review of management of ectopic pregnancy, Hajenius *et al.* (2000) found three studies suitable for meta-analysis to compare tubal preservation at laparoscopy with laparotomy (Vermesh *et al.* 1989[b]; Lundroff *et al.* 1991; Murphy *et al.* 1992). This review concluded that conservative surgery was significantly less successful when it was performed laparoscopically than when it was performed at the time of laparotomy (RR 0.90, 95% CI 0.83, 0.97) due to the higher rate of persistent trophoblast after laparoscopic management (RR 3.6, 95% CI 0.63, 21). In the short term, laparoscopic management was less costly than

open surgical management because blood loss and analgesic requirements were lower; also operative time, hospital stay and convalescence were shorter. The cost reduction for conservative laparoscopic surgery will, however, be offset to some extent, by the cost in medically treating persistent ectopic pregnancy. In the paper by Lundroff *et al.*, the majority of their patients with persistent trophoblast were treated surgically, which further reduces any saving made by treating ectopic pregnancy by laparoscopy.

In the long-term, conservative laparoscopic management offered similar tubal patency rates, similar intrauterine pregnancy rates and a non-significant reduction in the repeat ectopic pregnancy rate as conservative management at laparotomy.

1.7.3 Surgical – Salpingectomy v Salpingotomy

One of the problems encountered in comparing conservative and radical management of ectopic pregnancy is whether the two groups are similar. Smaller, unruptured and less symptomatic tubal pregnancies are likely to be selected for conservative surgery, whereas more complicated ectopic pregnancies will require salpingectomy. Similarly, for an ectopic pregnancy to be medically managed, the rise in hCG will be smaller and the levels lower – representing less viable trophoblast – than unsuitable cases requiring surgery.

Yao and Tulandi (1997) reviewed current management of ectopic pregnancy. They reviewed nine studies that compared the reproductive outcome of women undergoing conservative and radical surgery. There was a total of 528 women in

the conservative and 1,246 in the radical group. Of those desiring fertility, 53.0% in the conservative group and 49.3% in the radical group subsequently achieved an intrauterine pregnancy, whilst 14.8% and 9.9% respectively had a further ectopic pregnancy. The studies considered were not strictly comparable, and Yao and Tulandi felt that they could only conclude that *"conservative surgery may provide a subsequent intrauterine pregnancy rate that is at least comparable to or possibly higher than that after radical surgery. Unfortunately, the recurrent ectopic pregnancy rate may also be higher after conservative surgery"*. They felt a trial, randomising women with ectopic pregnancy to either salpingectomy or salpingotomy, was necessary to determine whether salpingotomy offered any long-term advantage when a diagnosis of ectopic pregnancy was made. Such a trial has still not been performed.

Data published after the Yao and Tulandi study has been contradictory. A retrospective cohort study (Mol *et al.*, 1998[b]) found a two-year cumulative pregnancy rate of 62% in women who had undergone conservative surgery for ectopic pregnancy and 30% in women who had undergone radical surgery. A study of laparotomy versus laparoscopic management of ectopic pregnancy (Fernandez *et al.*, 1998[a]) found the opposite, with a 75% two-year cumulative pregnancy rate following radical surgery and a 40% rate following conservative surgery or medical management, although the follow-up was shorter (eighteen months) in the latter group.

It might be thought that the relatively small difference in the intrauterine pregnancy rate, between salpingectomy and salpingotomy, is a result of any intra-uterine

pregnancy being conceived largely through the unaffected tube, with the conserved tube contributing little to the intra-uterine pregnancy rate after salpingotomy. The higher repeat ectopic pregnancy rate after salpingotomy being a result, therefore, of those conceptions that are achieved through the damaged tube. In Yao and Tulandi's review, data from 176 women in whom conservative surgery had been performed in a solitary fallopian tube, found similar pregnancy rates to women with both tubes present at the start of surgery, with 54.5% of those attempting to conceive achieving an intrauterine pregnancy whilst 20.5% had recurrent ectopic pregnancies. This confirms that damaged tubes do not inevitably lead to ectopic pregnancy and successful intra-uterine pregnancy can be achieved.

Other factors are likely to be more important than the method of treatment of ectopic pregnancy in determining the chances of a successful intrauterine pregnancy in the future. The subsequent pregnancy rate is lower in women with a history of prior infertility (Sultana *et al.*, 1992; Ory *et al.*, 1993). Pouly *et al.* (1991) found a lower intrauterine pregnancy rate in women in whom there was evidence of damage to the contra-lateral tube at the time of surgery for ectopic pregnancy.

The risk of persistent trophoblast, i.e. incomplete elimination of all active trophoblastic tissue, is a potential complication when conservative surgery is used in the treatment of ectopic pregnancy. Any conservative procedure requires post-operative surveillance of serum hCG levels. The risk of persistent trophoblast appears to be higher with smaller ectopic pregnancies (i.e. <2cm diameter), earlier

therapy (<42 days from LMP), initial hCG levels of >3,000miu/ml and implantation medial to the salpingotomy site (Seifer, 1997).

In Yao and Tulandi's review (1997) of the management of ectopic pregnancy, they reported rates of persistent trophoblast following conservative surgery of between 3 and 20%. Overall, patients treated with conservative surgery at laparotomy had a 3.9% rate of persistent trophoblast, and in equivalent women treated laparoscopically the rate was 8.3%. Persistent trophoblast, and its treatment, did not appear to have any detrimental effect on subsequent pregnancy rates.

Graczykowski and Mishell (1997) proposed prophylactic methotrexate after conservative surgery to reduce the risk of persistent trophoblast. The same argument can be used against this treatment regime as laparoscopic infiltration with methotrexate, the patient is electively exposed to the side effects and risks of two procedures. However, methotrexate successfully reduced the incidence of persistent trophoblast and the duration of hCG monitoring post-operatively.

Methotrexate can be used more selectively after salpingotomy, being given when hCG levels do not support resolution of the trophoblast. This limits the number of women exposed to dual management and avoids the necessity for a second surgical procedure. In their series, Hoppe *et al.* (1994) successfully treated all 19 of their patients with persistent trophoblast with single dose, systemic methotrexate.

Ben-Arie *et al.* (2001) reported disseminated intra-abdominal implants after laparoscopic salpingectomy. In this case, the woman re-presented with a

haemoperitoneum three weeks after her surgery. Disseminated peritoneal implants have been found after salpingotomy as well (Giuliani *et al.*, 1998).

Dwarakanath *et al.* (1996) looked at the management of persistent ectopic pregnancy following conservative laparoscopic surgery. In their experience, they found further surgical intervention was not required in women whose post-operative hCG levels rose unless they became symptomatic. They do not state whether the hCG levels eventually fell, or how long this process took. They did not use methotrexate in the management of persistent trophoblast, if it had been used, it might have reduced the length of follow-up and might have been a less invasive alternative for those who eventually became symptomatic and required surgery.

Radical surgical treatment is considered unlikely to result in residual trophoblastic tissue but this assumption does not always hold true, 1 of 39 women having laparoscopic salpingectomy required intervention for persistent trophoblast (Mol *et al.* 1997[b]). In this non-randomised comparison of salpingectomy and salpingotomy, the spontaneous intrauterine pregnancy rates within three years were 39% and 47% respectively.

Suturing the tube after salpingotomy might affect future fertility. Tulandi and Guralnick, (1991) found the intrauterine pregnancy rate was higher in women whose tubes were left unsutured during the first twelve months after surgery. This advantage appeared to be short lived, with similar cumulative intra-uterine pregnancy rates at two years.

"Milking" of the ectopic gestation sac through the tube describes the technique whereby attempts are made to expel the trophoblast through the tubal ostium without incising the tube. It is associated with continued bleeding from the implantation site and a persistent ectopic rate of 33.3%, Vermesh (1989). Therefore, unless a tubal abortion is found at the time of surgery, this technique is not to be recommended.

1.7.4 Medical – Methotrexate

Various agents have been used to treat ectopic pregnancy medically – RU486, prostaglandins F-2α and E-2, potassium chloride, hyperosmolal glucose – however, the agent with the greatest use, remains methotrexate.

Various criteria to predict the success of methotrexate have been considered – the size of the ectopic mass on ultrasound scan (in Lipscomb *et al.*, 1999, they allowed up to 4cm diameter), the initial hCG and progesterone levels, the presence of fetal heart activity and the presence of pelvic fluid. Lipscomb *et al.* (1999) considered all these factors in 350 women undergoing a single dose regime of methotrexate, and hCG level at the start of therapy was the only factor that had any significance ($p<0.001$) in predicting success. With initial values of hCG of <1000miu/ml the success rate was 98% (95% CI 96-100), of 1000-1999miu/ml, 93% (95% CI 85-100) and of 2000-4999miu/ml, 92% (95% CI 86-97).

Tawfiq *et al.* (2000) found a cut-off for successful medical treatment with an hCG level of 4,000miu/ml or less; at levels greater than this there was a 65% failure

rate. They do not quantify the success rates at lower levels. They also found that medically treated women who presented with a history of pain and vaginal bleeding had a lower (unquantified) success rate.

Methotrexate has been given by various routes: local infiltration, either laparoscopically or ultrasonically guided, or parentally, either as single or multiple dose regimes.

Parental regimes might be either multiple or single dose. Multiple dose regimes consist of repeated injections of methotrexate with citrovorin rescue. A commonly used regime is methotrexate 1mg/kg intramuscularly on alternate days with citrovorin 0.1mg/kg, until either the hCG level falls by more than 15% in 48 hours, or, four doses of methotrexate have been given (Pisarska *et al.*, 1998). Single dose regimes have been developed as the side effects are considerably less, and citrovorin rescue is not required. The most frequently used regime is 50mg/m^2. The single dose regime requires repeat administration of methotrexate in some cases, but only if the levels of hCG are not falling adequately. Levels that fail to fall by 15% between days 4 and 7 post methotrexate require a second dose of methotrexate.

Single dose intra-muscular regimes would seem to have similar long-term outcomes as surgical treatment. In the Yao and Tulandi review (1997), three prospective trials (Stovall and Ling, 1993[b]; Glock *et al.*, 1994; Gross *et al.*, 1994)

with a total of 172 patients, found 58% of patients had subsequent intrauterine pregnancies and 9% had recurrent ectopic pregnancies.

Hajenius *et al* (1997) compared multiple dose methotrexate and laparoscopic salpingotomy and found similar outcomes by randomly assigning patients to one or other of the treatments. All laparoscopically confirmed ectopic pregnancies were included. In the methotrexate group 82% required no further treatment, 4% required an additional course of methotrexate and 14% surgical intervention. This compared to 72% who required no further treatment after salpingotomy, 20% requiring post-operative methotrexate and 8% requiring surgical intervention. Ipsilateral tubal patency was confirmed in 55% and 59% of the patients respectively.

There have been no randomised comparisons of single dose and multiple dose regimes, although one unit reported a 96.0% success rate with a multiple dose (Stovall *et al.* 1991) and 91.5% success rate with a single dose regime (Lipscomb *et al.*, 1998). This is despite a liberalisation of the treatment criteria after initiating the single dose regime.

In their Cochrane Library review, Hajenius *et al.* (2000) found that multiple dose regimes were as effective in eliminating ectopic pregnancy as laparoscopic salpingotomy, with similar long-term outcomes. They did not feel that single-dose treatment was sufficiently effective when compared to laparoscopic salpingotomy. However, multiple dose regimes are considerably more expensive and are

associated with a greater impairment in quality of life. They concluded that multiple dose methotrexate had a place in the management of ectopic pregnancy in haemodynamically stable women, unlike single dose therapy. There was no direct comparison of single and multiple dose regimes; the comparison was indirect, both regimes being compared independently to laparoscopic salpingotomy.

Fernandez *et al.* (1998[b]) randomised women with ectopic pregnancy to either laparoscopic salpingotomy or medical treatment. The preferred route was local infiltration of methotrexate under ultrasound guidance, single dose systemic methotrexate only being used when the ectopic pregnancy could not be safely accessed with ultrasound guidance. hCG levels were not the primary means of determining suitability for inclusion. 88.2% of the methotrexate group were successfully treated and 95.9% in the surgical group. The lower rate of success in the medically treated group was largely down to the greater rate of persistent ectopic pregnancy. The subsequent spontaneous intrauterine pregnancy rate was higher, and the repeat ectopic rate lower, in the medically treated group.

Saraj *et al.* (1998) randomised women with a diagnosis of ectopic pregnancy to single dose systemic methotrexate or laparoscopic salpingotomy. Resolution of ectopic pregnancy was similar in both groups, 94.7% in the methotrexate group, 15.8% requiring a second dose seven days post-treatment, and 91.4% in the surgically managed group. Subjects with all levels of hCG were included, and those requiring a second dose of methotrexate had higher initial mean hCG levels

than those subjects in which a single dose was successful (4830 +/- 1588miu/ml and 2133 +/- 393miu/ml respectively).

A further study of single-dose systemic methotrexate and laparoscopic salpingotomy by Sowter *et al.* (2001[8]) included all women with a diagnosis of ectopic pregnancy whose initial hCG was <5000miu/ml and an adnexal mass of less than 3.5cm on ultrasound scan. In the methotrexate group, 64.7% were successful with a single dose of methotrexate, 20.5% required one or more additional doses and 14.7% required surgical management. In those treated surgically, 82.1% were successfully treated at the time of laparoscopy, in 10.7% an ectopic pregnancy was not found and 7.1% had persistent trophoblast. They concluded that single dose methotrexate is less effective than laparoscopic salpingectomy.

In the Cochrane review, Hajenius *et al.* (2000) considered the three trials discussed above (Fernandez *et al.*, Saraj *et al.* and Sowter *et al.*,) to be robust enough to allow comparison. It is these trials that lead them to conclude that single dose methotrexate is not as effective as either treatment with multiple dose methotrexate or laparoscopic salpingectomy. However, as can been seen, one of the trials was, in fact, a comparison of ultrasound infiltration and laparoscopic salpingectomy and none of the trials limited cases to lower levels of initial hCG, in which medical treatment has been shown to be more effective. Future reproductive performance was similar in the two groups and a non-significant lower rate of repeat ectopic was found in the medically treated group.

Bouyer *et al.* (2000) found a higher intrauterine pregnancy rate in women treated medically over those treated surgically. However, women treated medically were better educated and the numbers much smaller, suggesting some bias in the selection of patients for medical treatment. In a similar study (Dias Pereira *et al.*, 1999), salpingotomy was compared with a multiple dose methotrexate regime no significant difference in subsequent intrauterine pregnancy or ectopic pregnancy rates was found.

Olofsson *et al.* (2001) found a similar probability of intrauterine pregnancy in the subsequent 2.5 years following medically treated pregnancies as after surgery. The study was not randomised and did not differentiate between different surgical techniques.

Pharmacokinetic studies comparing systemic and local methotrexate have shown that the maximum plasma concentration and area-under the curve are similar in local and systemic regimes (Schiff *et al.*, 1992; Fernandez *et al.*, 1994).

Fernandez *et al* (1995), found similar short-term outcomes when laparoscopic salpingotomy was compared with ultrasound guided infiltration with methotrexate combined with aspiration of the gestation sac. They looked at resolution of the ectopic pregnancy; the trial did not examine subsequent fertility rates.

In their Cochrane Library review, Hajenius *et al.* (2000) concluded that their was no place for local infiltration with methotrexate, either at laparoscopy or under

ultrasound guidance, as these methods are significantly less successful than surgery at eliminating ectopic pregnancy.

When methotrexate is administered locally at laparoscopy, the patient is exposed to both the risks of surgery and the risks of medical management. Ultrasound guided local infiltration does not expose the patient to the additional operative risk, but, unlike parenteral administration, it is operator dependent.

The use of methotrexate is associated with an increase in size and vascularity of the ectopic pregnancy (Atri *et al.*, 1992); this is a normal finding post-methotrexate and does not denote treatment failure. It is for this reason, that repeat ultrasound is not recommended until hCG returns to non-pregnant levels. Levels of hCG can be expected to rise between days 1 and 4 post-methotrexate. Stovall and Ling (1993) found a transient rise in the hCG in 86% of subjects between days 1 and 4.

Treatment of ectopic pregnancy with methotrexate leads to pain in a substantial proportion of women around 3-4 days after treatment. Predicting women who are at risk of haemorrhage is, therefore, problematic. Lipscomb *et al.* (2000) followed 258 women who had single-dose methotrexate. 21.7% had concerning symptoms, of these 14.3% required surgery, although this is only 3% of the cohort. They suggest that early surgical intervention is not indicated in haemodynamically stable women with severe pain following treatment single-dose methotrexate.

Patients having either expectant or medical treatment (or conservative surgical treatment) must be warned that tubal rupture might occur until there is complete

resolution of the trophoblast. It is, therefore, important that they attend for tracking of hCG levels and that methotrexate/repeat methotrexate is considered if the levels fail to decline. Tubal rupture can occur at any time whilst viable trophoblast remains. Lipscomb *et al.* (2000) record a case of tubal rupture 42 days after treatment with methotrexate.

In Lipscomb *et al.'s* 1999 paper, they found the mean for hCG levels to return to non-pregnant levels after medical treatment was 33.6 days, with the longest being 109 days. 17.5% of their patients required more than one dose of methotrexate, though it must be remembered that they treated any suitable case regardless of initial hCG level.

Perdu *et al.* (1998) gave mifepristone in combination with methotrexate, resulting in a substantially reduced failure rate, with only 3.3% of those receiving medical management failing to resolve. This was against a failure rate of 26.2% in those treated with methotrexate alone, which might be explained by medical treatment being offered to all suitable women with hCGs of 10,000miu/ml or less. Also, the trial was not randomised - the control group being historical.

There are various potential side-effects of high dose methotrexate, for example, bone marrow suppression, acute and chronic hepatotoxic effects, stomatitis, gastritis, pulmonary fibrosis, alopecia and photosensitivity (Pisarska *et al.*, 1998). These are unlikely with single dose regimes and any additional risk in multiple dose regimes can be minimised by the use of citrovorin rescue. Life-threatening

neutropenia has been reported in patients given methotrexate as treatment for ectopic pregnancy, in one case using multiple dose, the other a single dose regime (Isaacs *et al.,* 1996). Transient pneumonitis has also been described following local infiltration of an ectopic pregnancy (Schoenfeld *et al.,* 1992) and use of a parental single dose methotrexate regime (Horrigan *et al.,* 1997). Interestingly, in the case reported by Horrigan *et al.,* the patient had had uncomplicated medical management of a previous ectopic pregnancy.

Ben-Shlomo *et al.* (1997) found multiple ovarian cysts (maximum diameter 9.4cm) in 15% of women who had local methotrexate infiltration of ectopic pregnancy. Similar cysts were found in just 1.8% of women after salpingotomy.

1.7.5 Expectant Management

The rise in incidence of ectopic pregnancy might, in part, be explained by an increase in its early diagnosis. Ectopic pregnancies, that might have spontaneously resolved in the past, are now treated because pregnancy, and hence its complications, can be diagnosed at much earlier gestations than was previously possible. The pressure to treat all ectopic pregnancies comes from the morbidity and mortality from the uncontrolled bleeding associated with some cases of ectopic pregnancy. For these reasons, many women with ectopic pregnancy may be over treated.

In 1955, Lund described the expectant management of 119 patients with ectopic pregnancy. 57% did not require surgical intervention. Of those patients in whom

expectant management failed, many had significant symptoms with haemoperitoneum or collapse. Subsequently, 46% of those desiring a further pregnancy achieved an intrauterine pregnancy, 15% had a further ectopic pregnancy. However, this management required a protracted hospital stay, which would be financially unacceptable today, even if patients tolerated it.

Ylöstalo *et al.* (1991) observed 48 women with ectopic pregnancy selected for expectant management. Ectopic pregnancy was diagnosed when hCG level fell between samples taken 48 hours apart, there was no evidence of an intrauterine pregnancy and any adnexal mass was less than 4cm on ultrasound and no signs of rupture or acute bleeding. 23% of all cases of suspected ectopic pregnancy fitted these criteria. Spontaneous resolution occurred in 65%.

Shalev *et al.* (1995) expectantly managed all ectopic pregnancies in which the hCG level was seen to decline in consecutive samples taken 48 hours apart. Women in whom an ultrasound scan demonstrated an adnexal fetal heart pulsation or a haemopertitoneum of >100mls were excluded. The ectopic pregnancies were confirmed at laparoscopy. 46.7% of cases were successfully expectantly managed, 60% of cases where the initial hCG was <2000mi/ml, whereas 93.3% failed if the initial hCG was >2000miu/ml (i.e. 1 of 28 cases succeeded). In one woman, tubal rupture occurred when the hCG level was <10miu/ml. Their fertility rates following expectant management were similar to those after surgical management, with recurrent ectopic pregnancy rates of 12.5% and ongoing pregnancy rates of 45.8% at one year.

Ylöstalo *et al.* (1992) considered expectant management if the initial hCG levels were declining and an adnexal mass of <4cm on ultrasound. 26% of all their ectopic pregnancies were suitable for expectant management, in 69% spontaneous resolution occurred. Shalev *et al.* (1995) argued that this higher success rate might be because a proportion of their adnexal masses were not ectopic pregnancies. But to treat a woman expectantly and to add in the risk of a laparoscopic assessment of the ectopic pregnancy, increases the overall risk of this course of management without any improvement in her chances of a successful pregnancy in the future.

In the study by Fernandez (1988), 10 out of 14 ectopic pregnancies resolved spontaneously. These pregnancies were carefully selected at laparoscopy. This illustrates the problem with all non-surgical treatments of ectopic pregnancy: if the diagnosis, or in this case assessment, of the tubal pregnancy cannot be made by non-surgical means, little advantage is offered to the patient, whilst they are exposed to the risk of a second operative procedure if the initial management fails.

Banerjee *et al.* (2001) followed all women in whom the location of pregnancy could not be determined at initial presentation. All these women were managed expectantly until an intrauterine gestation sac was found, or a deterioration in the clinical state, or hCG levels failed to fall. 69% of these pregnancies resolved spontaneously and a serum progesterone level of 20nmol/l or less had a positive predictive value of 97% for spontaneous resolution.

Strobelt *et al.* (2000) found similar rates of subsequent intrauterine pregnancy in women with successful expectant management of their ectopic pregnancy as those whose primary treatment was surgical (63% v 51%, p=0.37). Those women who failed expectant management and required surgery as a secondary procedure also had similar rates of subsequent intrauterine pregnancy as those who had primary surgical management (54% v 65%, p=0.44).

1.7.6 Impact on Quality of Life

Nieuwkerk *et al.* (1998[a]) compared women who had medical treatment with those having laparoscopic salpingostomy. They found that medical treatment of ectopic pregnancy had a greater negative impact on physical, role and social functioning; they had worse health perceptions, greater pain, depression and physical symptoms, less energy and overall, a worse quality of life, than those treated surgically. This study is limited by the fact that all women had a diagnostic laparoscopy to confirm the ectopic pregnancy, the avoidance of a surgical procedure being one of the attractive features to women who choose medical management, and also that a multiple dose methotrexate regime was used.

In a paper, by the same authors, published simultaneously, (Nieuwkerk *et al.*, 1998[b]) patient treatment preferences were explored. Treatment with methotrexate was portrayed as better preserving tubal patency than salpingostomy, at the expense of more initial intervention. Few patients would trade any gain in tubal patency, if treatment with methotrexate were preceded by diagnostic laparoscopy.

However, most patients preferred treatment with methotrexate, even without any improvement in tubal fertility, if this avoided a diagnostic laparoscopy.

1.7.7 Financial Implications

In their paper evaluating the economic implications of radical and conservative surgery, Mol *et al.* (1997[c]) concluded that conservative surgery has an additional economic cost that can only be justified if a higher rate of future intrauterine pregnancy leads to at least an equivalent reduction in the cost of investigation and management of subsequent infertility. All surgery was laparoscopic. Patients undergoing salpingectomy had a marginally shorter (non significant) in-patient stay (2.8 v 3.0 days). Persistent trophoblast was found in 1 of 39 women who underwent salpingectomy and 17 of 76 women undergoing salpingotomy. Treatment was not determined by randomisation. Salpingectomy took significantly longer to perform (77 versus 64 minutes, p=0.018). But because of the need for routine hCG surveillance and the greater number of women who required treatment for persistent trophoblast, the short-term unit cost of salpingotomy was greater. (Women undergoing salpingectomy routinely had two post-operative hCG levels taken). They demonstrated that an increase of 2.2% in the subsequent intrauterine pregnancy rate for salpingotomy over salpingectomy was cost effective when the additional costs of future assisted conception techniques are considered.

The same authors made an economic comparison of multiple dose systemic methotrexate and laparoscopic salpingotomy (Mol *et al.*, 1999[c]). Treatment with

methotrexate was more expensive (US$5721 for medical treatment, versus US$4066 for laparoscopic salpingostomy). Their trial required laparoscopic confirmation of the ectopic pregnancy before treatment. If this could be avoided, medical management with a multiple dose regime became the cheaper option when starting hCG levels were less than 1500miu/ml, single dose regimes were marginally cheaper still, despite the greater rate of second interventions when hCG level failed to fall. When initial hCG levels were greater than 3000miu/ml, methotrexate became a more expensive option, even in the absence of a diagnostic laparoscopy.

Sowter *et al.* (2001[b]) compared the direct and indirect cost of treatment for patients treated in their trial of single dose methotrexate versus laparoscopic management of ectopic pregnancy. In subjects suitable for inclusion in the trial, the mean direct costs were half that of surgical treatment for methotrexate (NZ$3083 and NZ$1470 respectively) and the indirect cost for women treated surgically were also greater than with medical treatment, though the difference was not as great (NZ$1899 and NZ$1141 respectively). As subsequent reproductive outcome appears similar in groups of women treated medically and by laparoscopic salpingotomy, the long term costs of recurrent ectopic pregnancy and assisted conception are likely to be similar.

Lecuru *et al.* (2001) prospectively costed the treatment of women undergoing medical and surgical treatment of ectopic pregnancy. Single dose methotrexate was given to women whose hCG level was <5000miu/ml. Those women who

did not wish to have medical management, or were unsuitable, had laparoscopic salpingotomies. There were similar outcomes in both groups, but hCG follow-up took longer in those medically treated. However, significant savings were still made with medical management because of the reduced hospital stay. Laciano *et al.* (2001) estimated a saving of US$3,000 for each patient treated medically, rather than surgically.

Chapter 2 - Aims and Objectives

2.1 Aims and Objectives

1. **To evaluate the diagnosis and management of ectopic pregnancy locally and nationally**

Two questionnaires were designed to look at the service available for the diagnosis and management of ectopic pregnancy, both from the point of view of those who deliver the service, and from that of the patients who access the service.

The first questionnaire was designed to assess the facilities for the diagnosis and management of ectopic pregnancy throughout the United Kingdom and Northern Ireland. Questionnaires were sent to all units with an acute gynaecological service asking about Early Pregnancy Units:

- their opening hours

- diagnostic facilities, particularly pertaining to the use of ultrasound and serum hCG

- how ectopic pregnancy is managed within the unit, their ability to deliver laparoscopic management of ectopic pregnancy and willingness to consider medical management

A second questionnaire was designed in conjunction with the Ectopic Pregnancy Trust to survey the experiences of women, as patients, who had had an ectopic pregnancy:

- who made the diagnosis

- how long it took for the diagnosis to be made

- the choices that were offered for management

- information they were given about their diagnosis and its implication for the future

2. **To look at changes in the diagnosis and management of ectopic pregnancy between 1993 and 1999**

This compromised an audit of practice at St. James's University Hospital in 1993, before the introduction of serum hCG estimations and 1999, when hCG estimations were an established component in the diagnosis of ectopic pregnancy.

3. **To discuss the impact that any changes in diagnosis and management of ectopic pregnancy might have on service provision**

4. **To develop a protocol for the management of ectopic pregnancy to be used within St James's University Hospital that can be used by both medical and nursing staff**

Ectopic pregnancy has a measurable mortality and is also responsible for much short-term and long-term morbidity. An examination of the literature was made to determine the optimal diagnostic protocol and recommendations for management to prevent maternal death and reduce morbidity to a minimum. As specialist nurses are often the practitioners who manage patients until a diagnosis is made, a protocol should support them in this practice, giving clear guidelines within which they can work, and at what point a senior doctor should be involved. A protocol should also aim to make the best use of resources, limiting unnecessary use of ultrasound scans and biochemical testing. It should also encourage good practice in the management of ectopic pregnancy, making clear the full range of medical and surgical options and in what circumstances they should be employed.

5. **To consider scope for changes in the diagnosis and management of ectopic pregnancy**

Review of the literature for the design of the protocol will consider the medical experience of diagnosis and management of ectopic pregnancy. This will also be considered from the perspective of the patient.

Experiences with the ROCET trial, a pilot trial to compare conservative and radical surgical treatment for ectopic pregnancy, will be discussed. This pilot did not offer an answer to what was the optimal mode of surgical management, but was revealing in what it showed about the choices the women made about their management.

Conjoint Analysis is a tool used in Transport Studies to observe how people trade choices off against each other. It was used here to see if women were prepared to trade choices for the management of ectopic pregnancy.

This is also covered, in part, by the Ectopic Pregnancy Trust questionnaire regarding women's experiences of ectopic pregnancy.

6. **To explore fetal fibronectin in early pregnancy, its potential as a diagnostic test for ectopic pregnancy and its use in differentiating between ectopic pregnancy and other complications of early pregnancy**

Even with effective protocols for the diagnosis and management of ectopic pregnancy, there will still be cases in which the diagnosis is delayed or when a diagnostic laparoscopy is performed in the absence of an extra-uterine pregnancy. At present, making a diagnosis means deciding which is most likely out of a range of possibilities. If a test were to be devised that could discriminate between abnormal and normal early pregnancy and between intra- and extra-uterine pregnancy, mortality and morbidity related to ectopic pregnancy and its treatment, might be reduced.

Measurement of fetal fibronectin in the endo-cervical and vaginal secretions is well established in the diagnosis of complications of pregnancy in the third trimester. A commercially available assay is used. Fetal fibronectin is produced by trophoblast and so it is also found the endo-cervical and vaginal secretions in first trimester. I aimed to assess its potential as an aid to the diagnosis of first trimester complications.

- I wished to establish levels of fetal fibronectin in normal early pregnancy.

- Miscarriage is an important differential diagnosis with ectopic pregnancy. I aimed to see if fetal fibronectin might be used to differentiate between viable early pregnancy and non-viable early pregnancy, at gestations too early for this distinction to be made by ultrasound.

- I next aimed to measure levels of fetal fibronectin found in ectopic pregnancy. With information about the levels found in ectopic pregnancy and levels found in the two situations that are part of the differential diagnosis of ectopic pregnancy, the role of fetal fibronectin in differentiating between these situations would be assessed.

- As further evaluation of the assay, situations such contamination with blood and samples taken in the non-pregnant state would be examined.

3. Local and National Management of Ectopic Pregnancy

3.1 Assessment of Current Local and National Management of Ectopic Pregnancy

In order to assess how to improve management guidelines, it was important to investigate current practice in the management of ectopic pregnancy and where this is deficient. There are three components to this assessment: local, national, and the patient perspective.

(i) audit of practice within St. James's University Hospital (SJUH).

(ii) the current practice of UK units in the diagnosis and management of ectopic pregnancy using a national postal questionnaire to assess practice in the diagnosis and management of ectopic pregnancy that was sent to all UK units offering a gynaecological service.

(iii) the experiences of women in whom an ectopic pregnancy has been diagnosed. The Ectopic Pregnancy Trust Questionnaire of Women's Experiences of Ectopic Pregnancy was designed in conjunction with the UK based charity *The Ectopic Pregnancy Trust* (EPT) and distributed, by them, to women who had experienced ectopic pregnancy.

Examples of the questionnaires used are given in *Appendices 1 and 2.*

3.2 Audit of the Management of Ectopic Pregnancy in St. James's University Hospital (SJUH), 1993 and 1999.

Although there was an early pregnancy unit established before 1994, it was not until then that the use of serum hCG estimations was introduced. This innovation should have improved the diagnosis of ectopic pregnancies, with fewer women having the diagnosis missed and presenting with collapse, whilst at the same time, reducing the number of unnecessary laparoscopies in women with normal intra-uterine pregnancies and miscarriages. Use of serum hCG levels also opens up different possibilities for management of ectopic pregnancy, allowing doctors to consider expectant or medical management.

Since its introduction, there has been concern that too many levels are being carried out since it is the "easy option". This leads to normal early pregnancies being tracked and doctors requesting a repeat sample after 48 hours when a diagnosis should have been possible.

The impact of this change was assessed by auditing the management of ectopic pregnancy before and after introduction of this service.

3.2.1 Method

There was an assumption that all women with ectopic pregnancy would end up with a laparoscopy and/or tissue being sent to pathology. However, women who had a laparoscopy but the diagnosis was negative would not be coded as ectopic pregnancies and would have no tissue sent. Therefore I studied:

(a) all emergency laparoscopies (ie laparoscopies done outside scheduled operating lists)

(b) all surgical procedures coded for ectopic pregnancy in 1993 and 1999.

In SJUH, all surgical procedures are Reed coded and stored on a database for the administrative purposes. This provides a simple way of identifying women who have had either a diagnostic laparoscopy or surgical procedures for the management of ectopic pregnancy as acute cases. A search was performed for all procedures that were coded as including salpingectomy, salpingotomy, salpingostomy, salpingoophorectomy or ectopic pregnancy. A second search was also performed for all laparoscopies performed on acute lists. For all the procedures to be found, this would require that codings are reliably and accurately entered. In order to check this, the theatre books from all the theatres where gynaecological and acute cases were carried out were checked for two months of the years in 1999 (1993 theatre books being unobtainable) and the list appeared to be complete and reliable.

Second approach was to look for specimens sent for pathological assessment. All tissue is "SNOMED" coded according to the findings. I performed a search looking for all samples coded as ectopic pregnancy, or trophoblast and fallopian tube. However, this gave a poor return with only a handful of cases.

A computer-generated list of all these cases was produced and a large proportion of cases that were obviously unrelated were then removed – for example, "total abdominal hysterectomy and bilateral salpingoophorectomy". The notes of the remaining cases (acute laparoscopies and other procedures that could possibly have been performed for ectopic pregnancy) were retrieved from the medical records library. There was one group of patients that might be underrepresented in this sample, women who had negative diagnostic laparoscopies on scheduled lists. However, since most acute cases are done on designated acute lists in SJUH, this number is likely to be small.

Medical management of ectopic pregnancy was not available in this unit in 1993 and only routinely used in 1999. These cases are not Reed coded in the same fashion, as they do not usually have a surgical procedure, however, all such cases from 1999 were known through the records of the Early Pregnancy Unit (EPU).

Therefore, all the cases of ectopic pregnancy from both years were retrieved and most of the cases of suspected ectopic that went for laparoscopy. These cases were examined to evaluate the impact of hCG estimations on the diagnosis and management of ectopic pregnancy. The number and timing of estimations, the length of pre- and post-operative stay, the findings at laparoscopy and final diagnosis were all recorded and compared.

3.2.2 Results

3.2.2a Diagnosis

In 1993 there were 158 emergency laparoscopies for suspected ectopic compared with 88 in 1999. Figure 3.1 shows the final diagnosis reached in women requiring an acute diagnostic laparoscopy for both years.

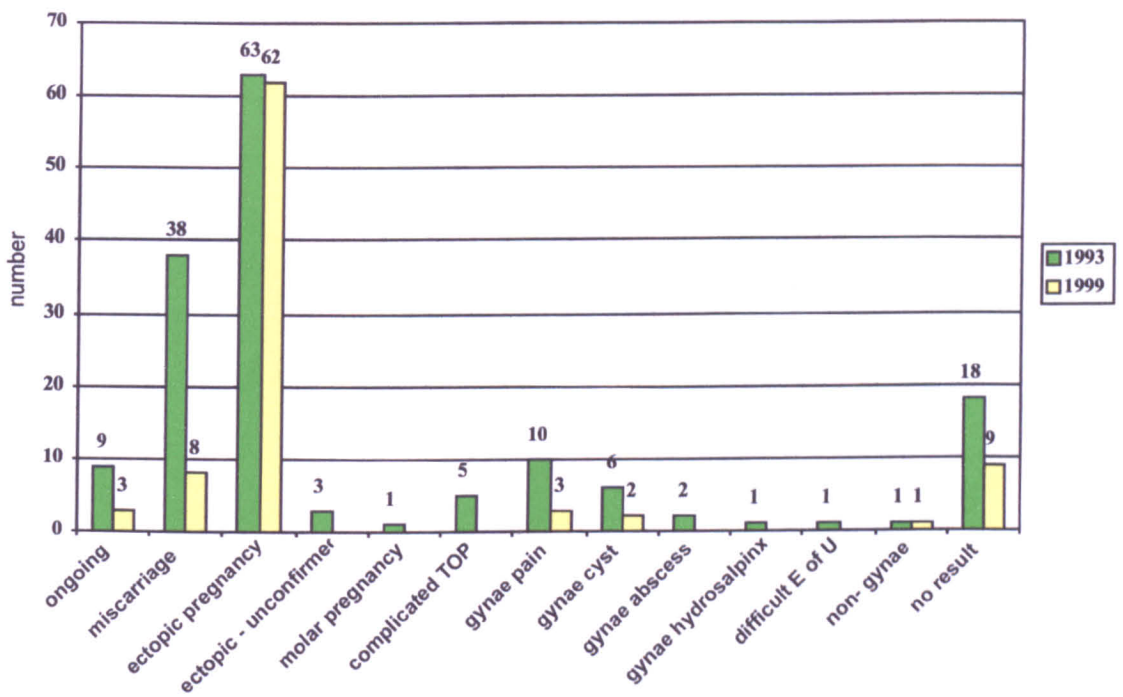


Fig.3.1 final diagnosis in women having acute diagnostic laparoscopies, comparing 1993 and 1999

Compared with 1993, the number of ectopic pregnancies diagnosed in 1999 was similar (fig. 3.1). However, the total number of emergency laparoscopies in 1993

was almost double that in 1999. The difference between the two years was due two distinct groups (fig. 3.2)

(i) fewer women with viable intra-uterine pregnancies and miscarriages were subjected to laparoscopies (48 laparoscopies in 1993 and 11 in 1999).

(ii) there has been a decline in acute laparoscopies done in the *non*-pregnant woman over this time.

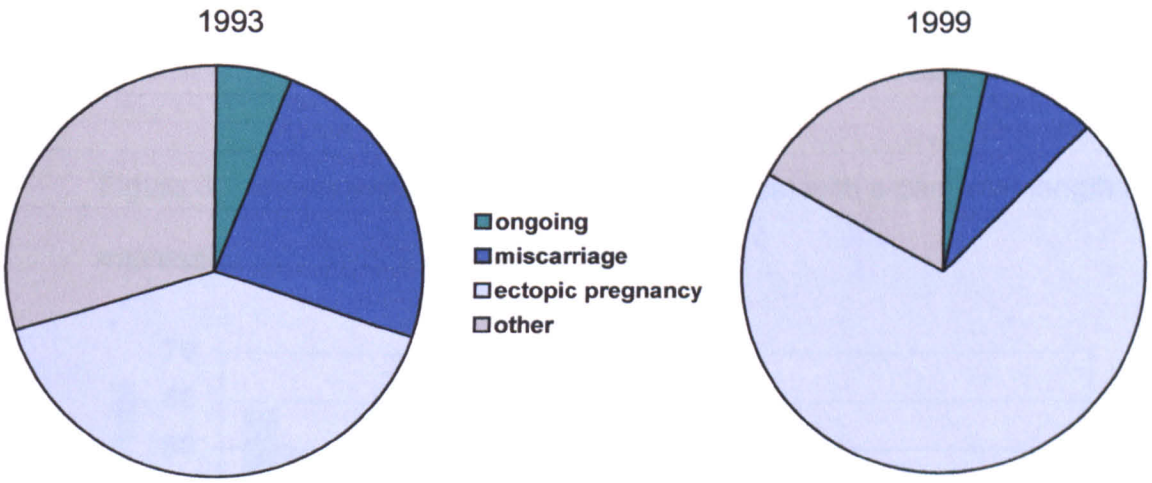


Fig. 3.2 Final diagnosis as a proportion of all acute laparoscopies

3.2.2b Length of in-patient treatment

Figure 3.3 shows the period of time, in days, that women spent as in-patients before they were taken to theatre.

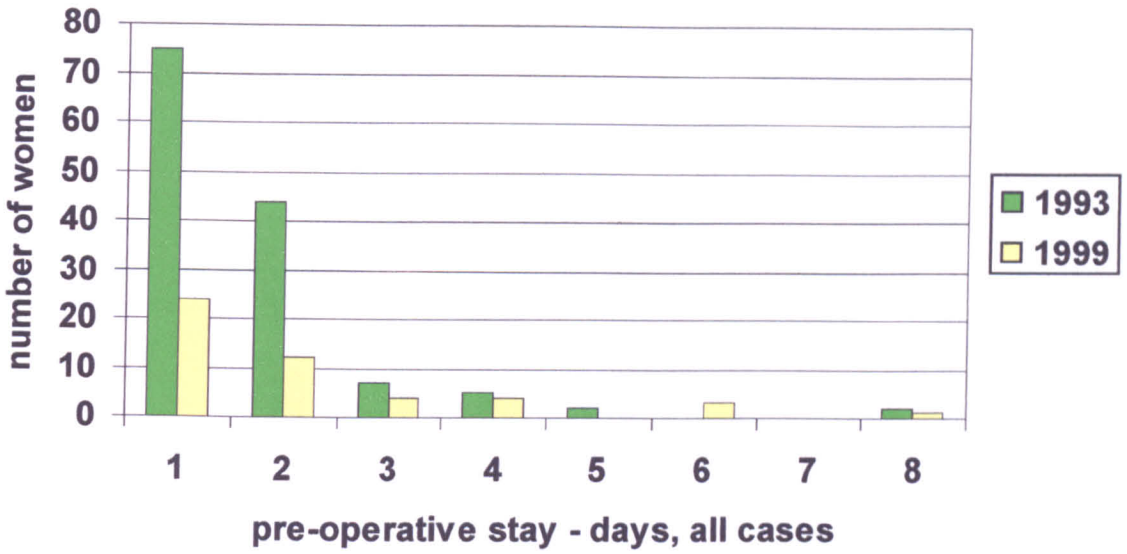


Figure 3.3 pre-operative stay, in days, for all diagnoses

Figure 3.4 shows the number of women (all cases) with a particular length of stay expressed as a percentage as all cases.

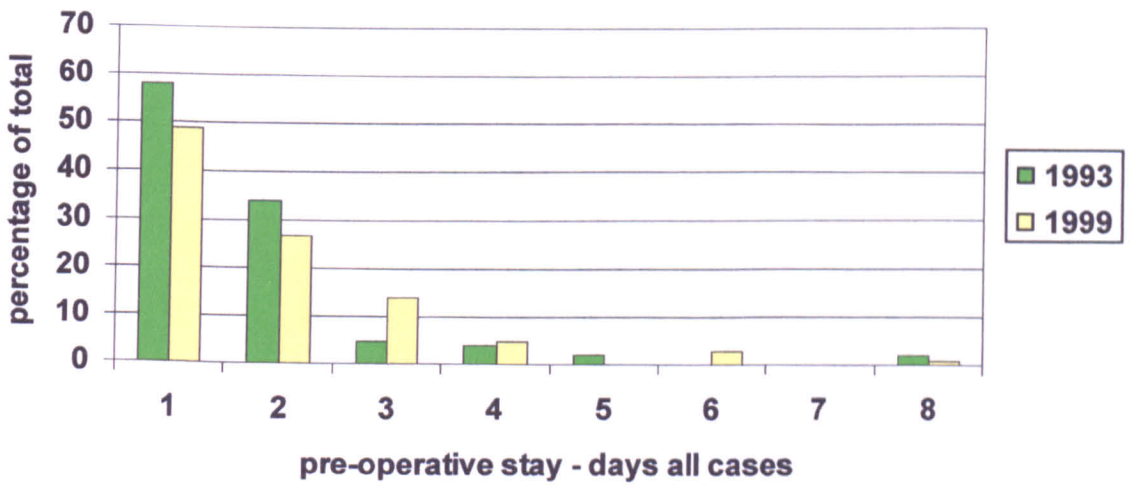


Figure 3.4 Length of pre-operative stay for all diagnostic laparoscopies, expressed as a percentage of all cases

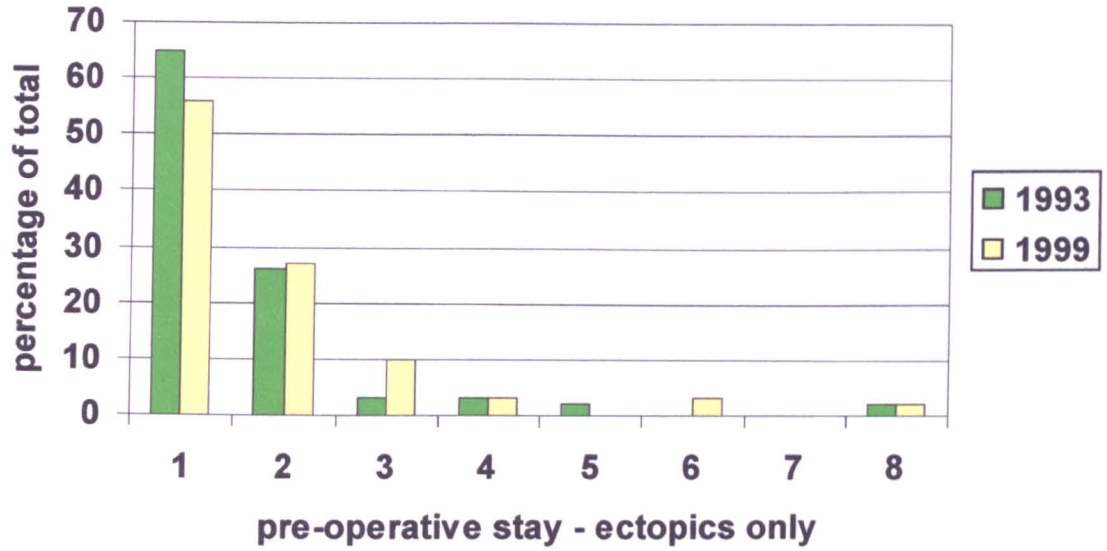


Fig.3.5 Length of inpatient pre-operative stay, ectopic pregnancies only, expressed as a percentage of all ectopic pregnancies

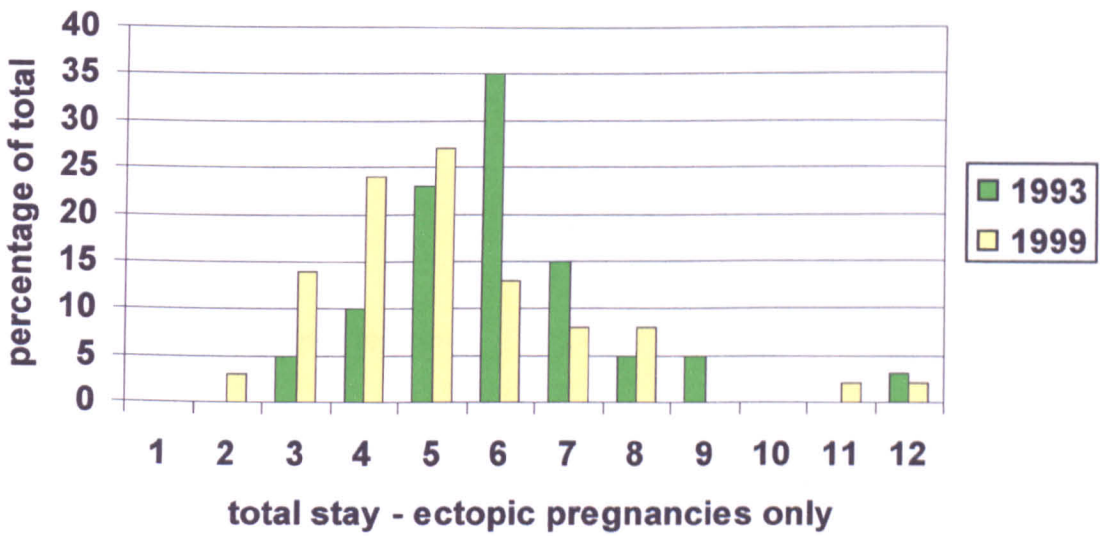


Fig. 3.6 Length of total hospital stay, ectopic pregnancies only, expressed as a percentage of all ectopic pregnancies

3.2.2c Management of ectopic pregnancy

The majority of surgery is still radical with 87.3% of women in 1993 and 87.1% of women in 1999 having the tube containing the ectopic pregnancy removed. There was an increase in the number of women requesting bilateral salpingectomy, with three in 1993 and seven in 1999. With small numbers from just two years it is difficult to attach too much significance to this change, however, bilateral salpingectomy is a management option discussed with women who have ectopic pregnancies whilst undergoing assisted conception, and this might have brought about the increase.

Table 3.1 How ectopic pregnancies were managed in 1993 and 1999

Management	**1993** *(%)*	**1999** *(%)*
salpingectomy	52 *(82.5)*	46 *(74.2)*
salpingotomy	7 *(11.1)*	4 *(6.5)*
bilateral salpingectomy	3 *(4.8)*	7 *(11.3)*
"milking" of ectopic	1 *(1.6)*	1 *(1.6)*
salpingoophorectomy	0	1 *(1.6)*
methotrexate	0	3 *(4.8)*

Table 3.2 Route of surgical management of ectopic pregnancy

Route	1993	1999
laparotomy	63 (100%)	34 (69.3%)
laparoscopy	0	15 (30.6%)

Whilst all ectopic pregnancies were managed by laparotomy in 1993, the number of laparoscopic procedures in 1999 remains low, with only 30.6% of ectopic pregnancies being managed laparoscopically within the unit (Table 3.2). This was partly related to the problem of a lack of appropriately trained personnel.

Table 3.3 Site of ectopic pregnancy

Site	1993	1999
right side	34	40
left side	26	18

3.2.2d Use of serum hCGs

The purpose of the study was to investigate if any change in practice is associated with the use of serum hCG estimations. It certainly would appear it has made an impact on the accuracy of the diagnosis since there was a reduction

in the number of women with normal pregnancies and miscarriages who underwent laparoscopy.

Table 3.4 The number of women undergoing laparoscopy who were found to have an ectopic pregnancy (positive result)

	1993	1999
Positive	63 (PPV – 40%)	62 (PPV – 70%)
Negative	94	26
Total	157	88

Figure 3.7 demonstrates how many pre-operative hCG levels were taken for those pregnant subjects in whom the outcome was known. In only 17 (23.0%) was the optimum number of two hCG levels taken.

Conservative management runs the risk of persistent trophoblast and it is recommended that all such cases should be tracked post-operatively until non-pregnant levels of hCG are reached. In this study only 3 of the 4 women undergoing a conservative surgical procedure had follow-up hCGs.

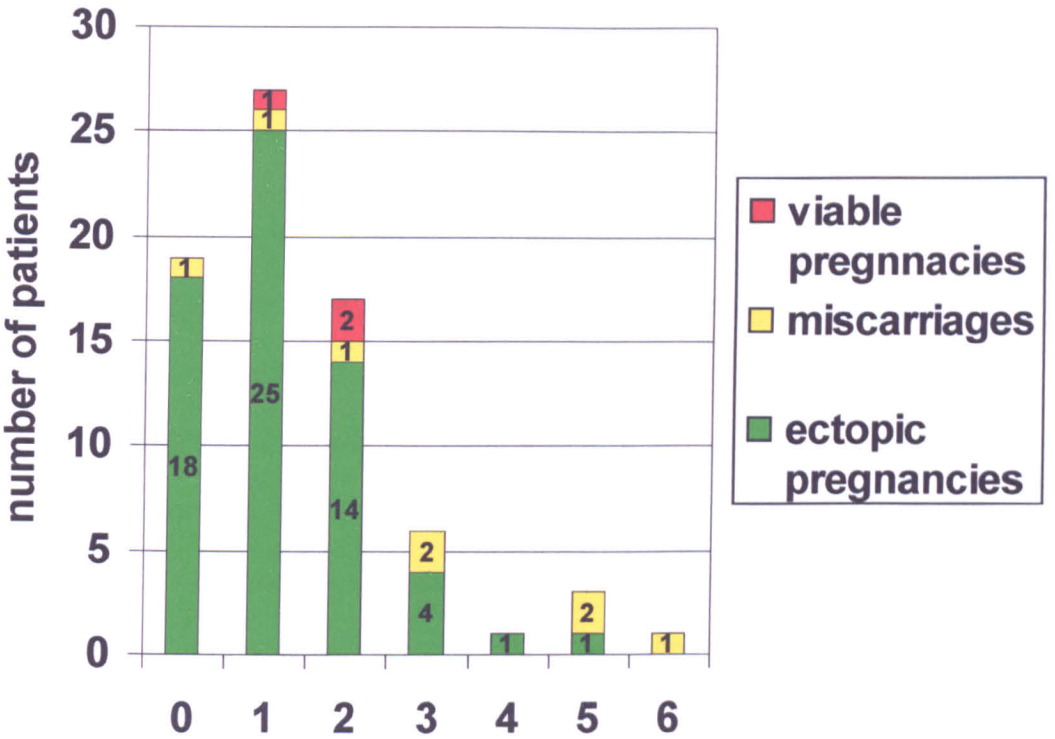


Fig. 3.7 The number of diagnostic preoperative hCG levels taken according to pregnancy outcome

3.2.3 Discussion

It is clear that there are less laparoscopies being carried out and more are positive for ectopic pregnancy implying increased accuracy of diagnosis. This difference is split evenly between those who are non-pregnant and those who have miscarriages or viable pregnancies. There are two factors that may have lead to this reduction. Firstly, a negative pregnancy test will exclude ectopic pregnancy in most cases removing the need for laparoscopy, and secondly the

diagnosis prior to laparoscopy was more accurate making more of the remaining laparoscopies positive. The use of serial hCG may be the reason for this.

Although bed occupancy in this population has decreased between 1993 and 1999 (fig. 3.3), this is because of the reduction in the total number of acute laparoscopies. When length of pre-operative stay as proportion of cases is considered (fig 3.4) it can be seen that there is a tendency towards women in 1999 having a longer stay before surgery, but this did not reach significance. The difference is only a matter of an extension of two days. However, there was not a large number of patients who were admitted for a long period before surgery.

If just the population in whom a diagnosis of ectopic pregnancy was made is considered, the length of pre-operative stay is again shown to have increased slightly between 1993 and 1999 (fig. 3.5). This might be because doctors are waiting for serial hCG estimations before taking the patient to theatre. In a cardio-vascularly stable woman with few symptoms, this may be an inappropriate use of beds. Protocols giving guidance as to when hCG levels can be tracked on an out-patient basis may result in a reduction in pre-operative stay. Designated theatre time would lead to a further reduction, as patients do not have to wait for time on the acute list. However, this does not appear to be a significant problem and there is a reduction in the total length of stay between the two years.

Figure 3.6 shows a decline in the total length of stay between 1993 and 1999. This is statistically significant (X^2 $p<0.001$). Since this is only slightly due to

pre-operative stay, it is likely to be because of increased use of laparoscopic surgery to manage ectopic pregnancy and a reduced post operative stay.

There appears to be a predominance of right-sided ectopic pregnancies in the St.James's population (Table 3.3), although this reaches significance (X^2 $p<0.01$), a preference for the right tube is not supported in the literature and conclusions should not be drawn from such small numbers.

Of those who did have a laparoscopy, the diagnosis of ectopic was more likely in 1999, with the positive predictive value rising from 40% in 1993 to 70% in 1999 (X^2 $p<0.001$) (Table 3.4).

This means that clinical and biochemical management allows a more accurate diagnosis, opening up the possibility of an alternative management approach without laparoscopy. Medical management is successful in the majority of cases if the starting hCG is less than 2000miu/ml (Lipscomb *et al.;* 1999). In the St.James's study, 22 women (29.0%) had hCG levels of <2000 when they were taken to theatre; these could have been offered medical management. Half of these went to theatre without the hCG level being known and none had any cardio-vascular compromise. There was no hurry to carry out the laparoscopy and if the result had been reviewed as part of the decision making process this might have been avoided.

In 1999, despite the widespread availability of hCG estimations to help diagnostic accuracy, a further 18 women (32.3%) had no pre-op level taken. Not only does

this mean less management options are available for discussion, but if laparoscopy were to be negative an important stage in considering the differential diagnosis would have been omitted. It might also be possible that a laparoscopy is carried out too early in pregnancy, and although present, the ectopic pregnancy is as yet too small to be visualised (Lipscomb *et al.*, 2000).

The more levels that are taken before the woman is taken to theatre, the more likely it is that the woman has a miscarriage.

Therefore, it is the under usage of hCG levels that is most striking, 48 cases (64.9%) of cases having too few levels taken to be of value in determine diagnosis and management options. In particular, a spontaneously resolving ectopic pregnancy will be over-treated if paired samples are not obtained. However, a negative level will exclude an ectopic and may explain the reduction in non-pregnant laparoscopies. As 30% of the laparoscopies were still negative it suggests that improving the uptake of hCG use may help to reduce this level further.

3.3 National Postal Questionnaire to Assess Practice in the Diagnosis and Management of Ectopic Pregnancy.

In order to assess whether the practice in SJUH is comparable with the national practice in the UK, a national survey was carried out.

3.3.1 Method

The aim of the questionnaire was to gather information on the early pregnancy assessment service offered by every gynaecology unit in the UK. Specific questions were directed at the availability of Early Pregnancy Units (EPUs) and the management of Ectopic Pregnancy.

A draft questionnaire covering areas of interest – availability of an early pregnancy assessment service, and facilities for diagnosis and treatment, was designed. This questionnaire was piloted locally, to correct any obvious deficiencies of clarity and content, and a final version produced.

It was assumed that most units with an acute gynaecological service will have junior doctors in training, and so can be identified from the RCOG list of District Tutors. In June 1999, the questionnaire was sent out to every UK District Tutor for obstetrics and gynaecology.

3.3.2 Results

A total of 262 questionnaires were sent out and 155 (59.2%) were returned. Five units did not have any acute gynaecological service. Of the 107 units who did not

send a reply to the questionnaire, it is possible that more of them did not provide facilities for early pregnancy assessment, which led them to be less inclined to reply to the questionnaire. I did not follow up the initial questionnaire to investigate this. This left 150 units providing care for those with problems of early pregnancy and the results of the analysis of these is presented.

3.3.2a Availability of Early Pregnancy Assessment Services.

Units were asked if they had a specific provision for women with early pregnancy problems to be assessed without requiring admission. This can take several forms, from a dedicated early pregnancy unit to a dedicated space on a ward. The important thing is that time and facilities are set aside for women to be referred directly for assessment. Overall, 127 (84.7%) units had a dedicated early pregnancy assessment service. The other 15.3% provided acute gynaecological care with no dedicated services for early pregnancy.

Table 3.5 Number of days the service was open each week (126 respondents)

	1	2	3	4	5	6	7
no.	0	1	2	3	95	5	20
%	0	0.8	1.7	1.7	76.0	4.1	15.7

Those units with EPUs were asked to indicate their availability, both the number of days per week that they were open, and how many hours they were open each day.

Average hours open - weekdays

Only 99 units gave sufficient information to estimate the average number of hours they were open and the results are shown in figure 3.8.

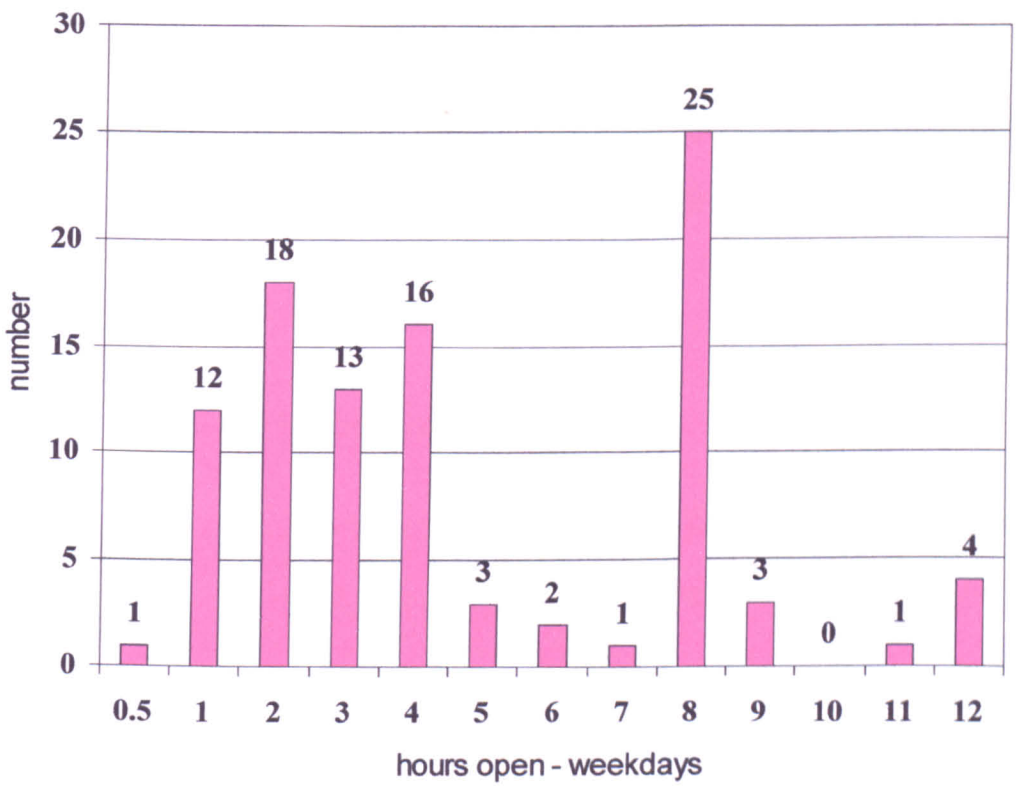


Fig 3.8 Chart to demonstrate the number of hours units were open on weekdays (99 responses)

Average hours open – weekends

Of the units that are open at the weekend, only 9 of the 25 gave enough information to calculate the length of time they were open.

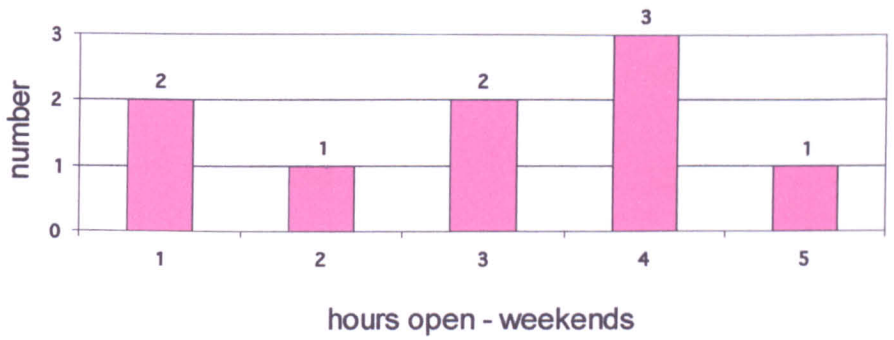


Fig 3.9 Chart to demonstrate the number of hours units were open at weekends (9 responses)

3.3.2b Facilities for Diagnosis

Units with access to trans-vaginal ultrasound

Ultrasound is the basic tool for assessment of early pregnancy complications. Viable pregnancy and many miscarriages can be assessed by ultrasound alone. All units had access to ultrasound, and all except one had at least some access to trans-vaginal scanning. Availability of trans-vaginal ultrasound is fundamental in the diagnosis of ectopic pregnancy as its closer proximity to the pregnancy and greater magnification means a diagnosis can be reached at an earlier gestation.

Table 3.6 Units with access to trans-vaginal ultrasound (148 responses)

TV US	Number	%
Yes	127	84.7%
Limited	20	13.3%
No	1	0.6%
No response	2	1.3%

Investigation of Suspected Ectopic Pregnancy

Table 3.7 Availability of ultrasound and biochemical investigations in the diagnosis of suspected ectopic pregnancy

	Serial use	Single use	Nil available	No response
ultrasound	129 (86%)	19 (12.7%)		2 (1.3%)
Serum hCG	141 (94%)	4 (2.7%)	2 (1.3%)	3 (2%)
progesterone	11 (7.3%)	6 (4%)	47 (31.3%)	86 (57.3%)

If ultrasound cannot confirm a normally placed viable pregnancy or miscarriage, further investigation is required. Serum hCG estimations are the main-stay of further investigation.

Only 91 *(60.7%)* of units had a protocol for managing ectopic pregnancy. This survey showed that 113 *(75.3%)* would be willing to consider out-patient management until diagnosis was confirmed but 27 *(18%)* would admit all possible ectopic pregnancies (10 *(6.7%)* did not reply).

3.3.2c Treatment of Ectopic Pregnancy

Surgical management

Surgery remains the mainstay of management of ectopic pregnancy. This will be discussed at length in chapter 9 , but questions were included in this questionnaire about the treatment offered by the units when ectopic pregnancy is diagnosed. Laparoscopic management is considered to be the gold standard for the surgical management of ectopic pregnancy. Whilst all units offer surgical management, not all offer this laparoscopically

Availability of Laparoscopic Management of Ectopic Pregnancy

- EP always managed laparoscopically when appropriate 12 *(7.9%)*
- EP sometimes managed laparoscopically when appropriate 116*(77.3%)*
- EP never managed laparoscopically when appropriate 19 *(12.7%)*

- No reply 3 *(2%)*

Table 3.8 Reasons given as to why not all (appropriate) ectopic pregnancies are not managed laparoscopically (120 responses):

Reasons given	Number
Trained staff not always available	118
Facilities only available out of hours	5
Facilities only available in normal hours	8
No reply	30

The questionnaire asked for the number of consultants and middle grades in each unit, and whether there were trained in the laparoscopic management of ectopic pregnancy. Overall, less than 50% of consultants and middle grade doctors were reported to be appropriately trained:

- 656.2 consultants in 121 units = 5.4 per unit
    - 295 *(45.0%)* manage EP laparoscopically = 2.4 per unit
- 667 middle grades in 108 units = 6.2 per unit
    - 332 *(49.8%)* manage EP laparoscopically = 3.1 per unit.

Medical Management

Table 3.9 Units using medical management of confirmed ectopic pregnancy (147 responses)

	Number (%)
Confirmed ectopic pregnancy	42 (28.0%)
Persistent ectopic pregnancy only	18 (12.0%)
No use	87 (58.0%)
No reply	3 (2.0%)

Table 3.10 The agents used for medical management (60 respondents with some units using more than one agent)

Agent	Number
Systemic MXT	57
Local MXT	5
Mifepristone	1
misoprostol	1
KCl	1
PGF2α	1

Medical management of ectopic pregnancy is an alternative in certain cases of ectopic pregnancy. Using this method, the women can avoid the need for surgery and sometimes admission.

3.3.2d Follow-up and Support

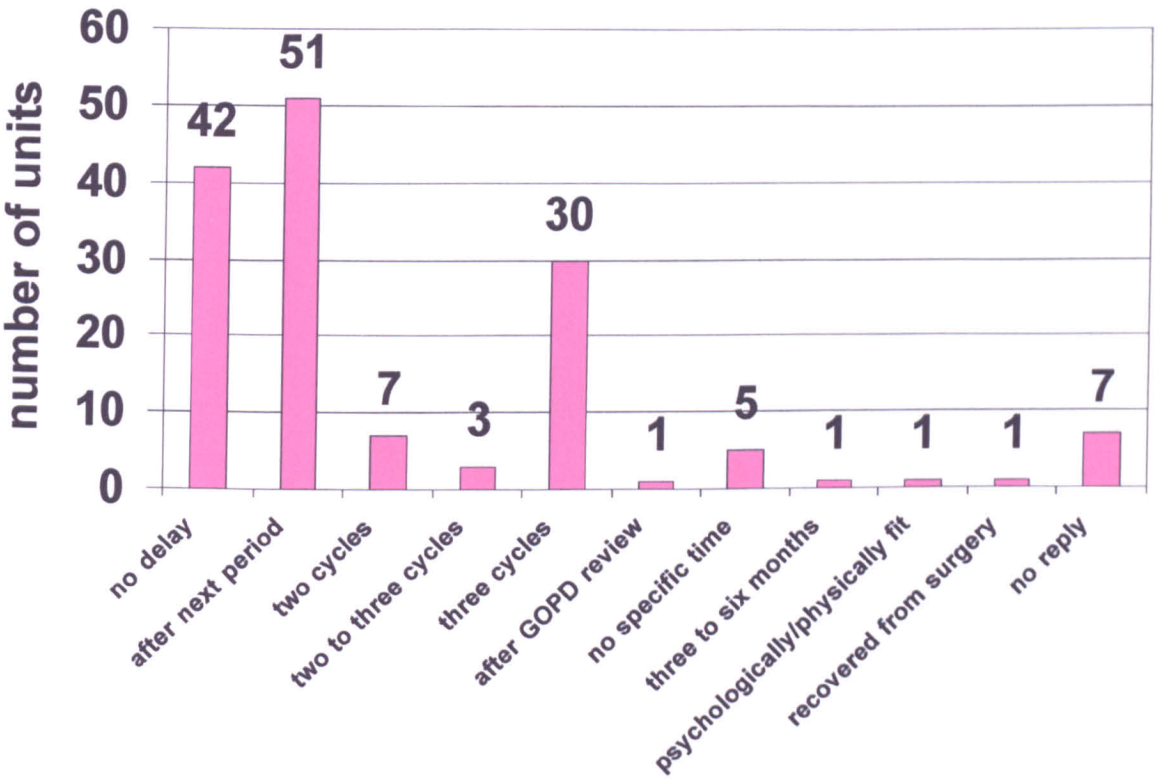


Figure 3.10 Advise given to women about timing of next pregnancy following an ectopic pregnancy (149 responses)

The questionnaire asked about the post-operative discussion and support offered to patient. Discussion of the operative findings was almost universal with 149 units saying this is part of their care. Discussion of the implications for fertility was less common, with only 58.0% of units providing this, and in 17.3% this

discussion would only take place post-operatively and not at follow-up in the outpatients. The implication for fertility is an important area for women who have had an ectopic. In total, 69.3% of units offered outpatient follow-up after an ectopic pregnancy. 138 (92.0%) of units recommended a scan in any future pregnancy.

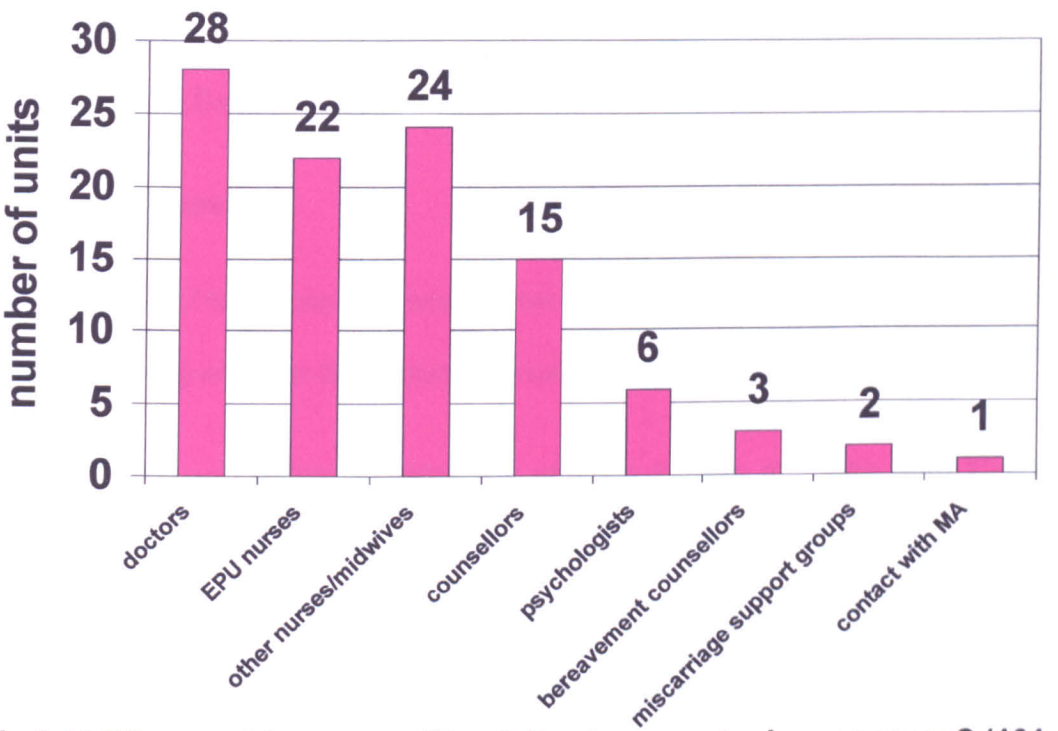


Fig 3.11 Who provides counselling following an ectopic pregnancy? (101 responses)

44 (29.3%) of units offered no access to counselling for women who had had an ectopic pregnancy. However, it is important to be critical of what is meant by counselling, as only 67 (44.7%) of units had access to counsellors with any training.

73 (48.7%) of units provided information leaflets about ectopic pregnancy to women before discharge, 63 produced their own leaflets about ectopic pregnancy and 10 used externally produced leaflets. 61 (40.7%) did not. The remainder did not give this information.

33 units knew of support groups for women who had had an Ectopic Pregnancy in their area, 142 units were aware of the Miscarriage Association and 39 units were aware of the Ectopic Pregnancy Trust.

3.3.3 Discussion

That there are 84.7% of units with some form of EPU is very encouraging, but it is not possible to say whether this would be true of the UK as a whole.

Over 95% of the units were available for at least 5 days although only 19.8% provided some sort of weekend service. It can be seen that the majority of units (59.8%) are open for half a day or less, though most of the rest offer an all day service (fig. 3.8). As most hospitals provide only emergency cover at weekends, it is not surprising that EPUs have reduced hours of opening at this time.

The majority of units (94%) employ the use of serial hCG sampling. Only a small proportion use progesterone in the investigation of ectopic pregnancy (11.3%), but it is interesting that 7.3% claim to use serial progesterone levels, when this offers no advantage over a single estimation.

Wider use of protocols might improve both diagnosis and use of resources. Both ultrasound and serum investigation of ectopic pregnancy are expensive resources, and review of early pregnancy complications is often left to the most junior doctors on call. Without clear guidelines about what action should be taken, and when this is appropriate, there can be a tendency to delay diagnosis by arranging a further scan or blood test. These women are often admitted to hospital. Protocols not only guide the safe use of resources, but also facilitate appropriate and prompt diagnosis and who should be admitted and who can be managed as an outpatient. They can be followed by specialist nurses, only referring to senior doctors when cases lie outside the scope of protocols. These nurses provide expertise and continuity for patients, as they are likely to be continuing to care for the patient day by day, rather than passing decisions on.

If an empty uterus is found, a large proportion of women will subsequently be found to have an ongoing pregnancy, or to have miscarried. The decision as to whether these women require admission is important as this has a considerable effect on resources if all these women are inpatients until a final diagnosis is reached.

Admitting women does not prevent catastrophic haemorrhage, but allows rapid treatment should this occur. The risk of complications during outpatient management can be reduced by careful patient selection, consistency of advice and direct admission to the wards if symptoms cause concern. Catastrophic haemorrhage can also occur after a patient is discharged home following

conservative treatment (conservative surgery, medical or expectant management) and the same conditions should apply. A seven-day hCG service is required, so that women who require treatment are not left at home over weekends when they will find it most difficult to access medical care.

Very few units (7.9%) were able to offer a complete service for the laparoscopic management of ectopic pregnancy. The main reason for this would seem to be a lack of trained personnel (Table 3.8).

28.0% of units said they currently considered medical management for ectopic pregnancy (Table 3.9). However, poor design of the questionnaire at this point means it was impossible to tell whether this is an occasional event, or a standard part of practice. It would have been useful to know how many times the units had used medical management in the preceding year.

Where medical management is offered, systemic methotrexate is the agent of choice and this was the one generally used by units responding to the questionnaire.

Following an ectopic pregnancy, many women have questions that were not answered at the time of diagnosis; they also require information about what was found and advice for the future. Specialist clinics in the Early Pregnancy Units might be a more appropriate setting for follow-up after an ectopic pregnancy than general gynaecology out-patient clinics.

There was no consensus of advice on the timing of the next pregnancy after an ectopic pregnancy. If the woman has waited for a period before conceiving, it allows a more meaningful expected gestation to be determined, which is important information when assessing the likelihood of an empty uterus representing another ectopic pregnancy. Advice to wait until psychologically prepared is sensible, as women described the fear of being unable to conceive at the same time as described fear conception, in case it is a further ectopic pregnancy.

Counselling is something doctors are expected to do, often without training, and is often understood as giving information. Although this is an important part of post-operative care, being able to listen and facilitate problem solving is also an important aspect for some women, as they acknowledge the loss of their pregnancy, the threat to life posed by ectopic pregnancy, try to address their fears about infertility and discuss the possibility of another ectopic pregnancy.

3.4 Ectopic Pregnancy Trust Questionnaire of Women's Experiences of Ectopic Pregnancy.

A third method of assessing the early pregnancy care provided for ectopic pregnancy is to ask the women themselves. This allows a different view to be obtained. There are obvious biases, as there are with hospital questionnaires, but the combination of approaches should give a good overview of practice throughout the country. Because of links with the Ectopic Pregnancy Trust, a questionnaire was sent to all women who contacted them.

3.4.1 Method

A questionnaire was designed in conjunction with the Ectopic Pregnancy Trust (EPT). The EPT is a national organisation providing support and information to people affected by ectopic pregnancy. Areas of interest to the EPT and to me were listed. I produced a draft questionnaire covering these areas and ensuring that medical aspects were presented in an accurate form. The questionnaire was then re-organised into a final draft within the EPT by its officers, who are lay-women who have experienced an ectopic pregnancy. They ensured that the questionnaire was presented in a way that would be accessible to a non-medical person. I then checked this final draft from a medical point of view.

The questionnaire covers many aspects of ectopic pregnancy, and as the two parties involved in the design required different things from the data, some of the results are difficult to interpret, reflecting this dual authorship. For example, I felt

data on the risk factors for ectopic pregnancy would be difficult to relate to the time of the ectopic pregnancy through the use of this questionnaire, but this area was still covered despite this limitation because it was of interest to the EPT members. There is a compromise between what information is wanted, and what it is possible to obtain.

The questionnaire also provided free space for women to write about the impact ectopic pregnancy has had on themselves and their relationships. The responses to this part of the questionnaire are not discussed in this thesis.

The questionnaire was sent to all the women on the mailing list of the EPT in June 1999. The population to whom the questionnaire was sent is self-selected, being those women who had approached the EPT for advice/support. The response was good, although around 100 further replies were sent in after the data base had been analysed and, therefore, are not included in the analysis that follows.

The responses from all the questionnaires were entered into a data-base which I designed for this purpose. I entered all the results personally, to ensure consistency.

3.4.2 Results

400 questionnaires were sent out, 221 replies with 263 ectopic pregnancies were received and added to the data base. Most (70.1%), but not all, of the ectopic

pregnancies had occurred in the three years prior to the questionnaire being distributed. Information giving the year of first ectopic pregnancy was available on 174 women and is shown in figure 3.12 below. In 18.9% of cases, women had contacted the Trust about ectopic pregnancies that had occurred 5 or more years before.

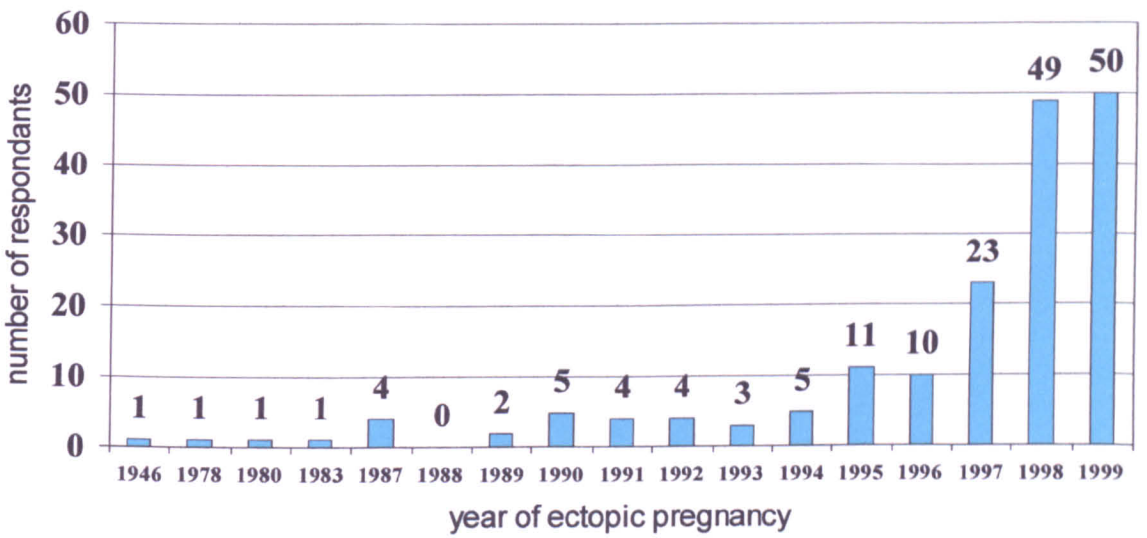


Fig 3.12 Year in which respondents experienced their first ectopic pregnancy (174 responses)

Most of the women had had a single ectopic pregnancy, 14.4% had experienced two or more ectopic pregnancies, one woman had five. A woman who has had more than one ectopic pregnancy might be more inclined to contact the EPT, and it is possible that women who have had multiple ectopic pregnancies are over represented. However, this is unlikely, since a large number of women sort help

soon after their first ectopic pregnancy, and a recurrence risk of around 15% is compatible with these figures.

Table 3.11 Number of ectopic pregnancies experienced by respondents (221 responses)

Number of EP	Number
1 ectopic pregnancy	189 (85.5%)
2 or more	32 (14.4%)

3.4.2a Background of respondents -

Ethnic Origin

The respondents were asked to indicate their ethnic group. 93.7% of this population described themselves as white (Table 3.12). This is similar to the general population as the most recent UK census found 92.1% of the population described themselves as white (ONS; 2001).

Age

In 168 women it was possible to calculate their age at the time of their first ectopic pregnancy. This is shown in figure 3.13.

If the number of ectopic pregnancies in each age group is taken as a proportion of the number of maternities for the triennia of 1994-1996 (The Stationary Office,

Table 3.12 Racial Group (216 responses)

Ethnic group	number
European	207
Black Afro-Caribbean	4
Indo-Asian	2
Mediterranean	1
"other – white"	2
did not state	5

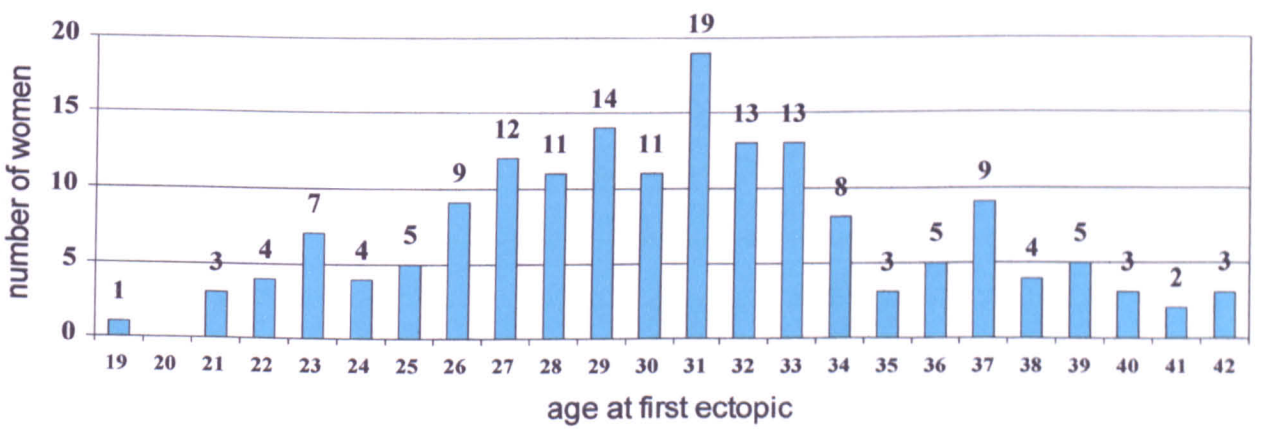


Fig. 3.13 Calculated age of respondents at the time of their first ectopic

1998) the incidence of ectopic pregnancy is seen to increase with age of the population of respondents (Table 3.13 and fig. 3.13):

Table 3.13 Number of ectopics pregnancies in respondents per thousand maternities according to age. Figures for number of maternities taken from the 1994 – 1999 Confidential Enquiries into Maternal Deaths.

age	ectopics	% of all ectopics	Maternities (x 1000)	% of all maternities	ectopics per 1000 maternities	OR (95%CI)
< 25	19	11.3	590.4	26.9	0.032	0.466 (0.272-0.798)
25-29	51	30.4	738.4	33.6	0.069	1
30-34	64	38.1	610.7	27.8	0.105	1.518 (1.035-2.227)
35-39	26	15.5	220.0	10.0	0.118	1.710 (1.042-2.808)
40+	8	4.8	37.8	1.7	0.210	3.046 (1.350-6.872)

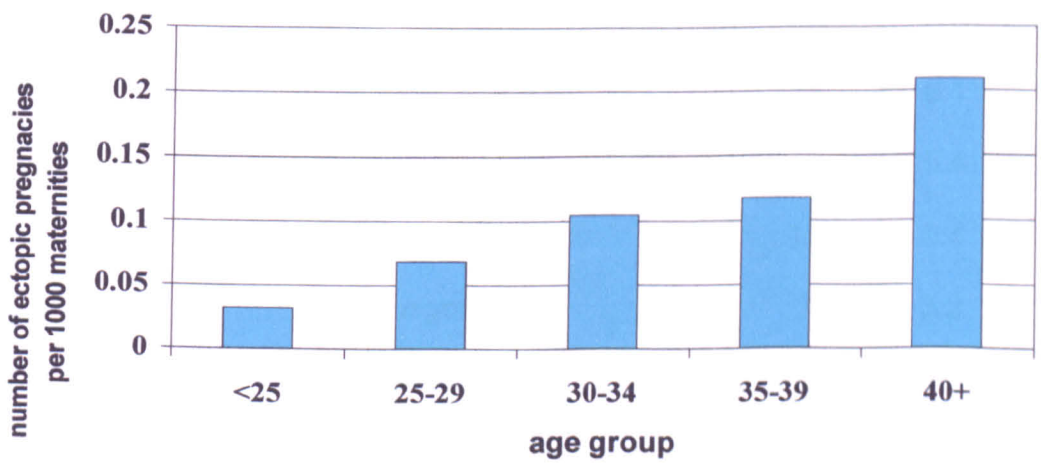


Fig 3.14 Number of ectopic pregnancies as a proportion of total maternities in the same age-group

Risk factors for ectopic pregnancy

Table 3.14 "Have you suffered from or received treatment for any of the following conditions prior to your first ectopic pregnancy?" Risk factors identified by respondents (221 responses).

Risk factor	Number	%
miscarriage	44	19.9
progestogen only pill	30	13.6
termination of pregnancy	30	13.6
"D&C"	29	13.1
fertility treatment	28	12.7
appendicitis	24	10.9
caesarean section	20	9.0
intra-uterine device	20	9.0
pelvic infection	19	8.6
abdominal surgery	18	8.1
chlamydia	12	5.4
endometriosis	12	5.4
tubal surgery	7	3.2
sterilisation	4	1.8
none of the factors identified	80	36.2

The respondents were given a list of possible risk factors. As this was not timed against their ectopic pregnancy, it was difficult to assess the significance of some

of the risk factors. This information would be better assessed by structured interview.

Eighty women ticked none of the boxes identifying risk factors, some of these women may have simply omitted this question, but this might mean that up to 36.2% did not have any of the risk factors for ectopic pregnancy suggested in the questionnaire.

Twenty-four had had an appendicectomy, in eight this was the only factor they identified.

Smoking

Table 3.15 "Do you smoke?" Smoking status of respondents (219 responses).

Smoking status	number
non-smokers	136
ex-smokers	33
current smokers	50
not stated	2

3.4.2b Knowledge about Ectopic Pregnancy

An important component in reducing both number of mortalities resulting from ectopic pregnancy, and the number of women who present with cardio-vascular collapse secondary to ectopic pregnancy, is education of the population at risk of ectopic pregnancy. If women are aware of ectopic pregnancy and its symptoms, potentially they will present earlier. The respondents were asked whether they were aware of ectopic pregnancy before they were affected themselves.

Table 3.16 "Before your first ectopic pregnancy, did you know what an ectopic pregnancy was?" Women's knowledge of ectopic pregnancy before their first experience of ectopic pregnancy (221 responses).

	Number	%
Women with no prior knowledge of ectopic pregnancy	62	28.1
Women with prior knowledge of ectopic pregnancy	149	67.4
Women who did not know another with ectopic	106	48.0
Women with 1st degree relative with ectopic	5	2.3
Women with other relative with ectopic	19	8.6
Women with friend with ectopic	84	38.0

3.4.2c Clinical Diagnosis of Ectopic Pregnancy

The total number of ectopic pregnancies (263) was considered.

Table 3.17 "By which Health Care Professional were you first seen?" The first Health professional respondents saw at the time of the Ectopic Pregnancy (252 responses).

Who	Number	%
General Practitioner (G.P.)	176	*66.9*
Casualty doctor	33	*12.5*
Gynaecologist	20	*7.6*
Collapsed – did not know	13	*4.9*
Midwife	2	*0.8*
Emergency doctor	2	*0.8*
Assisted conception unit	2	*0.8*
Practice nurse	1	*0.4*
Chest physician	1	*0.4*
Don't know	2	*0.8*
Not stated	11	*4.2*

Was the patient known to be pregnant at first presentation?

18 did not know they were pregnant and were not asked about the possibility of pregnancy or had a pregnancy test performed. Only 110 had a pregnancy test performed, the rest, 132, did not. Of those that did not have a pregnancy test

performed, many women had already performed this themselves before they presented to a doctor, and a repeat test is not generally required. The information was not available in the other 21 ectopic pregnancies. Therefore, of the women who gave this information, the diagnosis of pregnancy was not considered by either the patient or the doctor in 12.7% of women.

Presenting symptoms

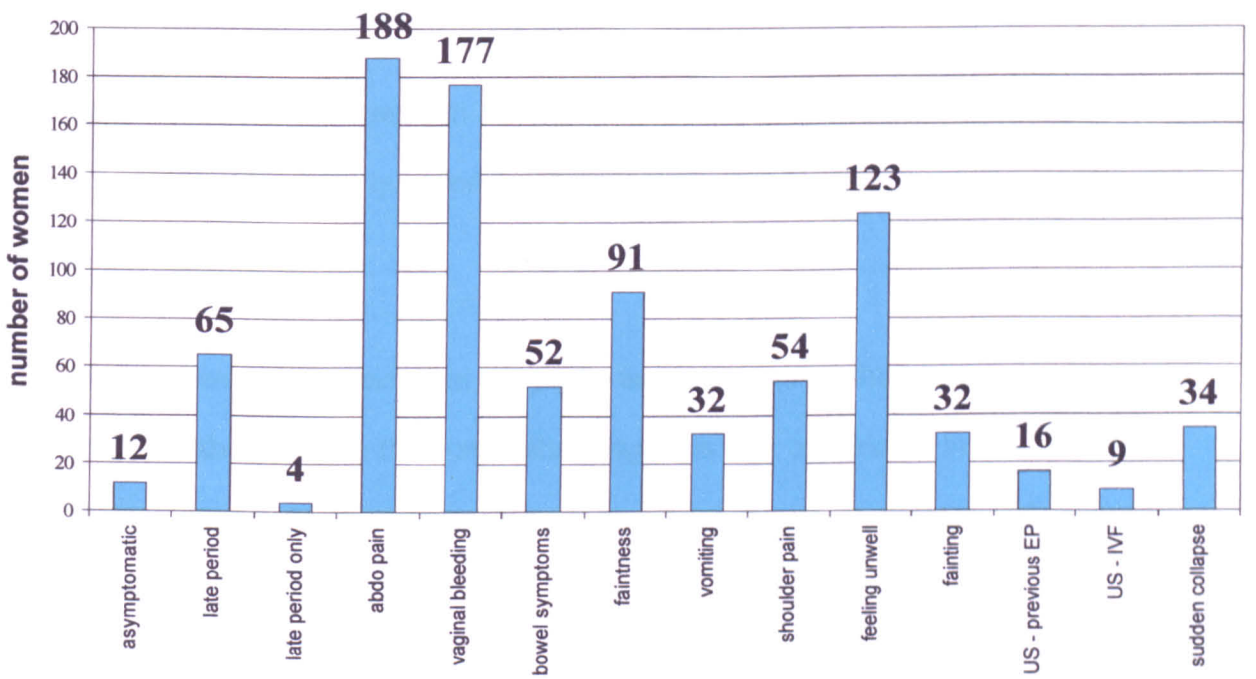


Fig. 3.15 "What symptoms did you have when you were first seen by a Health Care Professional?" Presenting symptoms of ectopic pregnancy – more than one symptom was described by many respondents

Did the woman suspect an ectopic pregnancy when she first presented?

184 women did not suspect the diagnosis when they first presented. In 12 of these cases, the woman had previously had an ectopic pregnancy. 60 women did suspect the diagnosis. In 37 cases, this was the first ectopic pregnancy, in 23 the woman had had an ectopic pregnancy before. In 19, no information was given.

Involvement of Early Pregnancy Units

Only 74 women were seen in EPUs and 166 women reported that they were not. 23 did not answer the question but may not have known.

Initial diagnosis

The women were asked what diagnosis was made when they first presented for medical advice. (More than one initial diagnosis was considered in some cases). Overall, in 51.8% of women, where an initial diagnosis was stated, ectopic pregnancy was considered.

Of those women first seen by their G.P., the diagnosis of ectopic pregnancy was made in 74 out of 172 women (43.0 %).

In those women first seen by a casualty officer, an ectopic pregnancy was diagnosed in 14 out of 31 cases (45.2%).

In those women first seen by a gynaecologist, an ectopic pregnancy was diagnosed in 13 (65.0%) out of 20 cases.

Table 3.18 "What was the initial diagnosis?" Diagnosis made at first presentation (231 respondents gave at least one diagnosis).

Initial Diagnosis	Number
Ectopic Pregnancy Suspected	118
? miscarriage	44
Various gastro-intestinal problems	23
Recalled after managed as miscarriage	18
Normal pregnancy	9
Menstrual disturbance	9
Managed as a miscarriage, but not recalled	8
"Womb infection"	4
Ovarian cyst	4
Other	14
Not stated	32

Time the woman first noted symptoms to diagnosis

Most women presented between 6 and 8 weeks gestation. In only 36.3% of cases was the diagnosis of ectopic pregnancy made within the first week of symptoms. However, 15 women reported symptoms before their menstrual period was due. Seven of these women stated that the diagnosis was made at

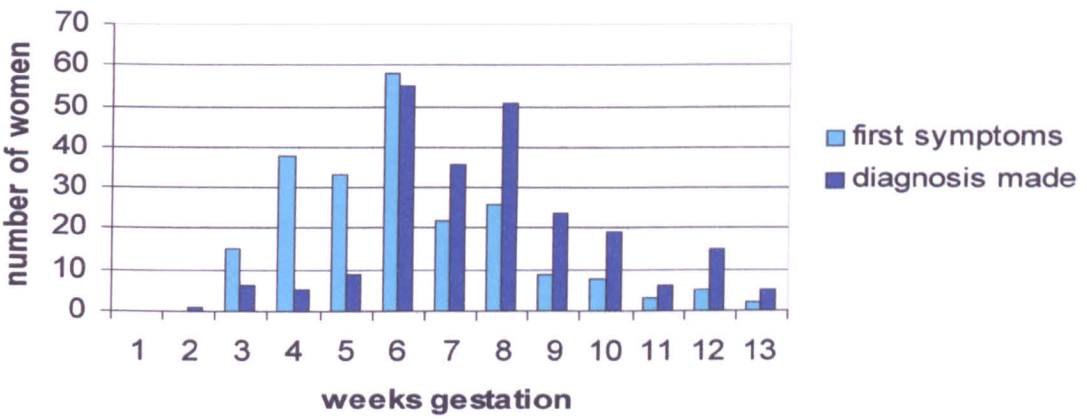


Fig. 3.16 "At what stage of your pregnancy did your symptoms first appear?" (219 responses) "How many weeks pregnant were you when diagnosed you're your ectopic pregnancy?" (232 responses) Chart demonstrating the time at which symptoms first appear and time at which the diagnosis of ectopic pregnancy is made.

this time which seems unlikely. Because of the way the questionnaire was set-up, it is not possible to verify this early diagnosis or the reliability of the respondent's memory about the length of pregnancy in relation to last menstrual period.

In cases where the information was given (215), 73.9% were diagnosed as having an ectopic pregnancy within three weeks of first seeking medical advice, with 22.3% in the second and 36.3% in the first week.

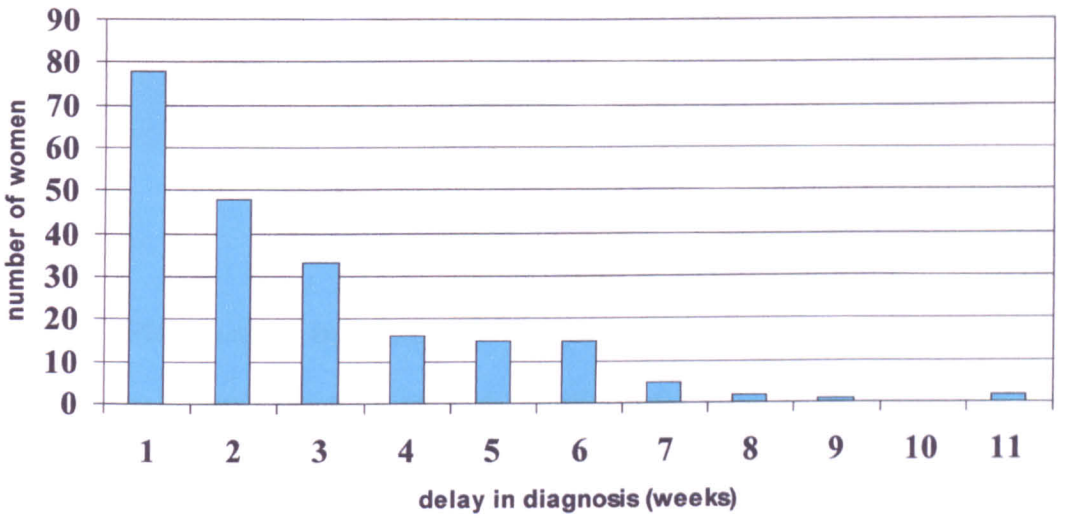


Fig. 3.17 Delay in weeks between first noting symptoms and the diagnosis of ectopic pregnancy being made calculate from those questionnaires where both onset of symptoms and time of diagnosis were given

Time the woman first presented to medical services to diagnosis

Of those women who gave the information, 56.5% had a diagnosis of ectopic pregnancy made at their first visit to their General Practitioner, and 70.6% at the first visit to hospital.

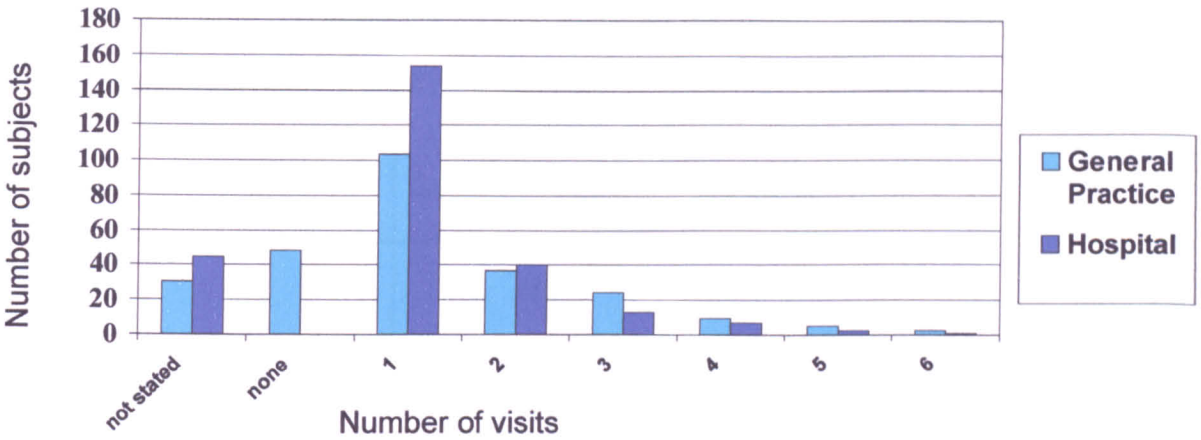


Fig. 3.18 "Please state how many times you visited your GP and/or hospital before your ectopic pregnancy was considered." Number of visits made to medical practitioners before the diagnosis of ectopic pregnancy was made

3.4.2d Diagnostic Tests

Respondents were asked what diagnostic tests were performed both in Primary Care and hospital.

In general practice, vaginal examination was the only investigation performed in 32 cases. In hospital practice, this was the case in just 5 women. 68 women reported not having an ultrasound scan performed when they first presented to hospital. What the questionnaire does not establish is whether a scan was organised at the first visit.

Table 3.19 "What tests were carried out and by whom." Diagnostic tests performed in General Practice and in hospital. Some respondents had more than one test performed (263 responses).

Test	General Practice	Hospital
no test	180	30
vaginal examination	43	98
urine pregnancy test	46	143
serum hCG – single	8	71
serum hCG – serial	0	50
ultrasound Scan	1	195 - TA 45 - TV 55 - both 95

3.4.2e Treatment of Ectopic Pregnancy

Treatment options for ectopic pregnancy are discussed at length in Chapter 9. The questionnaire on women's experiences included questions on whether these options were discussed.

Treatments offered to patients

In 227 pregnancies the management options were discussed pre-operatively. 91 women felt that management was not discussed with them because they were in a collapsed state.

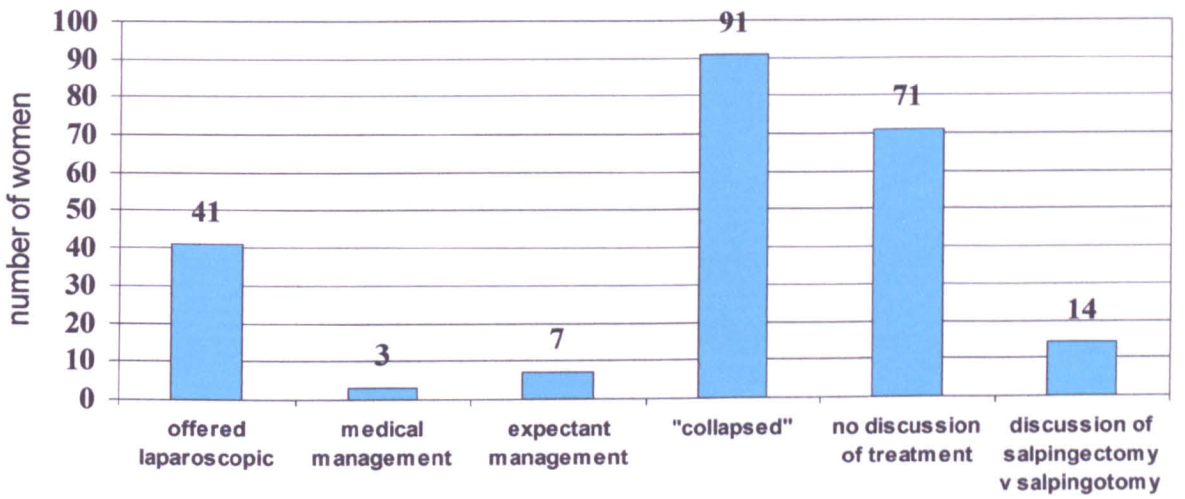


Fig. 3.19 "Were you given any options as to the treatment of your ectopic pregnancy." Respondents' recollection of the management options discussed once a diagnosis of ectopic pregnancy was made (227 responses).

Actual treatment

Chapter 9 will discuss, in detail, what should be considered optimal management of ectopic pregnancy, so there will be only a brief comment here. In general, respondents described the management of the first ectopic pregnancy.

Details of the treatment received from 217 first ectopic pregnancies were analysed.

Of those who had surgical management and gave information on the route (177 respondents), 80.2% had management by laparotomy and 19.8% had laparoscopic management.

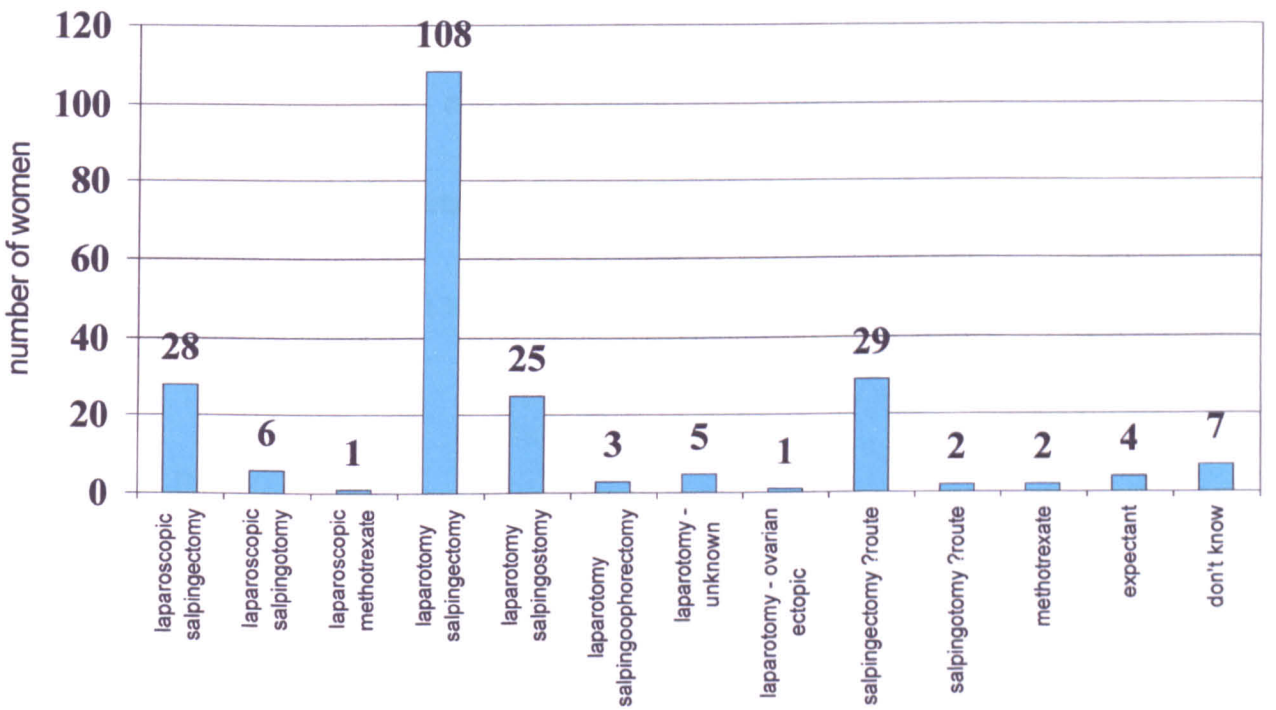


Fig. 3.20 "What treatment did you actually receive for your ectopic pregnancy?" Actual management of ectopic pregnancy. Chart demonstrates both the procedure performed and the route by which it was performed (221 responses).

Table 3.20 Number of respondents with conservative (tubal preservation) and radical (tubal excision) treatment of their first ectopic pregnancy. Surgical and non-surgical treatments considered (221 responses).

treatment	Number *(%)*
salpingectomy	168 *(76.0)*
salpingotomy	33 *(14.9)*
others (tube preserved)	8 *(3.6)*
not known to the woman	12 *(5.4)*

Tubal rupture

Table 3.21 "Did your tube rupture?" The number of ectopic pregnancies that were ruptured at the time of treatment

Rupture	Number
Yes	115
No	77
did not know	26
not stated	3
not applicable	4

Subjects were asked for each pregnancy whether or not the tube had ruptured by the time of surgery. There were 227 responses from the 263 ectopic pregnancies.

Side affected by ectopic pregnancy

The side in which the ectopic pregnancy was found was stated in 227 pregnancies.

Table 3.22 "Which tube was affected?" The side in which the ectopic pregnancy was found (217 responses).

Side	Number
right	107
left	91
don't know	8
both	5
not applicable	6

3.4.2f Information, Follow-up and Support

Communication of the diagnosis and its implications are an important part of the management of ectopic pregnancy. Adequate information and effective communication can lessen many of the long-term psychological sequelae.

Table 3.23 "Once diagnosed, was ectopic pregnancy fully explained to you?" Respondents' level of satisfaction with the explanation of their diagnosis once ectopic pregnancy was suspected (215 responses).

	Number *(%)*
Generally satisfied	146 *(66.1)*
Generally dissatisfied	69 *(31.2)*
Not stated	6 *(2.7)*

Table 3.24 "If you were given any information, how was this communicated to you?" Means of communicating treatment for ectopic pregnancy (182 responses).

	Number *(%)*
Verbal	143 *(64.7)*
Written	39 *(17.6)*
not stated	39 *(17.6)*

Table 3.25 "Do you feel you were given an adequate explanation of the treatment?" Respondents' satisfaction with the explanation of the treatment for ectopic pregnancy given to them after the procedure (209 responses).

	Number (%)
generally satisfied	140 (63.3)
generally dissatisfied	69 (31.2)
not stated	12 (5.4)

Risk of future ectopic pregnancy

Adequate management of ectopic pregnancy should include information about future pregnancies because of the higher risk of a further ectopic pregnancy. This should include information about early pregnancy assessment to establish location of the pregnancy.

At the time of their first ectopic pregnancy 167 (75.6%) women were warned that they were at risk of a further ectopic, 53 (24.0%) were not. In one (0.4%) the warning was not applicable.

161 (72.9%) women were advised to have an early pregnancy ultrasound to confirm a pregnancy was intrauterine, 55 (24.9%) were not so advised, 4 (1.8%) did not state and in one (0.4%) this was not applicable.

31 (14.0%) women were neither told of the risk of a future ectopic pregnancy, nor advised to have an early pregnancy ultrasound scan in subsequent pregnancies.

Information about ectopic pregnancy

Hospitals are generally not able to provide ongoing support for those women who have psychological sequelae after an ectopic pregnancy. It is important that women should have information about support groups that are available to fulfill this need as required. As discussed above, there is also some information that should always be conveyed to women for their future safety.

Table 3.26 "Were you given written information about ectopic pregnancy prior to leaving the hospital?" Leaflets given on discharge after an ectopic pregnancy (221 responses).

leaflet	Number of women
hospital designed on ectopic pregnancy	20
Miscarriage Association leaflet on ectopic pregnancy	12
Ectopic Pregnancy Trust leaflet on ectopic pregnancy	4
ectopic pregnancy leaflet - unknown	32
leaflet on miscarriage	2
hysterectomy	1
post-pregnancy exercise	1
no written information given	145
don't know	4

46 (20.8%) were given information about support groups available to them, 68 (30.8%) were given written information about ectopic pregnancy before leaving hospital (Table 3.23).

Table 3.27 "Pregnancies you have had." Obstetric history of respondents (221 responses).

Women with no living children	**96 *(43.4%)***
Ectopic pregnancy only	57 *(25.8%)*
Ectopic pregnancy and termination of pregnancy only	10 *(4.5%)*
Ectopic pregnancy and miscarriage only	28 *(12.7%)*
Ectopic pregnancy and stillbirth only	1 *(0.5%)*
Women with either living children or ongoing pregnancies at time of questionnaire	**125 *(56.6%)***
Currently pregnant	15 *(6.8%)*
Livebirth after ectopic	18 *(8.1%)*
Livebirth before ectopic	71 *(32.1%)*
Livebirth before and after ectopic	21 *(9.5%)*

3.4.2g Obstetric Outcome -

All 221 respondents gave details of their obstetric history which is summarised in Table 3.27. 167 (75.5%) women had not had an ongoing pregnancy since their ectopic pregnancy. They were asked to indicate the reasons. This is displayed in figure 3.21 with the responses of all 221 respondents.

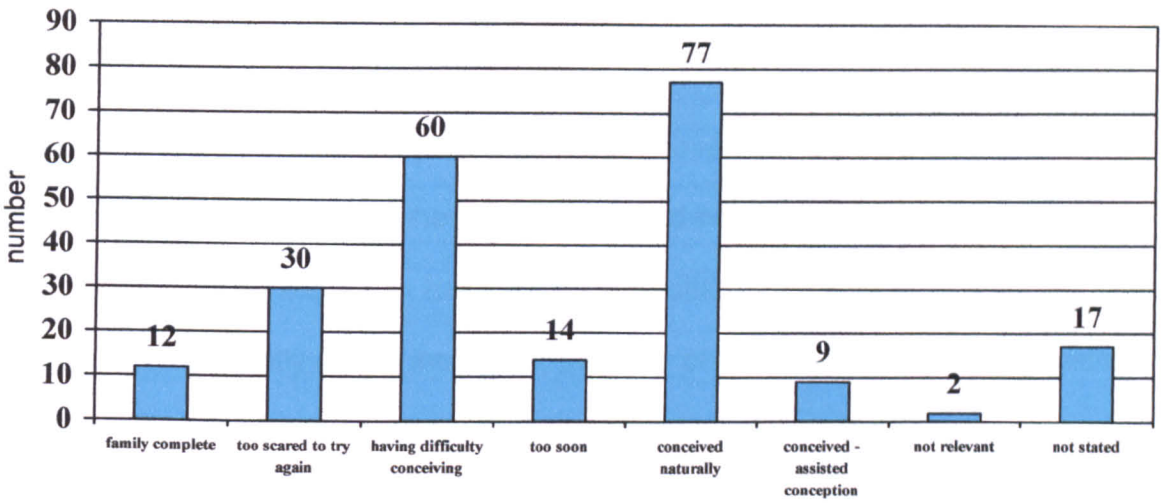


Fig. 3.21 "Pregnancies you have had after this ectopic." Obstetric history after an ectopic pregnancy (221 responses).

3.4.3 Discussion

Whilst, on first inspection, white Europeans appear to constitute the bulk of the respondents, in fact the proportion of white to non-white does reflect those of the UK population as shown in the last census. When considering ectopic pregnancy, it is of particular concern that all racial groups access services and information, as data suggest that ectopic pregnancy has a higher incidence in some minority groups, particularly black women (Gaydos *et al.*; 1998). The EPT is making efforts to target specifically at this population with the appropriate leaflets etc.

The results of the questionnaire also suggested an increase in incidence of ectopic pregnancy with age. Whilst this cannot be extrapolated to the entire UK population – perhaps younger women are under-represented, being less likely to

contact a support organization, it does fit with what is already known. As discussed in chapter 1, there is epidemiological data to support an increase in the incidence of ectopic pregnancy with advancing maternal age.

Appendicectomy/appendicitis has not been proven to be associated with ectopic pregnancy (Urbach and Cohen; 1999). It would be expected that about 6% of the population could expect to have an appendicitis at some time in their life, with men have a slightly higher incidence, the ratio of women to men effected being 1 to 1.4 (Al-Owran *et al.;* 2003). The number of women found to have previously had an appendicitis is higher than would have been expected. Urbach and Cohen emphasise that it is the quality of the studies of the association of ectopic pregnancy with appendicitis that means reliable conclusions cannot be drawn, rather than that an association is not found. This study suggests more women than would be expected had had an appendicectomy.

More than half (61.5%) of our respondents had never smoked. More women, and particularly younger women, are taking up smoking. Smoking is associated with an increased risk of ectopic pregnancy (Castles *et al.;* 1999), and it will be interesting to see if this trend has any impact on the incidence of ectopic pregnancy in future years. It is not possible to assess, because of the design of the questionnaire, whether the respondents were smokers at the time of their ectopic pregnancy/pregnancies.

Education of the fertile female population about ectopic pregnancy and its aetiology will hopefully reduce the incidence and serious complications of the disease. But if women are better placed to recognise ectopic pregnancy before serious complications arise, it must be possible for them to access assessment promptly. Allowing self referral by patients to Early Pregnancy Units is one step towards achieving this.

67.4% of respondents had some knowledge of ectopic pregnancy before their own, first, experience of ectopic pregnancy (Table 3.16). However, knowledge is only one factor in early detection of ectopic pregnancy, as, in this survey, 16.4% of women did not recognise their second ectopic pregnancy.

It is not surprising that the majority of women presented first in primary care. The next biggest group presents directly to casualty. Whether appropriate action is taken depends largely on whether this doctor considers ectopic pregnancy in the differential diagnosis. This can be facilitated by ongoing education of primary care and casualty doctors about the complications of early pregnancy, but also by providing a supportive early pregnancy service, which is easily contacted for advice and appointments, and has mechanisms in place for out of hours referrals. Both of the last two Confidential Enquiries into Maternal Deaths (The Stationary Office, 1998; RCOG Press 2001) have stressed that pregnancy should be considered in any fertile woman or girl and urine pregnancy test should be readily available in Primary Care and casualty departments.

In 12.9% of the ectopic pregnancies, the woman reports herself as being collapsed at the time of presentation. This is a very frightening experience and perhaps this group is over represented in our sample, as these women are more likely to require support. However, all the women presenting with self-reported sudden collapse experienced some other symptom before the collapse occurred, which opens the possibility of intervening sooner if patients are aware of what constitutes abnormal early pregnancy.

Only 26.2% of women reported their period being late. This is surprising, but since no corresponding question was asked to whether the period occurred normally, this may be reporting bias as the respondents may have considered other symptoms much more relevant. However, this does emphasize the importance of remaining vigilant with women with suspicious symptoms, even in the absence of a late period.

12.2% of women presented with vomiting and 19.8% with bowel symptoms. Another point that is emphasised in the two most recent Confidential Enquiries into Maternal Deaths is that a diagnosis of ectopic pregnancy should be considered in women presenting with gastro-intestinal problems.

It is disappointing that so few women attended an Early Pregnancy Unit , but there are several possible reasons for this. In a reasonable number of women, the diagnosis was not considered and therefore an EPU referral would not occur. Women with severe symptoms, or women presenting out of normal working

hours would be admitted directly to the ward. It might also mean that the respondent did not identify the Early Pregnancy Service in the hospital to which they presented as a "unit".

It would have been surprising if gynaecologists did not have a better success rate in diagnosis at first presentation than other doctors, as they have a narrower range of differential diagnoses to consider. Perhaps there should be more concern about the 35.0% of ectopic pregnancies missed by gynaecologists than those missed by other doctors, as wider use of pregnancy tests, easier access to early pregnancy assessment and ongoing support and education for Primary Care and casualty services can, potentially, have a big impact on missed diagnosis of ectopic pregnancy outside of gynaecology.

It is important for General Practitioners to have easy access to early pregnancy assessment for their patients when the need arises. Perhaps women presenting to their GPs in early pregnancy could be given a card/leaflet with details of their local early pregnancy assessment service, allowing the patients to self-refer if problems arise. This serves the dual purpose of

1. giving women important information in early pregnancy to increase their awareness of potential problems
2. encouraging direct referral to an Early Pregnancy Unit if problems arise.

This system could be open to abuse, with patients self-referring inappropriately as they know that they will be seen, assessed and probably have an ultrasound scan. However, many women have concerns in early pregnancy and attend the GP and/or hospital services anyway; a simple triage service that can make a diagnosis and reassure if possible could be very beneficial by relieving other services of the need, and diagnosing the problems early when morbidity is low.

There is a degree of delay in diagnosis, both from waiting for assessment through the early pregnancy service, and through the use of serum hCG estimations and ultrasound to establish diagnosis. Some degree of delay should not be seen as a failure if the woman is under review and acute admission, directly to the gynaecology ward, is possible if the woman's symptoms deteriorate. However, there is cause for concern in the 26.1% of women reported the diagnosis was delayed for more than three weeks. The long delays reported by some women are difficult to interpret as it would be expected that a tubal ectopic pregnancy might have either presented as an emergency or resolved in that time, although these women may have had atypical presentations resulting in delay. Rapid diagnosis is easier when the symptoms are typical of the disease.

Again, it is not clear how many of the women presenting to hospital were not diagnosed as potentially having an ectopic pregnancy at their first visit because the results of serum hCGs were awaited. It is important that the woman is aware that a life-threatening condition is part of the differential diagnosis, and it is a

failure of communication if the doctor's suspicions have not been shared with the patient.

Those women who reported that their General Practitioner did not investigate them will often have been managed appropriately as they do not investigate, rather refer the patient promptly for hospital assessment. Vaginal examination in the case of suspected ectopic pregnancy is inappropriate in Primary Care as there are concerns that vaginal examination can precipitate tubal rupture and haemorrhage, and Primary Care is not equipped to deal with this promptly.

The low reported use of serum hCG estimations (Table 3.19) could be partly explained by the women not understanding why blood had been taken from them. Also, hCG estimation may not have been in use at the time of their ectopic pregnancy.

The perception of not having their management option discussed because the respondents were collapsed before going to theatre is interesting. It may be there is a high proportion of severely ill, haemodynamically compromised women in this sample because it is these women that most require support from the EPT. But it might also be a reflection of the anxiety felt at this stage compounded by a sense of urgency on the part of the doctor. Only 34 women, when asked about symptoms at presentation, reported themselves to be collapsed, but 91 women offered this as an explanation as to why management options could not be discussed with them. It can be seen that few women were offered any options

(fig. 3.19). 31.2% had no discussion of management, and only 6.2% were offered any choice of management, and that was between salpingotomy and salpingectomy. Of the total number of women responding only 18.1% of women were offered laparoscopic management and only 16.4% actually underwent laparoscopic surgery.

Ectopic pregnancies are included from several years ago when provision for laparoscopic management would have been less likely. This being said, this is a worrying small proportion of ectopic pregnancies being managed laparoscopically. A long elapse of time since the ectopic pregnancy might explain why other women could not recall what treatment they had received.

Many respondents recall being told that their ectopic pregnancy had ruptured. This would limit the number of women in whom conservative surgery would be appropriate. The long length of time between onset of symptoms and the diagnosis being made in some of the respondents, might increase the number of women with tubal rupture. An earlier diagnosis prior to rupture would lead to greater treatment options as well as reduced morbidity.

Not all the women remembered being given this advice. It maybe that some were also given appropriate advice that they subsequently forgot. If this is the case, it illustrates how important it is for women to be given advice in a form that they will retain, and written leaflets are ideal for this purpose.

Any written information that is given to women should be appropriate. The women who were given leaflets on miscarriage found this was inappropriate for their needs, and the women who were given leaflets on hysterectomy and post-pregnancy exercise found this distressing.

There is reduced subsequent fertility in women who have had an ectopic pregnancy, and prior infertility is a predictor of poor subsequent fertility (Sultana *et al.*, 1992; Ory *et al.*, 1993). As most of the ectopic pregnancies occurred in the five years before the questionnaire was completed, it could well be that many of these women have gone on to have successful pregnancies, although most pregnancies are conceived in the first 18 months following the ectopic (Bouyer *et al.*; 2000[b]). Interestingly, 32.1% of women had experienced a miscarriage in their reproductive life to date. A miscarriage would be anticipated in 25% of women at some point in their reproductive life (Regan, 1997) suggesting that the population of women with ectopic pregnancy might be more prone to reproductive failure than would be expected.

Management of the psychological sequelae is just as important as the choices for management at the time of diagnosis. The Ectopic Pregnancy Trust questionnaire gave respondents the opportunity to discuss the effect of ectopic pregnancy on their lives. The findings from this part of the questionnaire are not reported here, but several, consistent themes emerged: fear of another ectopic pregnancy - effecting sexual and interpersonal relationships, fear of never having a baby and problems relating to the realisation that ectopic pregnancy is a life-

threatening condition. As previously discussed, many women considered themselves to have collapsed at the time of presentation, although this might be cardiovascular collapse and a medical emergency, it might also be a reflection of the fear of death that many women experience at some time during their ectopic pregnancy. 13.6% of the EPT women said they were too scared to try for another pregnancy. They also feel that hospital staff failed to acknowledge that they have lost a baby

3.5 Summary

This chapter has explored the experiences of women who have had ectopic pregnancies, the diagnostic facilities and tools available, their use in the United Kingdom and our local experience of the introduction of a diagnostic aid: serum hCG estimations.

For an ectopic pregnancy to be diagnosed, it must first be recognised. The more familiar a person is with ectopic pregnancy, the more likely they are to consider it. An increased awareness of the condition, and its presentation, in the female population would enable affected women to seek help at an earlier stage, reducing mortality and morbidity, and increasing their management options.

Practitioners who are more familiar with ectopic pregnancy are more likely to consider it in a differential diagnosis. The management of the complications of early pregnancy should be component of education programmes for Primary Care and Accident and Emergency staff, for whom pregnancy is only one of

many possibilities they must consider. In-house discussion of early pregnancy cases within gynaecology units is a means of maintaining awareness amongst those doctors who most frequently encounter ectopic pregnancy. This can also be a forum for trouble-shooting in those cases providing the greatest diagnostic and management dilemmas.

Once awareness is successfully raised, women in whom a diagnosis of ectopic pregnancy is suspected require rapid confirmation of the diagnosis, consistent and accurate information, a willingness to discuss management choices and access to ongoing support when that is required. Dedicated early pregnancy units are the ideal setting for this.

Early Pregnancy Units are now widespread, though not universal, in the UK. They are a means of trying to fulfil all these needs in a single setting. These units should be accessible to the women themselves, either for advice or self-referral when appropriate, as well as to medical practitioners. In cases that are straightforward, a diagnosis and management plan can be initiated by specialist nurses following protocols. In cases that do not fit within the guidance of the protocol, help from senior doctors with an interest in early pregnancy should be sort. The protocol I developed within the unit as a result of the work in this thesis can be found in *Appendix 14*. It draws on the experiences of others, as discussed in the review of literature in Chapter 1. It is written to answer the particular needs of our unit, as discussed in this Chapter. It also discusses the options that can be offered to a woman with an ectopic pregnancy, an area covered in Chapter 9.

Ultrasound and serum hCG levels have proved to be major innovations, improving the diagnosis of ectopic pregnancy. However, diagnosis can often take several days. It is important that women in whom the diagnosis is suspected are aware of the complications that can arise within that time and have direct access to the early pregnancy assessment service or out-of-hours gynaecology service of the unit in which they are known. It is inappropriate, and could be dangerous, if further assessment and diagnosis are delayed because the women can only be seen in casualty or primary care.

Use of hCG estimations has improved the management of ectopic pregnancy by increasing its detection and differentiating it from other early pregnancy complications. It has also reduced the morbidity (and mortality) associated with negative laparoscopies performed in women with miscarriages and normal early pregnancies. However, it is not the ideal test as it does not give a diagnosis at first presentation. Single estimation progesterone levels give a same-day answer, but poorly differentiate between normal and abnormal early pregnancy. The ideal test would both rapidly diagnose ectopic pregnancy but also accurately differentiate from miscarriage and normal early pregnancy.

The following chapters describe evaluation of fetal fibronectin as a possible rapid diagnostic test differentiating ectopic pregnancy from early viable and non-viable intra-uterine pregnancies. This is then followed by an exploration of modern treatment options for ectopic pregnancy and the choices they offer to women regarding future fertility and further ectopic pregnancies.

Chapter 4 – Fetal Fibronectin – the Assay

4.1 Introduction

One of the aims of the laboratory based work was to produce a normal curve of values of fFN in early pregnancy. This would require quantification of the levels of fFN found within the cervico-vaginal secretions. Leeson *et al.* (1996) sampled fluid obtained from the posterior fornix of the vagina, Morrison *et al.* (1993) and Hellemans *et al.* (1995) sampled the endo-cervix. Lockwood *et al.* (1991) sampled both and found there were more positive cervical than vaginal samples. I wished, in the first instance, to establish whether fFN was found in at both sites in early pregnancy, in the same subject, before embarking upon collection of samples for the quantitative assay.

In clinical practice where the aim is to establish the risk of premature labour, the amount of fFN is of little relevance, a result is considered positive if levels are greater than 0.05μg/ml. Women with uncomplicated pregnancies rarely had fFN above this level in the late second and early third trimesters (Lockwood *et al.*, 1991). Therefore, a clinically useful test would only show a positive result if levels greater than 0.05μg/ml were present. A bedside test fulfilling this requirement is available (Adeza Biomedical, USA; Mast Diagnostics, UK). For this project I had access to diagnostic kits used in the development of this product and these were used to develop the sampling technique.

A commercially available ELISA kit was used for the quantification of levels (Adeza Biomedical, USA; Mast Diagnostics, UK). This ELISA assay contains monoclonal antibody FDC-6 sensitive to the oncofetal fibronectin not found in normal maternal tissues. This antibody is said to be highly specific to the fetal form of fibronectin.

4.2 The Qualitative Assay

A self-contained kit was supplied by Adeza Biomedical. This contained a sterile Dacron swab, a resealable tube containing extraction buffer and a single dipstick on which is mounted the fFN immunoassay.

A sterile speculum was inserted to allow visualisation of the uterine cervix within the vault of the vagina. This allowed access to the cervix or posterior vaginal fornix. A swab was gently inserted either into the endocervical canal or into the posterior fornix and gently rolled for 10 seconds. The swab was then withdrawn and immediately inserted into the tube containing the extraction buffer. The swab was then mixed vigorously for 10 seconds to allow the absorbed secretions to mix with the buffer. The swab was then removed and disposed of. The fFN immunoassay dipstick was then inserted into the buffer/secretions mix for 10 minutes before removing it to read the result.

A positive result is denoted by a double pink line and a negative result by a single pink line.

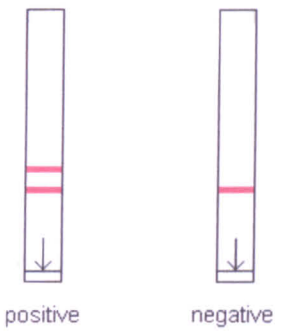


fig. 4.1 illustration of positive and negative results for qualitative assays

Samples were taken from both the endocervix and the posterior fornix for a direct comparison in each woman sampled.

4.3 The Quantitative Assay

Swabs were taken in a similar way to those taken for the qualitative assay. However, in this case the swab was inserted into a transport tube containing the buffer and the shaft snapped. The shaft of the swab was inserted in the cap of the transport tube, which was then sealed for processing later.

At the end of each collection session, the samples were processed in batches. The transport tubes were then gently vortexed for 30 seconds in a Gallenkamp mixer. Each swab was removed from its transport tube; the tip of the swab was squeezed against the transport tube to extract as much fluid as possible.

The collection kits were supplied with there own filter systems – each sample having an individual filter, which fitted tightly into the transport tube, forcing the buffer/secretions mix through the filter membrane as the filter was pushed to the

bottom of the transport tube. The filtrate was then decanted into a microcentrifuge tube and stored in a -80°C freezer until use.

When an assay was to be performed, the samples were defrosted in a 37°C water bath for ten minutes before use. The calibrators to be used in the assay were warmed, simultaneously, in the same way.

Wash buffer (buffer salts, detergent and preservative – sodium azide) was prepared for use during the assay, 20mls of concentrated wash buffer solution was diluted with ELGA water to make a 2l dilute solution of wash buffer.

The ELISA assay wells were supplied in a resealable, airtight pack. At the start of the assay process the appropriate number of wells would be removed from the pack. The pack would then be resealed to store the remaining wells for future use.

The calibrators were next removed from the water bath and gently mixed.

Calibrator A contained fFN at a concentration of 1.0μg/ml

Calibrator B contained fFN at a concentration of 0.5μg/ml

Calibrator C contained fFN at a concentration of 0.1μg/ml

Calibrator D contained fFN at a concentration of 0.05μg/ml

Calibrator E contained fFN at a concentration of 0.0μg/ml

100µl of each calibrator was pipetted into the wells, each calibrator being represented in duplicate. 100µl of each patient sample to be tested was, likewise, pipetted into the wells. The plate was then covered and incubated at room temperature for one hour. A thermometer ensured that the room temperature remained between 20 and 25°C, as recommended in the directional insert accompanying the kits.

The wells were next aspirated and washed three times using the diluted wash buffer solution.

100µl of antibody conjugate (affinity-purified goat polyclonal antibody to human fFN conjugated to alkaline phosphatase in a buffer matrix with sodium azide as a preservative) was pipetted into each well. Again the wells were covered and incubated for 30 minutes at room temperature.

The wells were again aspirated and washed three times with the diluted wash buffer solution.

Each well requires 100µl of substrate (phenolphthalein monophosphate substrate in buffer with sodium azide as preservative). Once removed from its container, surplus substrate cannot be replaced. Therefore, the amount required was calculated in advance and just sufficient for requirements on that occasion removed.

The wells were then covered and left to incubate for a further 30 minutes at room temperature. A colour change proportional to the amount of fFN develops over this time. Wells with no fFN appear clear, the well containing calibrator E is

used to assess the background colour change and any well in which the absorbency is less than, or equal to, this calibrator is considered to contain no fFN. A pink hue, of deepening intensity according to the amount of fFN present, develops in the other wells.

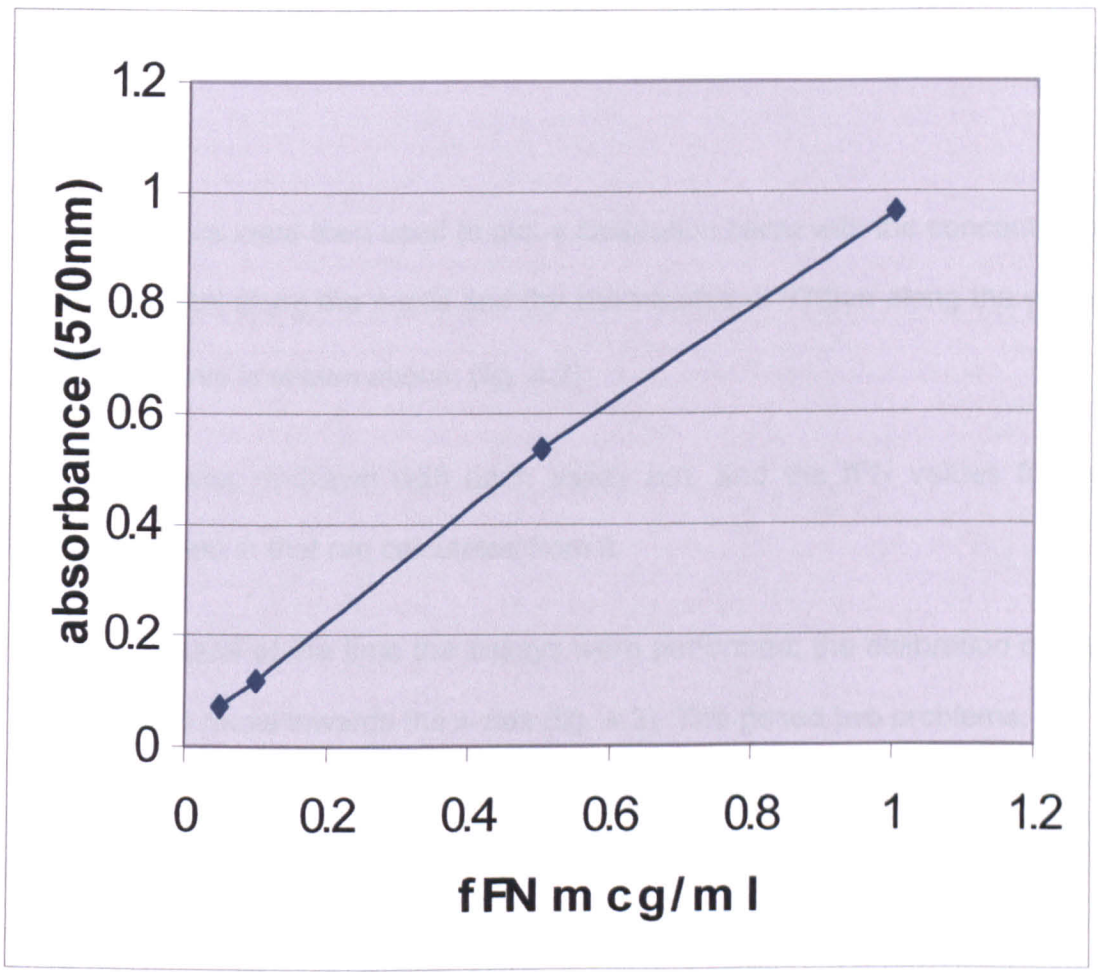


fig. 4.2 example of fFN calibration curve obtained from assay

The aspiration and washing stage is omitted on this occasion. 50μl of stopping solution (buffer containing a chelating agent) was added to each well. The plate was gently mixed to ensure even distribution of the colour in each well. The absorbance at 570nm was then read using a microtitre plate reader.

As calibrator E contained no fFN the value obtained from the wells containing it represents background levels and reflects the microtitre plate reader's sensitivity. The value obtained from calibrator E must be subtracted from all the other values obtained.

As each of the calibrators were measured in duplicate, the adjusted values of the two readings for each were added and divided by two to give the average result.

The calibrators were then used to plot a calibration curve with the concentration of fFN in μg/ml along the x-axis and the absorbance at 570nm along the y-axis. A sample curve is shown above. (fig. 4.2)

The curve was re-drawn with each assay run, and the fFN values for the samples tested in that run calculated from it.

Over the course of the time the assays were performed, the calibration curves were seen to move towards the x-axis (fig. 4.3). This posed two problems:

how reproducible were the results

why was the curve changing

Samples were retested on subsequent occasions to look for internal consistency. These are displayed in *Appendix 3.*

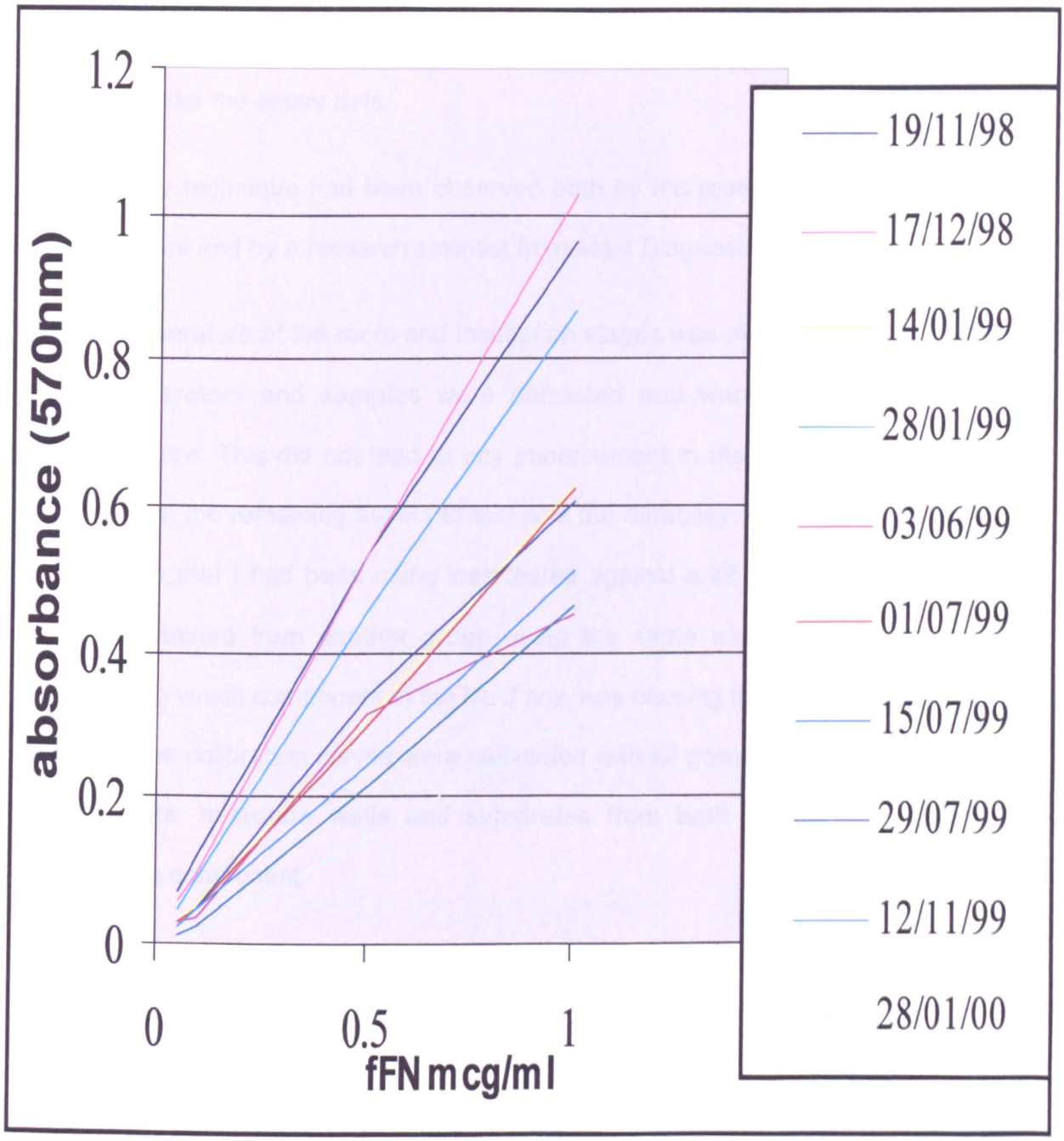


fig. 4.3 demonstration of change in calibration curve with time

The reasons for this were discussed within the department and with Mast Diagnostics.

The assay was well within the expiry date, and the information from Mast Diagnostics reputed the assay to be very robust, not degrading for many months after the expiry date.

My assay technique had been observed both by the research scientist in the department and by a research scientist from Mast Diagnostics.

The temperature of the room and incubation stages was monitored throughout. The calibrators and samples were defrosted and warmed to the correct temperature. This did not lead to any improvement in the angle of the curve. Therefore, the remaining aspect to test was the durability of the kits. A kit from the batch that I had been using was tested against a kit from a more recent batch obtained from another group using the same assay as a means of identifying which component of the kit, if any, was causing the problems with the curve. The calibration curves were calculated with all possible combinations of calibrators, microtitre wells and substrates from both kits to identify the unreliable component.

The results are demonstrated in figure 4.4. The "old" kit is represented by A, the "new" kit by B. The sequence of letters represents the calibrators, the substrate and the microtitre wells respectively as demonstrated in Table 4.1

As can be seen from the graph, the greater the proportion of components used from kit A, the older of the two kits, the nearer to the x-axis the curves went.

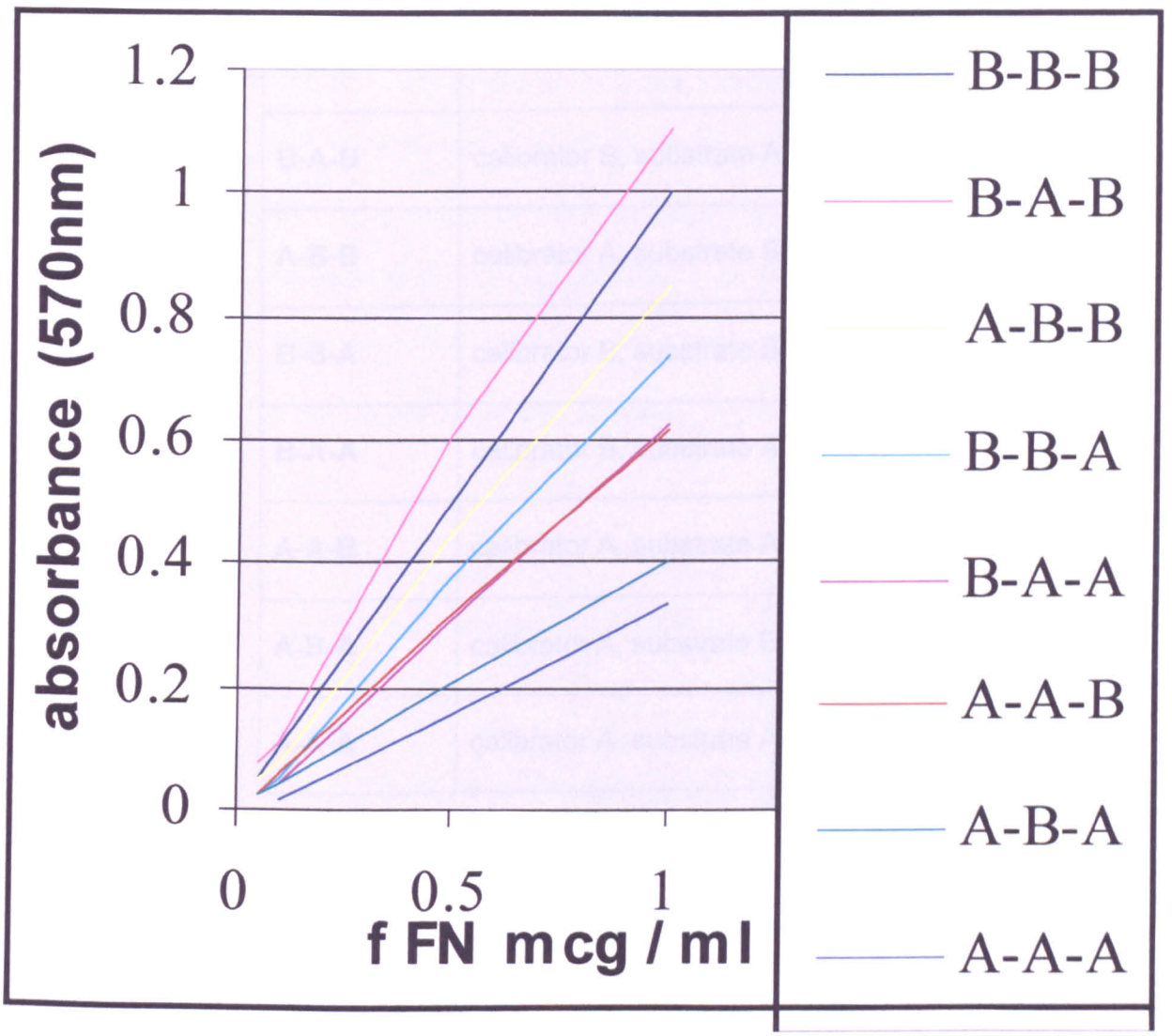


fig. 4.4 Chart displaying the curves obtained when different combinations of the two ELISA kits were used

In addition, when all the components came from kit A, there was no difference between calibrator D, containing 0.05μg/ml fFN and calibrator E which contained no fFN.

	Kit components
B-B-B	calibrator B, substrate B, microtitre wells B
B-A-B	calibrator B, substrate A, microtitre wells B
A-B-B	calibrator A, substrate B, microtitre wells B
B-B-A	calibrator B, substrate B, microtitre wells A
B-A-A	calibrator B, substrate A, microtitre wells A
A-A-B	calibrator A, substrate A, microtitre wells B
A-B-A	calibrator A, substrate B, microtitre wells A
A-A-A	calibrator A, substrate A, microtitre wells A

Table 4.1 explaining the key for fig. 4.4

The conclusion from this was that, even within the stated shelf-life of the assay all components of the assay were degrading.

This still left the task of validating the measured levels of fFN I had previously obtained – was the assay reliable despite the observed changes with time? Through the process of remeasuring the levels of fFN in samples previously tested, it was possible to establish that the levels obtained were consistent.

Mast Diagnostics' advice for use of the assay, was that samples need only be tested singularly. Once there appeared to be a problem with the assay, samples were tested in duplicate. The absorbance for these samples is shown in

Appendix 4. The results are represented in fig. 4.5 below. This shows a good correlation between the values obtained.

Part of the work in the following chapters looked at fFN in plasma. Some of these samples were tested in duplicate, these results are found in *Appendix 5* and a similar chart displaying these results is shown in fig. 4.6. These results are displayed separately to those obtained from the endocervical swabs as it is unclear exactly what the assay is detecting in plasma, and therefore how reproducible any result might be. However, again, a reasonable correlation is obtained.

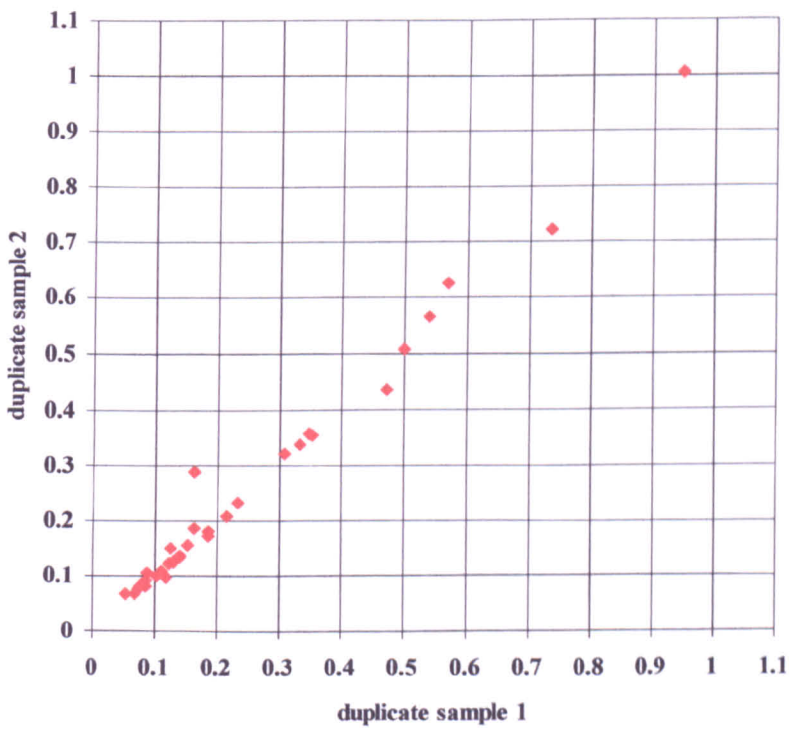


Figure 4.5 Scatter-chart showing the values for samples tested in duplicate

Correlation co-efficient = 0.99

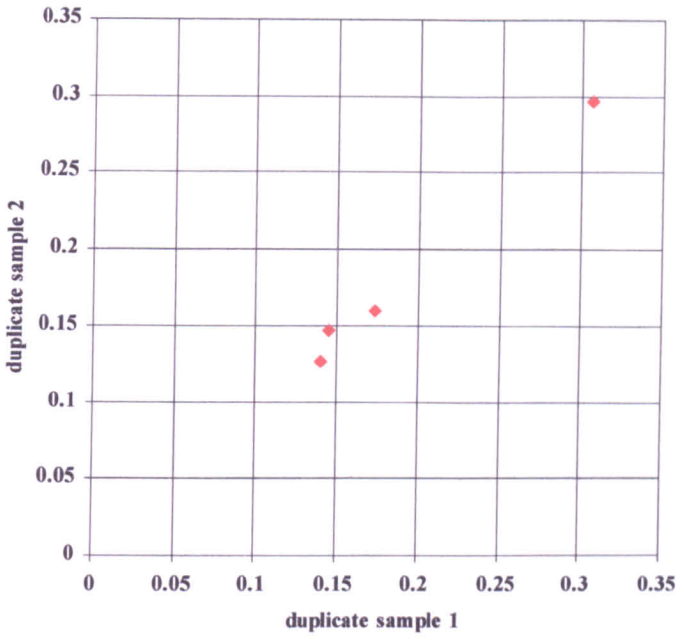


Figure 4.6 Plasma samples tested in duplicate at a single assay run

Correlation coefficient = 0.99

Once it was noted that the curve was changing with time, samples were retested on subsequent occasions. The change in the angle of the curve could mean that the results were unreliable, or alternatively, similar values for the level of fFN are obtained regardless. *Appendix 3* shows the results obtained from samples that were tested on more than one occasion to assess consistency of the assay despite the changes in the curve with time. Of particular note, all those samples tested on 3/6/99 with measurable levels of fFN, when the shape of the calculation curve was abnormal, were retested with the next run of the assay. A scatter-chart demonstrating samples tested on two occasions is shown in figure 4.7. The first two results (with the exception of those from 3/6/99) are shown.

Although the correlation is not as close as that obtained in figures 4.5 and 4.6 there is still a reasonable correlation demonstrated and the levels of fFN obtained can be said to be representative of the levels of fFN in the samples, despite the changes in the curve with time.

In the chapters that follow, the first result obtained is used as the value for fFN except as explained above for those samples obtained on 28/1/00 when the curve was so close to the x-axis, that the retested results were considered more reliable.

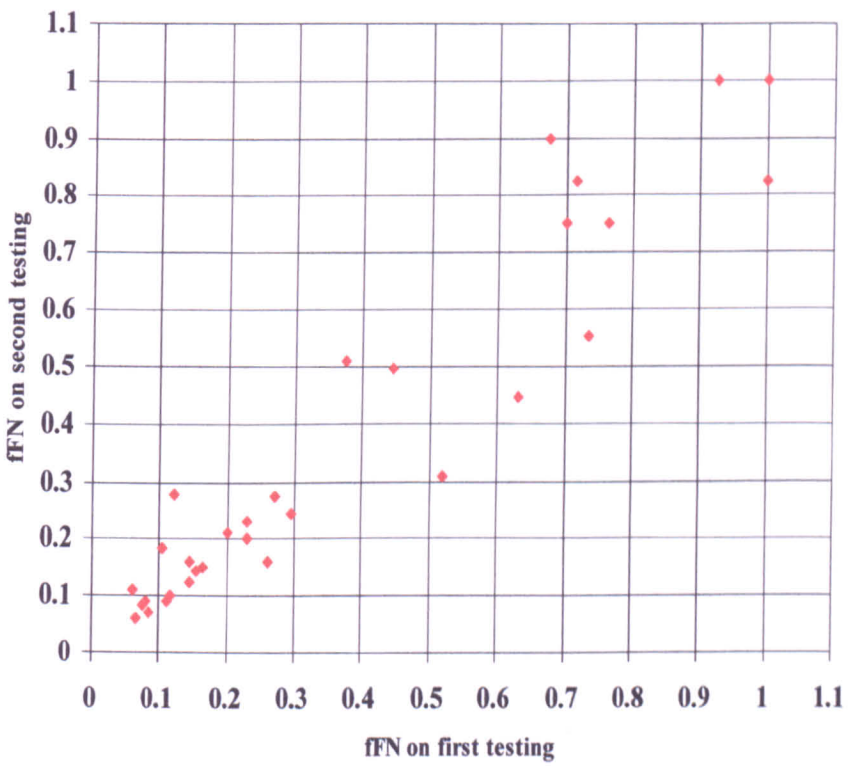


Figure 4.7 Scatter-chart showing samples tested on more than one occasion

Correlation coefficient = 0.96

Chapter 5 - Fetal Fibronectin in Normal Early Pregnancy

5.1 Introduction

In order to assess the normal range for fetal Fibronectin in cervical fluid in early pregnancy, samples were taken from women requesting termination of pregnancy. All referrals for termination of pregnancy to St. James's University Hospital are made through the Fertility Control Unit (FCU). Each woman is scanned to confirm viability and gestation before being councelled for termination. Although long term viability of these pregnancies can only be assumed, the majority would have survived as only 3% of pregnancies will miscarry if a viable fetus has been demonstrated ultrasonographically at 8 weeks from last menstrual period (Kline *et al.*, 1989).

Mast Diagnostics had provided us with their unpublished data on levels of fFN throughout pregnancy. Their results implied that fetal fibronectin was found in measurable amounts throughout first trimester. Their data did not, however, give any indication of range, or indeed if fFN was present in the cervix of every subject. It was difficult to establish how many women had been sampled at any given timepoint. The basis of their work had been done in establishing the role of fFN in premature labour. The theory being that fFN was to be found in the cervico-vaginal secretions until the decidua capsularis fused with the decidua parietalis prior to 20 weeks gestation.

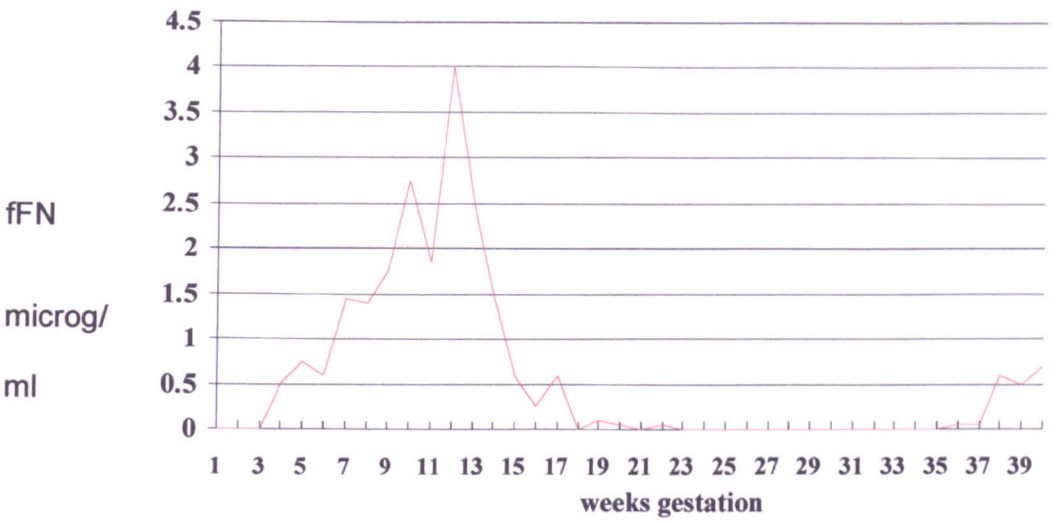


Fig. 5.1 values of fFN in normal pregnancy as defined by Mast Diagnostics

If fFN were to be found in the later half of pregnancy, this would indicate disruption of the pregnancy and predict premature labour. Therefore we felt that if fFN is measured in the endo-cervical secretions of normal early pregnancy, abnormal amounts may indicate abnormal early pregnancy. Ectopic pregnancy is located outside the uterus and its greater distance from the cervix might mean smaller quantities of fFN would be found in the cervico-vaginal secretions. In miscarriage, it might be that poor trophoblast formation and implantation would lead to smaller measurable quantities of fFN, or perhaps the disruption of the early fetal membranes might lead to higher measurable levels.

I had, therefore, first to establish my own normal curve for normal levels of fFN in early pregnancy.

5.2 The Qualitative assay

5.2.1 Aims

- A means of establishing the technique of obtaining samples within the setting of the FCU.
- Whether positive and negative swabs were of value, the qualitative swabs becoming positive at a cut-off value. The value of the cut-off value was not clear from the manufacturers; previous work has tended to use 0.05μg/ml fFN as the cut-off for positivity.
- To establish whether the endocervix or the posterior fornix had better pick-up of fFN.
- To establish if fFN was picked up at one site, whether it would then be consistently found at the other.

5.2.2 Method

Prior to quantifying the levels of fFN in first trimester, the qualitative assay was used to establish whether fFN could be detected and whether the endocervix or posterior fornix was the best site.

Each subject had a speculum examination performed prior to transvaginal ultrasound scan. A swab was taken from both the endo cervix and posterior fornix in each woman simultaneously. The swab was gently rolled within the endocervix and the posterior fornix of the vagina for 10 seconds. The assay was performed in the clinic and read after ten minutes as described in the

previous chapter. 21 women of varying gestations in first trimester had swabs taken.

5.2.3 Results

The results are shown below (Table 5.1 and figure 5.2). In all 8 (38%) were negative at both sites, less than half (10/21) positive at the cervix and only 6 postive at both sites.

Table 5.1 chart showing the positive and negative swabs in first trimester subjects (all gestations). Analysed using Fisher's Exact Test:

		high vaginal swab	
		+ve	**-ve**
cervical swab	**+ve**	6	4
	-ve	3	8

Positive Predictive Value (PPV) = 0.600

Negative Predictive Value (NPV) = 0.727

PPV = probability of the HVS being positive if the cervical swab positive

NPV = probability of the HVS being negative if the cervical swab is negative

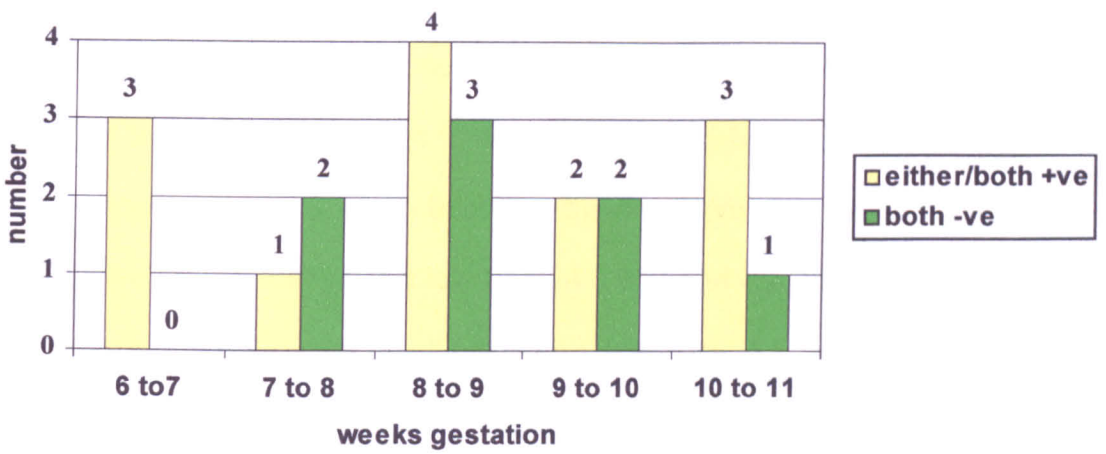


Fig 5.2 Chart showing any positive result against no positive result for each week of gestation

Odds Ratio that either/both samples are positive against neither sample being positive (OR) = 4.00 (CI 0.639 to 25.021)

5.2.4 Discussion.

1. Not all the swabs were positive for fFN, 8 (38%) were negative both at the endocervix and the posterior fornix. This differs from the results obtained from Mast Diagnostics which imply that positive results would be obtained in first trimester.
2. Neither the endocervix nor the posterior fornix gave consistently more positive results, 9 (43%) had positive high vaginal swabs, 10 (48%) had positive endocervical swabs. In only 6 (29%) both swabs were found to be

positive. However, because the cut-off point was not clear, it might well be that low levels of fFN were present that were beneath the cut-off of the test.

3. Because so many swabs were negative, it seemed less likely that the same high mean values for first trimester fFN would be obtained as have been demonstrated in the graph based on the data from Mast Diagnostics.
4. Fisher's exact test gave a low PPV of 0.600 and low NPV of 0.727, the OR crossing unity, when positive high vaginal swabs were compared with positive endocervical swabs. Based on the results obtained from the qualitative swab, there did not appear to be an optimum site for sampling.
5. The proportion of positive swabs was greater at earlier gestations, which again, was contrary to Mast's experiences. However, the small number of subjects sampled makes it difficult to know the significance of this.

As these results did not correspond with those obtained from Mast, and there was so little information on exactly what the qualitative test represented, it seemed advisable to test using the quantitative assay from then on.

5.3 The Quantitative Assay

5.3.1 Introduction

The decision was made to sample the secretions from the endocervix. The earliest work on fFN had used the endocervix as the sampling site, and Lockwood *et al* (1991) had found more positive results in the endo-cervical than the high vaginal samples. The amount of physiological discharge may have a dilutional effect on the fFN concentration, whether this is greater in the posterior

fornix where secretions will tend to pool, or in the endocervix where the secretions are produced, is not clear.

The disadvantage of using the endocervix was that it is more likely to produce contact bleeding. As the assay is said to be specific to fetal fibronectin and not to cross react with other fibronectins – particularly those in the blood, this was not thought to be important at this stage. If blood contamination were to be a problem, it would limit the assay's usefulness as a test at any stage of pregnancy, as small or large blood loss is likely to accompany both early and late pregnancy complications. If blood contamination is present is likely to be in both the endocervix and posterior fornix, even if it is not visible macroscopically. If blood was macroscopically obvious in the samples this was recorded so any effect of blood on fFN levels could be explored in the light of the results obtained.

5.3.2 Method.

Samples were obtained from the endo-cervices of consenting subjects attending the Fertility Control Clinic. Each woman requesting termination of pregnancy has a transvaginal ultrasound scan performed to accurately establish the gestation of the pregnancy. Samples were taken prior to ultrasound scan, as transvaginal scanning was considered to be likely to disrupt the cervix and might not give a true picture of what the levels of fFN were. Therefore, at the time of sampling, the gestation of the pregnancy was not known. Samples were taken by gently rolling the swab in the endocervix for 10

seconds. Ninety-two women were sampled. The gestations of the pregnancies at the time of sampling are shown in fig. 5.3.

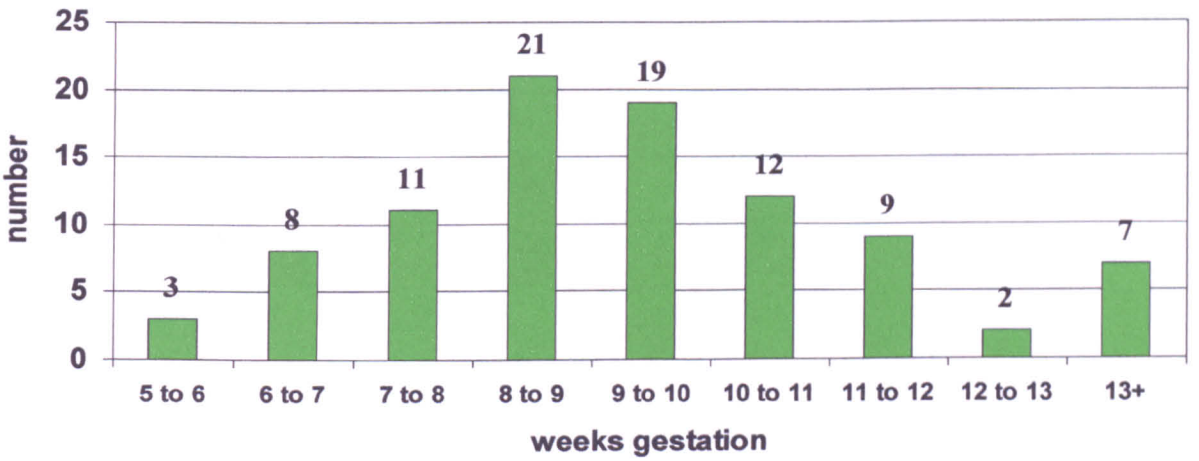


Fig. 5.3 Gestation at time of sampling of women with "normal" early pregnancy attending the FCU.

5.3.3 Results

The full table of assay results is found in *appendix 6.* It had been anticipated that it would be possible to translate these results into a similar curve to that shown in fig.5.1 however, 57 of the 92 results (62%) fell into the group where fFN was found, but in such small amounts that the levels could not be determined (i.e. <0.05 μg/ml). In 17 out of 92 (18%) no fFN was detected. In only 18 of the 92 (20%) was fFN found in sufficient quantities to be measured accurately. Because of the number of results in which a level for fFN was not obtained it was not possible to produce a mean value.

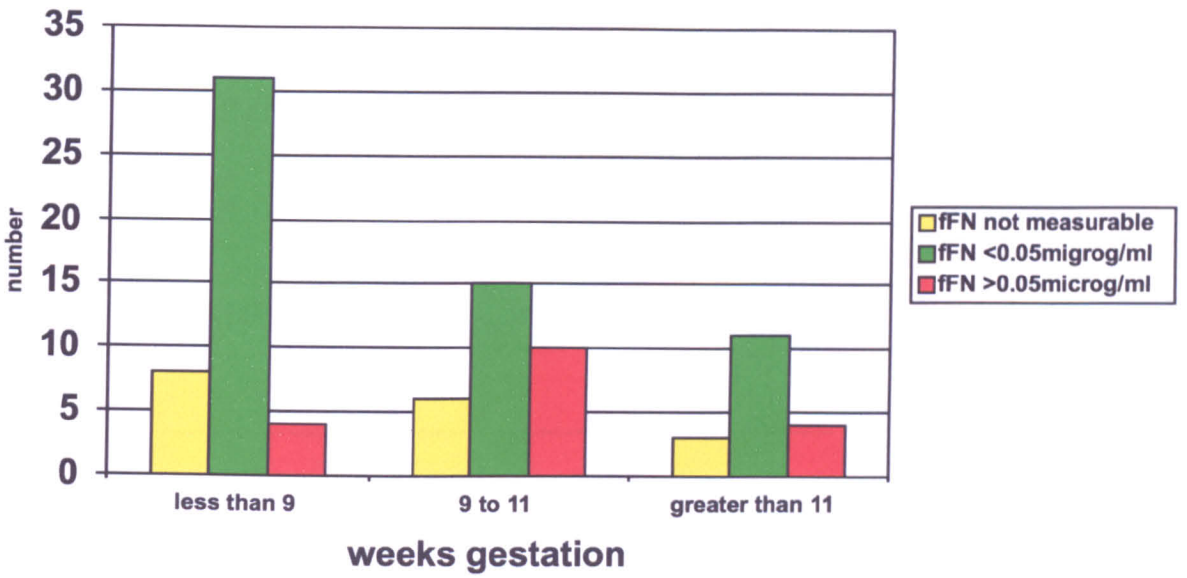


fig 5.4 Levels of fFN found in samples taken from subjects attending the FCU in first trimester

case		control		X^2
4	*8.1351*	10	*5.8649*	**5.0175**
31	*26.7297*	15	*19.2703*	**1.6285**
8	*8.1351*	6	*5.8649*	**0.0054**
totals	43		31	6.6513
		2 d.f.		P<0.05

fig 5.5 X^2 test comparing results obtained in pregnancies of less than 9 weeks gestation with those of between 9 and 11 weeks. This reaches significance.

case		control		X^2
10	*8.8571*	4	*5.1429*	**0.4014**
15	*16.4490*	11	*9.5510*	**0.3475**
6	*5.6939*	3	*3.3061*	**0.0448**
totals	31		18	0.7937
		2 d.f.		not significant

fig 5.6 X^2 test comparing results obtained in pregnancies of between 9 and 11 weeks with those of > 11 weeks. This does not reach significance.

case		control		X^2
8	*5.4286*	6	*8.5714*	**1.9895**
9	*10.0816*	17	*15.9184*	**0.1895**
2	*3.4898*	7	*5.5102*	**1.0388**
totals	19		30	3.2178
		2 d.f.		not significant

fig 5.7 X^2 test comparing results obtained in pregnancies of between 9 and 10 weeks with those of > 10 weeks. This does not reach significance.

For the purposes of comparison, if a value of 0.05μg/ml is assigned to those samples in which fFN is present, but at concentrations too small to be measured by the assay, the following curve is obtained for the **mean** value of fFN during first trimester fig 5.7.

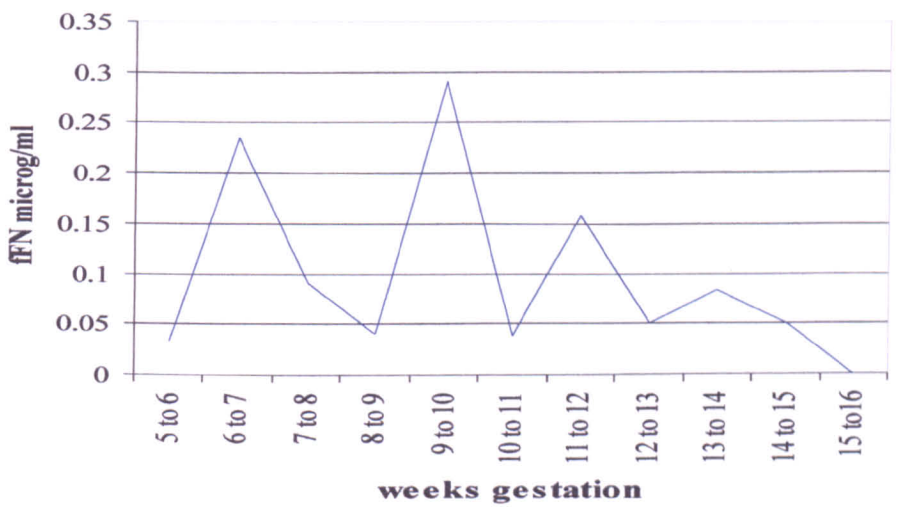


Fig 5.7 Showing mean values of fFN in samples taken in first trimester from women attending the FCU

5.3.4 Discussion

1. The information received from Mast Diagnostics, I had anticipated that much higher levels of fFN would be found, and I was surprised at how few had measurable quantities. 80% of the samples had little or no fFN present. This was in keeping with the findings using the qualitative assay when 71% were negative at one or both sites of sampling.
2. If arbitrary values are attributed to those samples in which fFN is present, but the levels are too small to quantify, a curve for fFN in first trimester can be produced. However, when this curve is compared to that obtained by

Mast Diagnostics, the levels obtained are only 10% of those obtained by Mast. The levels of fFN obtained during my analysis are of a similar order to those obtained in first trimester by Ness *et al.* (1998) and Nowacek *et al.* (1999). In the paper by Nowacek *et al.,* the same assay system was used; their confidence interval for fFN ranged to less than the 0.05μg lower limit of the assay, it would therefore seem likely that they attributed values in a similar way to figure 5.7.

3. The biggest group is that in which small, but not measurable amounts of fFN are found. In this, first trimester would not appear to be much different to later pregnancy.
4. When the different gestational bandings are compared, fFN in the 9 to 11 week banding is statistically higher to the <9 week banding, $p < 0.05$. The broad bandings of fFN in first trimester, figure 5.4, and the curve representing levels throughout first trimester, figure 5.7 support a rise in the level of fFN around 10 weeks gestation. In the curve obtained from Mast Diagnostics, the levels of fFN are at their greatest between 9 weeks and 13 weeks. After 10 weeks, the differences do not reach significance, but the trend in fFN levels is downwards.
5. In 20% of pregnancies, measurable levels of fFN were found. The significance of this is unclear, even supposing that it is a reflection of future pregnancy problems, given that the pregnancies were confirmed as viable at the time of sampling, only 3% (which is less than three pregnancies in this group) would have been expected to miscarry after sampling.

However variable the normal level of fFN in first trimester might be, it still remains a potentially useful diagnostic test in the complications of first trimester, if the levels obtained in abnormal early pregnancy are measurably different.

Chapter 6 – Fetal Fibronectin in Recurrent Miscarriage

6.1 Introduction

Sporadic miscarriage is a common problem, if all conceptions are considered, more than half will miscarry, and, of the pregnancies that are clinically recognised, up to 20% will miscarry. Sporadic miscarriage usually occurs because the pregnancy is either structurally or karyotypically abnormal. These pregnancies could never have progressed to a normal outcome. Overall, 25% of women will have a sporadic miscarriage during their reproductive life.

However, some conceptions will miscarry because of a recurring problem in early pregnancy, not because of fetal abnormality. There are well recognised causes for recurrent early pregnancy loss, for example, antiphospholipid syndrome (APS). With treatment, this might be overcome and the normal conceptus survives. In about half of these women with recurring early pregnancy loss, a cause can be identified. In the other cases the lack of an explanation does not exclude an underlying cause, and, indeed, a proportion of these women will go on to have repeated, further early pregnancy losses. It is likely there are other, as yet undetermined, causes for the loss of karyotypically and structurally normal pregnancies.

St James's University Hospital has an Early Pregnancy Unit (EPU) that gives access to support for women with early pregnancy complications.

- The Early Pregnancy Assessment Service (EPAS) provides a diagnostic and support service to women with early pregnancy bleeding, pain etc, with direct access for patients as well as referral from GPs, midwives and casualty.
- The Recurrent Miscarriage Clinic (RMC) provides investigation, treatment and early pregnancy support to women who have had two or more early pregnancy losses. Patients of the RMC contact the unit as soon as they have a positive pregnancy test. This means they are usually seen for the first time between 4 to 5 weeks after their last menstrual period (lmp). At this visit, pregnancy will be confirmed, the APS screen is repeated and swabs are taken to look for bacterial vaginosis (BV) and chlamydia. Patients of the RMC are, therefore, seen early in pregnancy and the practice of screening for BV provides an opportunity to take swabs for quantification of fFN up to two weeks before viability of the pregnancy can be established by ultrasound scan. Approximately 100 pregnancies in women with a history of recurrent miscarriage are supported through the RMC each year.

I set out to see whether fFN might be used to predict which pregnancies would be ongoing before viability could be confirmed by ultrasound scan – abnormal levels of fFN might predict early pregnancy loss independent of the reason for the pregnancy loss. In pregnancies destined to miscarry, fFN might be reduced if the trophoblast were not adequately established, or, alternatively the disruption of the trophoblast accompanying miscarriage might lead to increased levels of fFN at the endo-cervix. In this context, fFN was to be assessed as a

predictor of successful pregnancy, rather than as a means of investigating the aetiology of recurrent miscarriage.

During the time of the study, consenting women would have a swab taken to quantify the levels of fFN at the endocervix. These swabs would be taken before the first ultrasound scan was performed, ie before either the gestation or viability status had been determined.

6.2 Quantification of Levels of fFN Found in Pregnant Women attending the Recurrent Miscarriage Clinic

6.2.1 Method

Women under the care of the miscarriage clinic are asked to contact the unit when they have a positive pregnancy test. At this point a repeat APS screen and screen BV and chlamydia can be performed allowing the fFN swab to be taken at the same time. All swabs were taken before the first ultrasound scan assessment for viability of the pregnancy, regardless of suspected gestation.

The standard pattern of care for women under the care of the miscarriage clinic means that the pregnancies are followed on a weekly basis until the end of first trimester, the number of these pregnancies with first trimester complications is therefore known with a great degree of accuracy.

Women were recruited when they first reported a positive pregnancy test. The project was discussed with them and their consent for participation obtained. The sample was taken by gently rolling the swab within the endocervix for 10 seconds with the fFN sample collection kit. The fFN swab would be taken before the endocervical swab for chlamydia. The level of fFN was quantified, as described in chapter 4.

6.2.2 Results

Endocervical swabs were taken from 65 women attending the RMC. The gestation at sampling (by subsequent ultrasound scan) and the outcome at the end of first trimester were recorded. Four outcomes were considered:

ongoing pregnancy at end of first trimester

first trimester miscarriage – fetal heart pulsation never seen

first trimester miscarriage after fetal heart pulsation seen

ectopic pregnancy.

This is summarised in Table 6.1:

Table 6.1 Numbers of samples obtained in first trimester against outcome

gestation at sampling	ongoing	miscarriage – FH never seen	miscarriage after FH seen	ectopic
< 4 weeks		1		
4 – 5 weeks	11	3	2	
5 – 6 weeks	16	7	2	
6 – 7 weeks	9	1	2	2
7 + weeks	8		1	
total	*44 (67.7%)*	*12 (18.5%)*	*7 (10.8%)*	*2 (3.1%)*

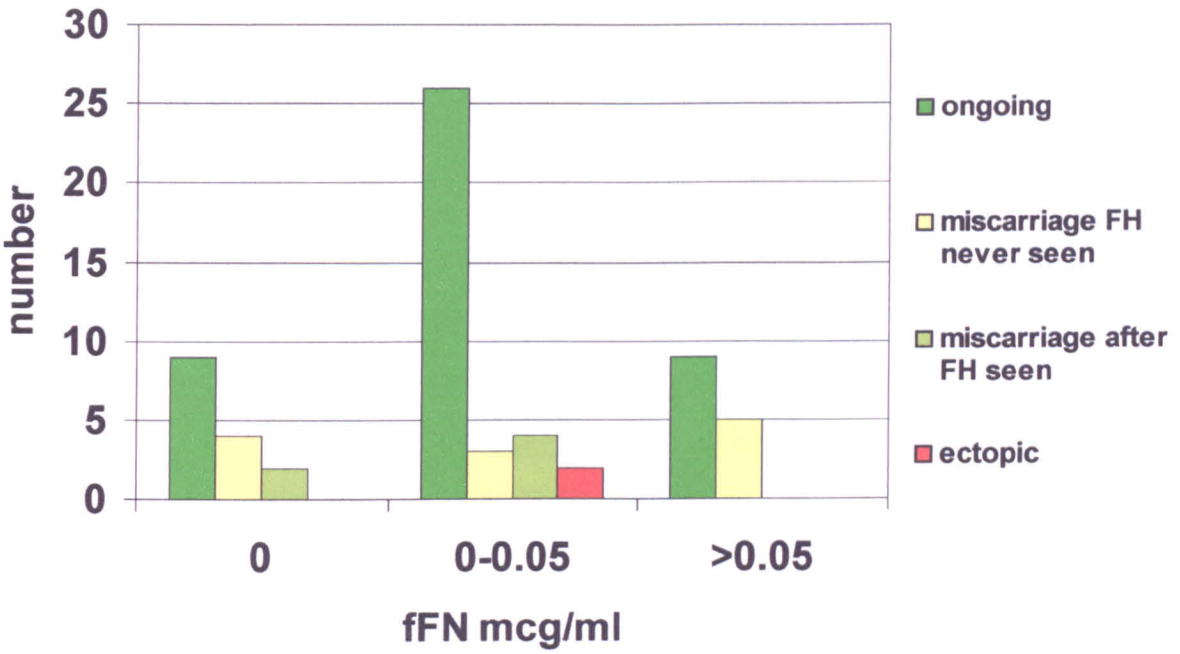


Fig 6.1 Levels of fFN obtained for different pregnancy outcomes

Figure 6.1 demonstrates the band into which the levels of fFN fell for different pregnancy outcomes. The levels are not displayed according to gestation as the numbers are small and a significant increase in fFN was not found before 9 weeks of gestation in normal early pregnancy. None of these samples were taken after 9 weeks gestation. *Appendix 7* gives the actual value and gestation of sampling for each specimen. The two ectopic pregnancies are not considered in the subsequent analysis in this chapter, firstly, because there were only two, and secondly, because ectopic pregnancy is considered in its own right in the next chapter.

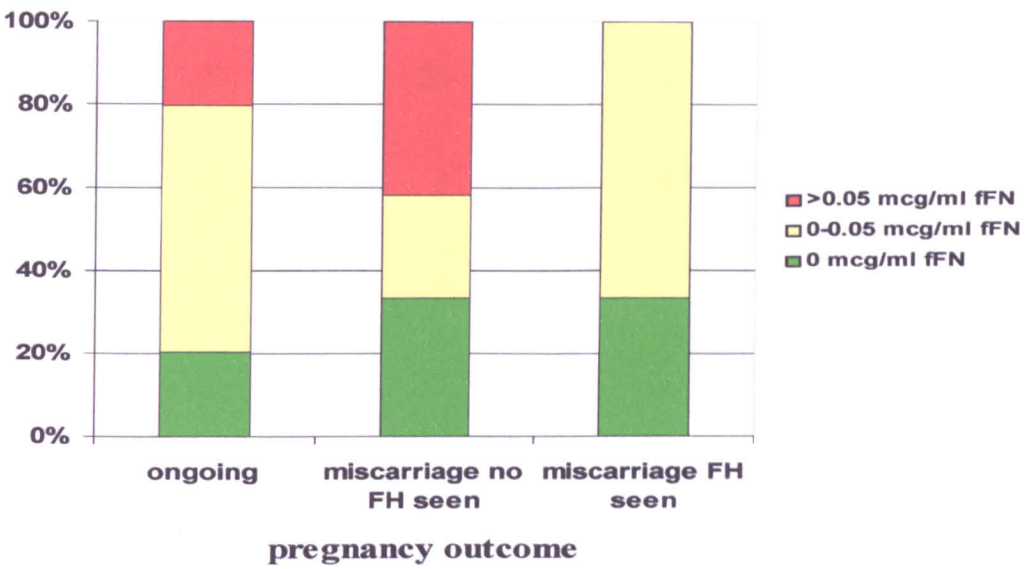


Fig 6.2 The percentage of samples that had measurable, recordable but not measurable and non recordable levels of fFN according to outcome.

Figure 6.2 illustrates the proportion of samples from women with each pregnancy outcome that had

1. measurable levels of fFN (ie >0.05μg/ml)
2. fFN found, but outside the measurable range (ie <0.05μg/ml)
3. fFN not detected

There is no significant difference in the levels of fFN for different outcomes of pregnancy.

fFN level	0	0.05 µg/ml	>0.05 µg/ml	total
ongoing	9	26	9	44
misc. – no FH	4	3	5	12
misc. – FH seen	2	4		6
total	15	33	14	62

X^2 = 6.539 4 d.f. p=0.162, not significant

Fig 6.3 X^2 test comparing all pregnancy outcomes with all bands of fFN result

fFN level	0 to 0.05 µg/ml	>0.05 µg/ml	total
ongoing	35	9	44
misc. – no FH	7	5	12
misc. – FH seen	6		6
total	48	14	62

X^2 = 4.364 2 d.f. p=0.113, not significant

Fig 6.4 X^2 test comparing all pregnancy outcomes with fFN <0.05µg/ml and >0.05µg/ml

fFN level	0 to 0.05 mcg/ml	>0.05 mcg/ml	total
ongoing/FH seen	41	9	50
FH never seen	7	5	12
total	48	14	62

$X^2 = 3.101$ 1 d.f. p<0.1, significant

Fig 6.5 X^2 test comparing pregnancies in which a FH was seen at some point in 1st trimesters and pregnancies in which a FH was never seen against measurable and non-measurable levels of fFN

fFN level	0 to 0.05 mcg/ml	>0.05 mcg/ml	total
ongoing	35	9	44
miscarriage	13	5	18
total	48	14	62

$X^2 = 0.392$ 1 d.f. p=0.531, not significant

Fig 6.6 X^2 test comparing viable pregnancies and non-viable pregnancies against measurable and non-measurable levels of fFN

6.2.3 Discussion

There is no significant difference between levels of fFN found in the endocervix of women in whom the pregnancy was found to continue and those in whom the pregnancy failed although there was an increase in the level of fFN if no FH was seen. However, fFN cannot be used to predict the outcome of pregnancy before viability is confirmed. The number of patients in the miscarriage group is small compared to those in the ongoing pregnancy group, but this is as would be expected, viable pregnancy being the outcome in the majority of patients, even in a recurrent miscarriage population.

This is a big disappointment. The only possible trend – higher levels of fFN in pregnancies in which a fetal pole never becomes established was not expected if fFN production is greater in well established pregnancies, but is of no clinical value as even in this situation, 9/14 pregnancies continued to term.

Chapter 7 – Fetal Fibronectin in Ectopic Pregnancy

7.1 Introduction

When a woman presents with a complication of early pregnancy her distress is likely to be compounded if diagnosis is delayed. Unfortunately, delay is usually a feature of the diagnosis of ectopic pregnancy. When an ultrasound scan shows an empty uterus, this might represent a normal early pregnancy, an ectopic pregnancy or a miscarriage. These women have to wait for the results of serial serum hCG testing before they can be told whether the pregnancy is ongoing and if it is not, whether treatment is required. Early Pregnancy Units are an efficient way of investigating and initiating management of early pregnancy complications (Bigrigg and Read, 1991) but they do not remove this delay.

Ultrasound scan can only make a definitive diagnosis of ectopic pregnancy when an adenexal fetal heart pulsation or yolk sac is seen. Such a definitive diagnosis will only be made in only a small proportion of ectopic pregnancies – Leibman *et al.* (1988) and Timor-Tritsch *et al.* (1989) suggested this was up to 20%, but when Mol *et al.* looked at the predictive value of ultrasound findings in 1998[a], a definitive diagnosis of ectopic pregnancy by ultrasound alone could only be made in 9.0% of their patients.

If a test could be developed that would differentiate an ectopic pregnancy from early normal pregnancy and miscarriage, not only would this remove the anxiety and uncertainty that surrounds suspected ectopic pregnancy, but it would widen the therapeutic choices. Medical management is more successful at lower levels of serum hCG (Lipscomb *et al.*, 1999), but ultrasound does not discriminate well between normal and abnormal pregnancy at these lower levels. It is particularly important to exclude normal early pregnancy if medical management is to be considered – it is unlikely that the women will suffer adverse consequences if a miscarriage is treated with methotrexate, but it is imperative that normal early pregnancy is not so treated.

If fetal fibronectin is found at the cervix in a normally situated early pregnancies, whether viable or non-viable, its absence, or presence in reduced quantities, might represent an ectopic pregnancy that is located at site distant to the cervix. The benefits of a test that can that can give a diagnosis of ectopic pregnancy at the time of presentation are not just of swifter diagnosis, but also allow the option of medical management to be considered at lower levels of hCG when the chance of success is at its greatest.

Ness *et al.* (1998) looked at fFN in women who presented with pain and bleeding in early pregnancy. They found fFN levels to have a similar range in women with ectopic pregnancy and ongoing pregnancies (i.e. threatened miscarriages). The mean fFN level was lower in the ectopic pregnancy group, though the range of values was greater. However, in their subjects, all women had a diagnosis at the time of sampling. I was interested to know whether there

were differences between women with ectopic pregnancy and women with normal early pregnancy at the stage when ultrasound findings are unhelpful.

Women who presented with incomplete or complete miscarriage had the highest levels of fFN, but there was sufficient overlap with the ectopic pregnancy group to prevent it discriminating between the two. This group of women is not likely to cause major confusion as the symptoms associated with passage of trophoblast in miscarriage usually lead to clinical diagnosis. The greatest problem arises in those women who have lesser degrees of bleeding, with or without pain in whom an ultrasound scan does not make the diagnosis any clearer.

The aim of this chapter is to measure levels of fFN found in women with suspected ectopic pregnancy and see if these levels differentiated them from women with normal pregnancy and miscarriage.

7.2 Fetal Fibronectin in Ectopic Pregnancy

7.2.1 Method

Two groups of women were recruited:

Group One: Women in first trimester in whom an ultrasound did not demonstrate an intra-uterine pregnancy. Although they presented with pain and/or vaginal bleeding, their symptoms were not consistent with a diagnosis of complete miscarriage. This group contained those pregnancies of primary interest in considering the use of fFN in the diagnosis of ectopic pregnancy. 21 women were recruited.

Group Two: Symptomatic women seen in the Early Pregnancy Unit (EPU) or the Fertility Control Unit in whom a diagnosis of miscarriage was made at their first visit were recruited as a comparison group for my own assessment whether levels of fFN found in miscarrying women overlap with levels found in women with ectopic pregnancy, thus reducing its value as a diagnostic test.. In this group there was no diagnostic dilemma, all women clearly had miscarriages when ultrasound scan was performed and as such they differ from the women recruited from the RMC in chapter 6. Women in the RMC did not have symptoms of miscarriage at the time of sampling and their pregnancies were assumed to be ongoing. 13 women were recruited.

Women recruited through the FCU had swabs taken prior to vaginal ultrasound. Women recruited through the EPU either had swabs taken at the time of speculum examination, if indicated, or prior to surgery.

Samples were obtained from the endo-cervices of consenting women. Samples were taken by gently rolling the swab, taken from the collection system supplied with the assay, in the endocervix for 10 seconds. The swabs were immediately placed in the buffer solution. At the end of each session in which samples were taken, the swabs would be filtered and stored, as described in chapter four.

The major difference with this group of patients in comparison with the previous groups in previous chapters is that they were symptomatic, ie vaginal bleeding was present. This meant that the swabs were more likely to pick up blood in the sampling process, but this reflects the clinical reality. A note was made of any samples that were macroscopically contaminated with blood.

7.2.2 Results

The outcomes of the 21 women in Group 1 are shown in Table 7.1.

Table 7.1 Final outcome in women from group 1

outcome	number
Ectopic pregnancy confirmed	16
Negative laparoscopy	3
ongoing	1
Resolving trophoblast	1

Table 7.2 Final outcome in women from group 2

outcome	number
Miscarriage – sac intact	11
Complete miscarriage	2

In 16 women, the diagnosis of ectopic pregnancy was confirmed laparoscopically. In three women laparoscopies were negative, as serum hCG levels were found to fall post-operatively, the presumed diagnosis was of complete miscarriage. One woman was subsequently found to have a normal intra-uterine pregnancy. One woman was managed conservatively, as her hCG levels fell, laparoscopy was not required and the site of trophoblast - tubal or intrauterine - was not confirmed.

The outcomes of the 13 women in Group two are shown in Table 7.2.

In FCU patients, swabs were taken in symptomatic women before ultrasound scanning, therefore, two of the samples taken were from women who were found to have had complete miscarriages when scanned.

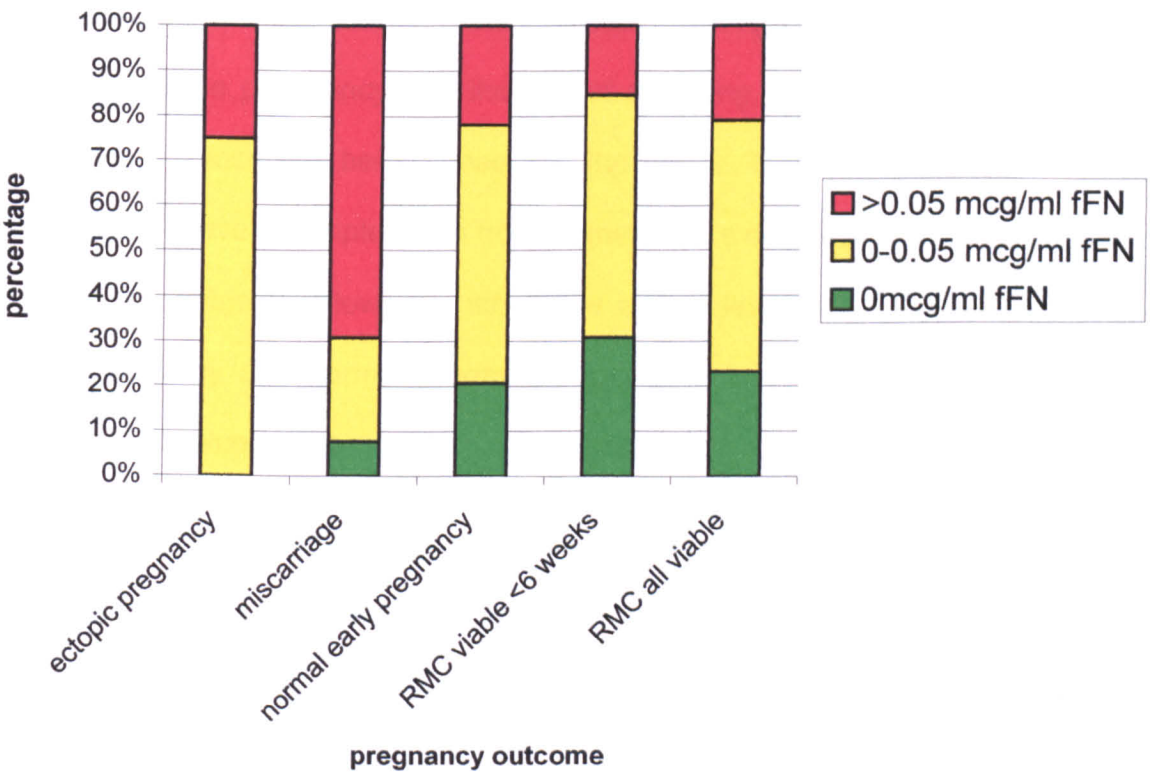
The levels of fFN were expressed in a similar manner to previous chapters, three levels of fFN were considered - samples where no fFN was found (0mcg/ml fFN), samples where fFN was found, but at levels too small to measure (0-0.05mcg/ml) and samples with measurable levels of fFN (>0.05mcg/ml). Fig 7.1 displays the results from this chapter as a percentage of the total number of samples in each group. The complete table of assay results is found in appendix 8. Three groups are displayed – ectopic pregnancies, miscarriages and normal early pregnancy. The group of ectopic pregnancies were the samples taken form those women in whom a diagnosis of ectopic pregnancy was confirmed. The miscarriage group represents the samples taken from women with confirmed miscarriage discussed in this chapter. It does not include the women who miscarried after being seen in the RMC. Three groups are considered in the normal early pregnancy category –

1. all the viable pregnancies sampled in the FCU. This has the disadvantage that the samples are taken from women at more than six weeks gestation, a stage of pregnancy when viability can be confirmed on ultrasound scan.

2. the group of RMC patients in whom samples had been taken before six weeks gestation. As these women present as soon as pregnancy is

confirmed by pregnancy test, they are often seen at a stage when ultrasound confirmation of the pregnancy is not possible. However, because of their higher risk of first trimester loss, the levels of fFN may differ from low risk pregnancies at this gestation.

3. because of this, the third group was included, this consisted of the



ongoing pregnancies of all gestations presenting through the RMC.

Fig 7.1 Levels of fFN in ectopic pregnancy, miscarriage and normal early pregnancy displayed as a percentage of all the results in each group. See text for explanation of groupings.

Considering the three groups of normal early pregnancy, they are broadly similar with the largest percentage of subjects having detectable, but not

All ectopic pregnancies had some detectable fFN.

The group in which a miscarriage was diagnosed had a larger proportion of subjects in which measurable levels of fFN were found, and a smaller proportion in which no fFN was detectable.

7.2.3 Discussion

Before starting this work, I had expected that the greater distance between the site of the pregnancy and the site of sampling, in ectopic pregnancy, would result in less fFN being present at the cervix. This is not the case. fFN was found in every sample taken from women with a diagnosis of ectopic pregnancy in my subjects. However, when the actual levels of fFN found in ectopic pregnancy and normal pregnancy are considered, this information is of no clinical value as the range of values is similar.

Whilst samples from women with ectopic pregnancy all had detectable levels of fFN, many more samples taken from women with confirmed miscarriage had the higher levels of fFN. Again, because of the overlap in the measured levels, this is not clinically useful.

If distance from the site of sampling does, in fact, make a difference to the amount of fFN detected, taking samples as close to the site of the ectopic pregnancy as endocervical samples are close to the site of a miscarriage might exaggerate the differences demonstrated in fig 7.1.

As it is physically impossible to get at the fallopian tube without an invasive procedure, I decided to see how much fFN could be found in circulating blood.

Unlike hCG, which is secreted into the blood, fFN is produced to act locally, having a functional role in the attachment of the pregnancy. I was unsure whether any fFN would be detectable in the circulating blood.

I had another concern. It would seem that the more bloody the first trimester complication, the greater were the amounts of fFN detected at the endocervix. The premise of this work is that the assay is specific to the onco-fetal form of fibronectin. I wished to explore whether contamination with blood might have an effect on the results.

Chapter 8 – Fetal Fibronectin in Blood

8.1 Introduction

fFN is produced by the trophoblast, and so it is to be expected that it would be found locally to the pregnancy. The original hypothesis was that in ectopic pregnancy, which is situated at a distance from the cervix, less fFN would be found on endocervical sampling than would be found in an intrauterine pregnancy which is in closer proximity to the cervix. It was, therefore, an unexpected finding that fFN was detected in all cases of ectopic pregnancy and not all intrauterine pregnancies. Fibronectins are found in abundant quantities in the plasma and Feinberg and Wang (1994) raised concerns about the specificity of antibody raised against the FDC-6 epitope and the possibility of cross-reaction with plasma fibronectins.

Levels of FDC-6 fibronectin have been noted to be raised in the plasma of women with pre-eclampsia (Paidas *et al.*, 1994; Kupferminc *et al.*, 1994). Increased amounts of circulating trophoblast have been suggested as the reason for this.

Here are two possible concerns about using the fFN assay –

1. The assay is not specific, and therefore contamination with blood will give unrealistically high levels of fFN as it detects other, plasma, fibronectins.

2. Pregnancy derived fFN is present in the blood, and therefore contamination with blood will increase the levels of fFN found in the cervix.

The later point may cause difficulties in interpreting results obtained at the cervix in the presence of blood contamination, but circulating trophoblast reacting with the antibody to the FDC-6 epitope might open up other possibilities for screening for pregnancy complications. Would levels of circulating fFN differ in normal, stable pregnancy and abnormal, disrupted pregnancy?

The next stage of my investigation was to explore testing of plasma samples with the quantitative assay.

8.2. Levels of fFN found in plasma of pregnant women

8.2.1 Method

All women attending the FCU have blood taken for a full blood count and blood grouping. I took consent to take extra blood to measure levels of fFN to establish whether fFN could be detected in the plasma of pregnant women. A further 6mls of blood was taken in an EDTA tube for the purpose of this study. All women were scanned at the same visit so the pregnancy was confirmed, and its viability and gestation established.

At the end of the clinic the samples were spun at 2200rpm for 10 minutes to separate the plasma from the blood cells. The plasma was then decanted and stored at -80°c until it was used for testing. I was unclear what to expect from

the plasma, all cervical samples are diluted in the buffer solution; the assay calculates the level of fFN in the secretions taking into account this dilutional factor. If only very small amounts of fFN were present in plasma, undiluted plasma might be required to obtain a measurable result. When calculating the final amount of fFN in the plasma, the results would have to be scaled down to allow for the omitted dilution. If fFN were present in plasma in similar amounts to the cervix, then the same dilution would be required to produce similar results. Therefore I stored and tested samples in two ways:

1. Neat plasma.

2. Plasma diluted in a similar way to the endocervical samples. A swab from the collection system was dipped into the plasma and left for 10 seconds, to mimic collection conditions for the endocervical swabs. The swab was then inserted into the buffer system. The collecting system was then treated in a similar fashion to when endo-cervical swabs were processed. The transport tubes were then gently vortexed for 30 seconds in a Gallenkamp mixer. Each swab was removed from its transport tube, the tip of the swab was squeezed against the transport tube to extract as much fluid as possible. The samples were then filtered in a similar fashion to the endo-cervical swabs. The filtrate was then decanted into a microcentrifuge tube for storage.

8.2.2 Results

All samples of undiluted plasma produced high levels of positivity, all recorded levels of >1.0μg/ml of fFN. As a result only the results obtained from the diluted

samples are considered. 30 samples of plasma from pregnant women were taken. The pregnancy outcome and level of fFN found are in *Appendix 9*. All the diluted samples of fFN gave results that were in the measurable range, with values between 0.2 and 0.8μg/ml of fFN. The scatter of results is shown in figure 8.1. Three additional samples were also taken from women with early pregnancy complications. These also had recordable levels of fFN falling within the same range.

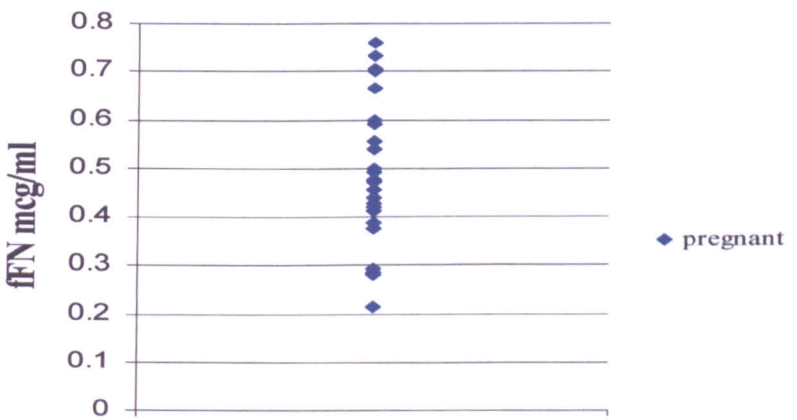


Fig 8.1 Scatter graph of the levels of fFN found in the plasma of pregnant women

8.2.3 Discussion

It is clear that the assay is giving a positive result for fFN. What is unclear, however, is why the assay gives a positive result. Does the positive result represent circulating trophoblast or trophoblastically derived fFN, or is this a false positive result, representing cross-reaction of the assay with circulating

plasma fibronectins. Before spending any more time considering any application in pregnancy, I wished to re-run a similar series using samples from non-pregnant subjects.

8.3 Levels of fFN found in plasma of non-pregnant subjects

8.3.1 Method

Samples were collected and processed in an identical manner to the samples in 8.2 above. Five samples were obtained from non-pregnant women and a further two samples were obtained from men, to exclude any possible interference from past or current pregnancies. All samples were obtained from members of staff within the Department of Obstetrics and Gynaecology.

8.3.2 Results

Levels of fFN found in each subject are displayed in *Appendix 10*.

Figure 8.2 displays the values of fFN obtained form non-pregnant subjects on a scatter graph. The levels obtained from the diluted plasma of pregnant subjects are displayed along-side.

The scatter graph demonstrates a similar distribution of results in pregnant and non-pregnant sample groups. The values obtained for male subjects lie within the same distribution as the female subjects.

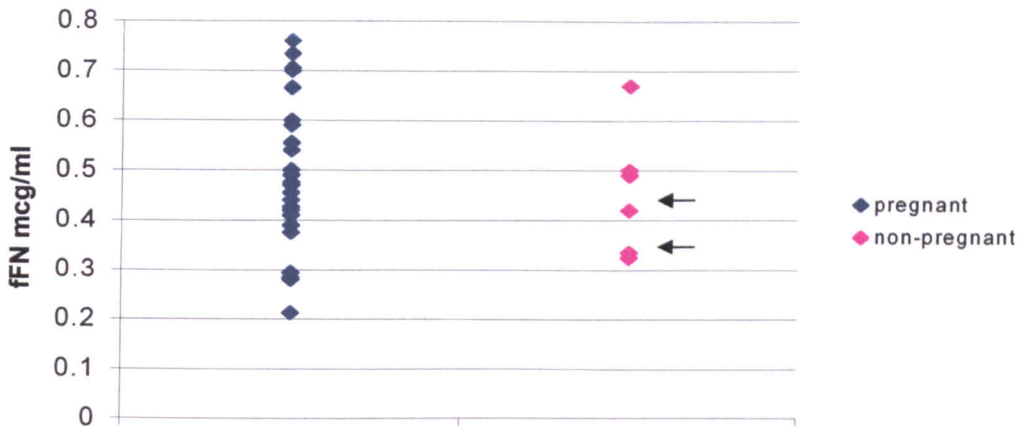


Fig 8.2 Levels of fFN found in the diluted plasma of non-pregnant (male and female) subjects displayed alongside the values obtained in pregnant subjects for comparison. Arrow denotes samples taken from male subjects.

8.3.3 Discussion

It is now clear that the assay is not as specific for fFN as claimed. It clearly cross-reacts with a substance in plasma. That could be either because the FDC-6 epitope is not as specific for the onco-fetal form of fibronectin, or that some of the onco-fetal form of fibronectin is present in plasma.

If the positive results were because of the inappropriate use of the assay to measure fFN in blood, this would raise doubt about its use in any pregnancy in the presence of blood. Perhaps the correlation in third trimester of positive results with imminent labour owes more to the presence of blood, than the presence of fFN.

Contamination with blood might not be clinically significant, the amount of trophoblastic fFN far outweighing any small amounts of cross-reacting plasma fibronectin present at the cervix. To test this I tried sampling the cervices of non-pregnant women.

8.4 fFN levels in endocervical samples from non-pregnant subjects.

8.4.1 Method

Women attending colposcopy clinics have a speculum examination as part of the colposcopy. This lent itself to taking a swab without requiring an examination that would not otherwise be required. Each woman was consented for a swab to be taken for research purposes before colposcopy was performed. Each woman was asked if she was pregnant, or might possibly be pregnant, before being recruited. Any woman in whom pregnancy was a possibility was excluded.

Two types of swab were taken.

1. Swabs were taken during loop biopsy of the cervix to mimic the heavy blood contamination that might occur during some early pregnancy complications.
2. Swabs were taken immediately after insertion of the cuscos speculum so that swabs could also be taken from non-pregnant subjects when the only blood that could be present is that of contact bleeding of the cervix from the swab itself.

8.4.2 Results

16 samples were taken. Five samples were taken during loop biopsies; all were heavily blood stained. 11 samples were taken in women who, either, were not having loop biopsies, or, prior to loop biopsy; three were visibly stained with blood. The complete table of fFN results is found in *appendix 11* (colposcopy samples) and *appendix 12* (loop biopsy samples).

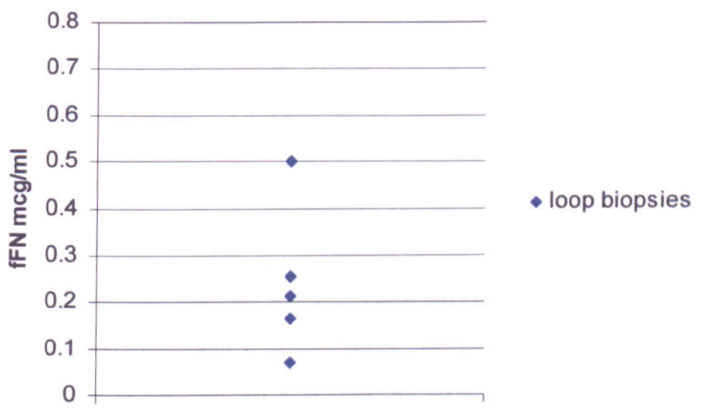


Fig 8.3 Scattergraph of levels of fFN found during loop biopsies

All the samples taken during loop biopsy had measurable levels of fFN, though slightly lower than those found in the plasma (range for loop biopsies: 0.07 to 0.5 μg/ml, range for plasma: 0.213 to 0.76 μg/ml). These results are displayed in the scattergraph figure 8.3. In the samples taken from cervices when a loop biopsy was not being performed, four samples detected the presence of fFN, in one of whom this levels was measurable. Interestingly, this was one of three samples that were macroscopically blood stained. These results are displayed in figure 8.4. These results are displayed as a bar chart, as in three positive results the levels were not high enough to quantify.

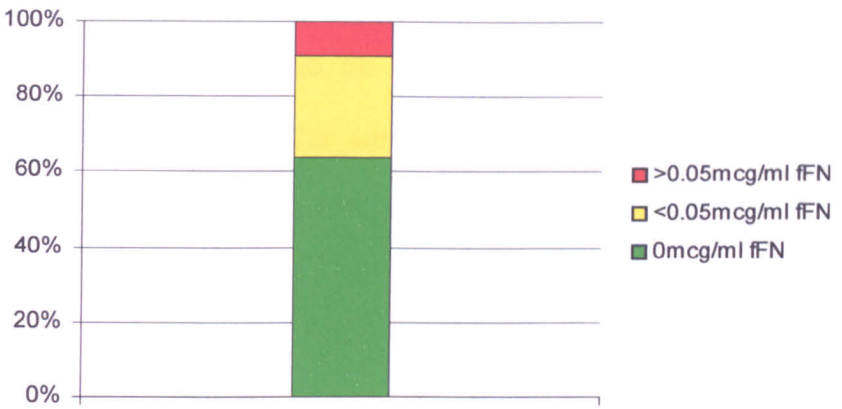


Fig. 8.4 Levels of fFN found in samples taken during colposcopy, but without loop biopsy.

8.4.3 Discussion

Although there are only small numbers, it is concerning that fFN can be detected in even such a small sample of non-pregnant subjects, the assay is clearly not specific for trophoblastic fibronectin. Either this represents cross reaction of the antibody produced to the FDC-6 epitope with plasma fibronectins, in which case an antibody produced to another epitope, more specific to the onco-fetal form of fibronectin may prove to be capable of differentiating different pregnancy complications in first trimester. It may also improve the specificity of fetal fibronectin in the detection of third trimester complications of pregnancy. Alternatively, quantifiable amounts of the onco-fetal form of fibronectin might be present in plasma of non-pregnant subjects.

All samples throughout this work had been examined for blood staining. Samples were considered to be blood stained if there was enough blood contamination to discolour the sample/buffer mixture. 27 out of 202 (13.4%) samples from women in early pregnancy were discoloured by blood. The actual levels found are recorded in *Appendix 13*.

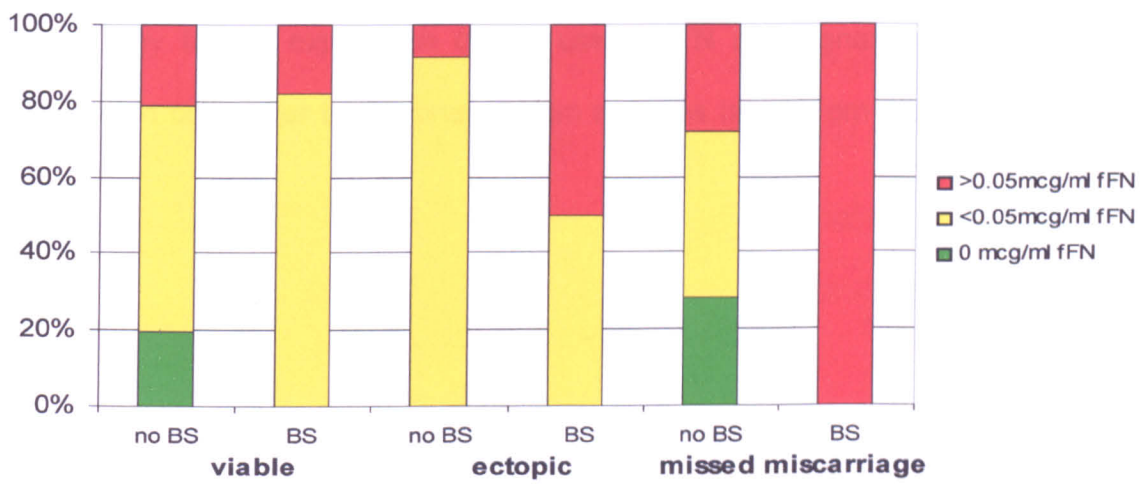


Fig 8.5 The effect of blood staining (BS) on positive results for fFN in viable pregnancies, ectopic pregnancies and missed miscarriages. Results are expressed as a percentage of the total results in each grouping.

Figure 8.5 above shows the proportion of positive results obtained in samples that were stained with blood and in samples in which there was no blood staining. Each of the pregnancy outcomes – viable pregnancy, ectopic pregnancy and missed miscarriage – is displayed. All samples in which there was some frank contamination with blood had detectable levels of fFN and in missed miscarriage, where contamination with blood might be expected to be at

its greatest, samples in which frank blood staining was found all had measurable levels of fFN.

Feinberg *et al.* (1994) estimated that between 1 and 4% of circulating plasma fibronectin will bind FDC-6. They do not explore whether this is a cross reaction with a component of the plasma fibronectins, or whether fibronectins identical to the onco-fetal form are circulating in the plasma. Answering this question is crucial to any further exploration of the use of fFN in pregnancy as blood contamination can never be eliminated from samples taken from the pregnant cervix.

Chapter 9 - Treating Ectopic Pregnancy

9.1 Evaluating Treatment for ectopic pregnancy

As discussed in chapter three, after an ectopic pregnancy, women are concerned about their future fertility and the risk of recurrence. This chapter discusses the treatment options for ectopic pregnancy and the impact on the woman's physical and psychological recovery, and the chances of a future normal pregnancy against the risk of a further ectopic pregnancy.

In addition to producing a diagnostic guideline for ectopic pregnancy, I wished to produce a guideline covering the treatment of ectopic pregnancy. To help me achieve this, I explored two aspects that would influence care:

1) does a woman's past history influence her choice of management of ectopic pregnancy?

This was done using Conjoint Analysis, which is a tool used within Transport Studies to assess the trade offs people are prepared to make in the decision making process. The literature suggests that with ectopic pregnancy, there is a trade off between optimising future fertility and reducing the risk of further ectopic pregnancy. In order to study this, a Conjoint Analysis questionnaire was devised to see if women's prior experiences influenced their choice of treatment of a subsequent ectopic pregnancy.

2) does salpingotomy offer an advantage over salpingectomy?

A pilot trial, randomising women to either salpingectomy or salpingotomy, was devised. Several outcome measures were to be considered - site of the next pregnancy, relative cost of the two treatments, impact on quality of life. If the trial had proven to be successful, it was to be used as a basis to apply for funding for a full-scale, multi-centre trial.

9.2 Conjoint Analysis – Women's Choices in the Management of Ectopic Pregnancy

Conjoint Analysis, or Stated Preference, is a tool that has been used extensively in Transport Studies to establish priorities in the planning of public transport. It consists of a questionnaire that provides a series of options, the different options trade various advantages and disadvantages (attributes) against each other. By varying the degree to which one item is traded-off against another, it aims to establish how important one component is, relative to another, to different groups within the population.

Conjoint Analysis has been used by health care providers to assess patient preferences – their priorities in the management of miscarriage (Ryan and Hughes, 1997), the management of menorrhagia (San Miguel *et al.*, 1997) and in Primary Health Care (Ryan *et al.*, 1998).

Conjoint Analysis relies on an individual's willingness to trade one option against another. In the management of ectopic pregnancy, both conservative and radical surgery is considered to have advantages and disadvantages. Conservative management aims to improve the woman's future fertility because she retains both Fallopian tubes through which to conceive - this is at the cost of an increased risk of recurrent ectopic pregnancy, as the tube is damaged, and incomplete removal of trophoblast at the time of the primary procedure, which may require a second procedure to be performed. On the other hand, radical surgery has a lower risk of persistent and recurrent ectopic pregnancy,

but this might be at the cost of reduced fertility. Conjoint Analysis was used to examine these trade-offs in women with different experiences of pregnancy.

9.2.1 Method - Constructing a Conjoint Analysis (San Miguel *et al.* 1997)

Stage 1 – **Determination of the attributes**

The factors considered important to the respondents are selected. In the case of ectopic pregnancy, these were;

1. chance in the future of normally placed pregnancy
2. chance in the future of ectopically placed pregnancy
3. chance of second operative procedure being required.

Stage 2 – **Assigning levels to the attributes**

The levels should be "plausible, feasible and capable of being traded off against each other." The review paper by Yao and Tulandi (1997) was used to judge plausible levels of risk

"chance of needing more than one operation"

was assigned 0% or 5% or 15%

"chance of next pregnancy being in the right place"

was assigned 40% or 60%

"risk of a repeat ectopic"

was assigned 10% or 20%

Stage 3 – **Definition of the scenarios to be presented**

Combinations of attributes at different levels produces many combinations would not require the respondent to trade e.g.

"chance of needing more than one operation"	0%	v	15%
"chance of next pregnancy being in the right place"	60%	v	40%
"risk of a repeat ectopic"	10%	v	20%

The first option is clearly advantageous in comparison to the second; every respondent should choose it. Such scenarios are placed with the questionnaire as a test of respondent comprehension and some scenarios are repeated to test for consistency.

In this questionnaire 28 scenarios were presented to the respondents to consider. An example follows (fig. 9.1).

Chance of needing more than one operation for	0%	0%
Chance of next pregnancy to be in the right place	40%	60%
Risk of a repeat ectopic	10%	20%
What option would **YOU** choose?		

Figure 9.1 example of a conjoint analysis question

In this example the respondent is asked to trade a higher chance of a normally placed pregnancy against the risk of an ectopic pregnancy. The analysis assesses to what degree one attribute is weighted against another.

Stage 4 – **Establishing preferences**

The questionnaire is given to the respondents to complete.

Stage 5 – **Analysis of the data**

Analysis was performed within the Institute of Transport Studies at the University of Leeds using the ALOGIT package (Hague Consulting Group).

The complete questionnaire is to be found in *appendix 13*.

9.2.2 Results

a) Characteristics of the Respondents

108 questionnaires were completed by patients and nurses recruited, opportunistically, through general gynaecological, colposcopy, early pregnancy and recurrent miscarriage clinics to provide adequate power and control.

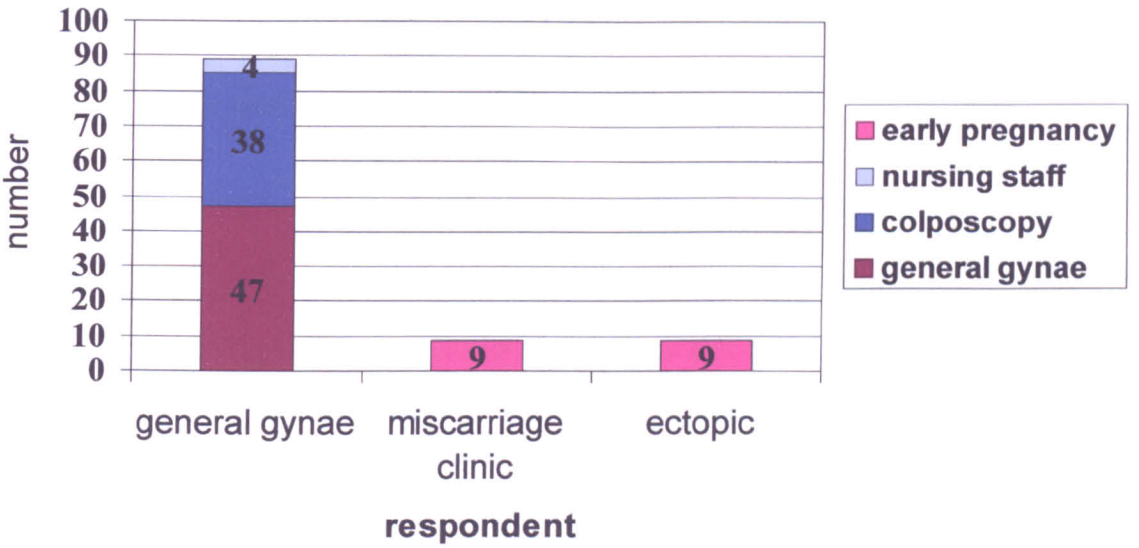


Figure 9.2 Source of respondent to questionnaire

The analysis was done according to 5 criteria:

(i) The source of the questionnaire

Most women (89) were recruited from general gynaecology clinics. These women were not pregnant at the time of completing the questionnaire. 18 women had encountered problems in early pregnancy with equal numbers having a history of recurrent miscarriage and ectopic pregnancy. The group of women with recurrent miscarriage was mixed, comprising both those who were currently pregnant and those who were being investigated prior to pregnancy. The women in the ectopic pregnancy group had all had a clinical diagnosis made and filled out the questionnaire whilst waiting to go to theatre. These two groups are similar in that they have both experienced early pregnancy losses and are both at risk of their problem recurring in future pregnancies, but in women

with recurrent miscarriage it is unlikely that their experience of miscarriage was life-threatening, unlike the ectopic pregnancy group.

(ii) Experiences of a general anaesthetic

If a woman is asked to choose between a procedure that might expose them to a second operation – salpingotomy carries a risk of persistent trophoblast – as opposed to a procedure that carries no such risk – salpingectomy – it might be expected that past experiences of general anaesthetics might influence their choice of treatment.

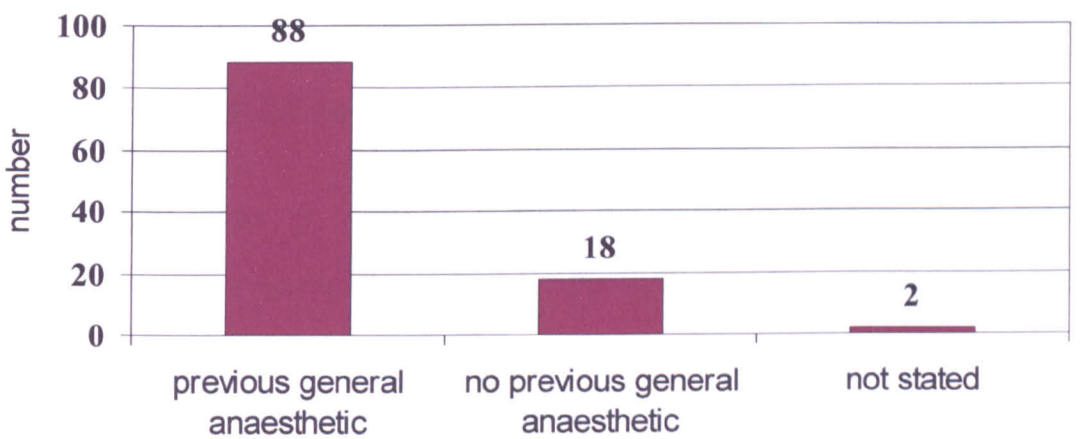


Figure 9.3 Past experience of a general anaesthetic

(iii) Employment

A woman's employment/family commitments might influence her decision, with women in employment or with young children being less able to commit to a procedure that requires repeated visits for follow-up, and might require readmission for management of persistent trophoblast, as is the case with salpingotomy. They may prefer a more definitive treatment.

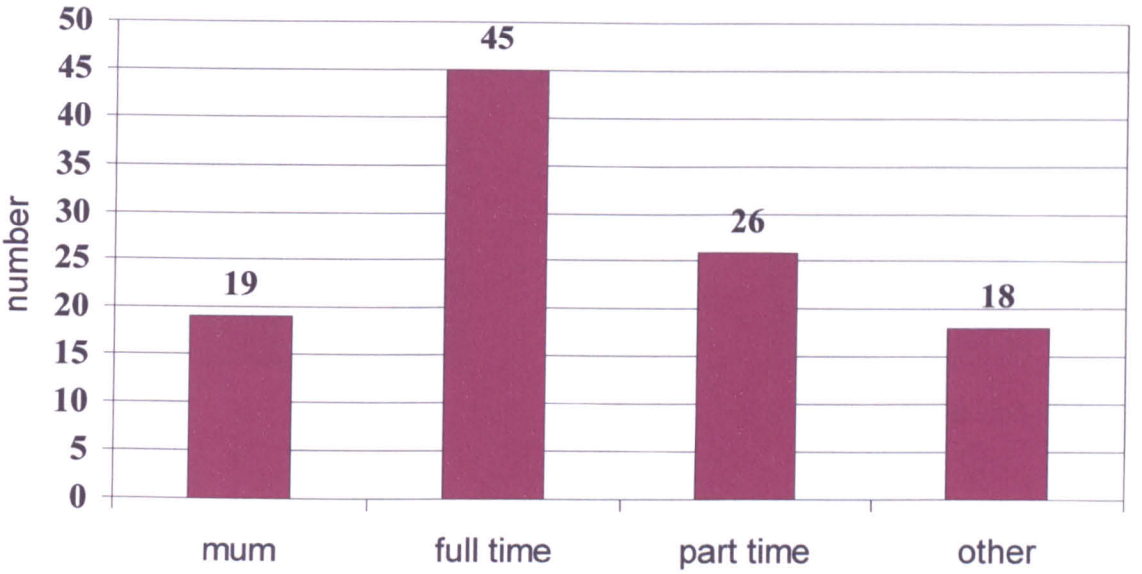


Figure 9.4 Respondents employment status

(iv) Number of children

Women with larger or complete families are likely to put less value on a procedure that increases their fertility at the expense of increasing the risk of another ectopic pregnancy (fig. 9.5).

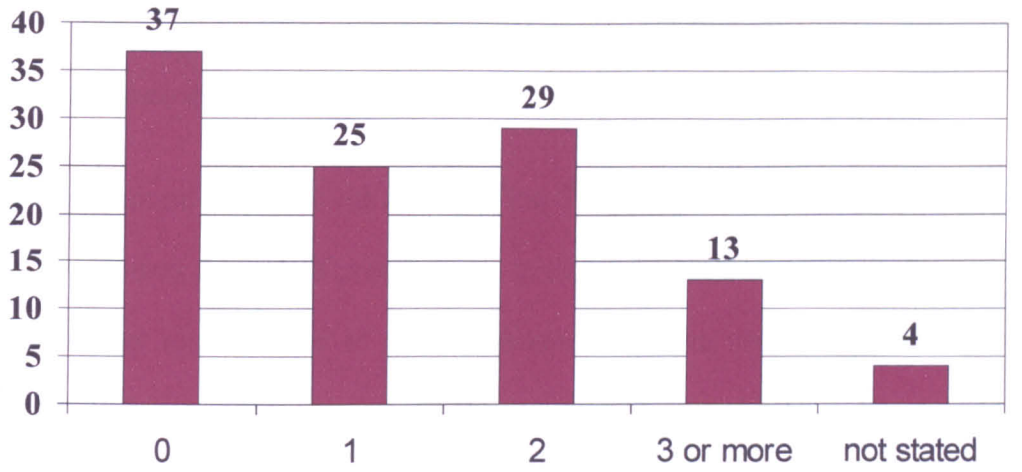


Figure 9.5 number of children of respondents

(v) Age

Women at the extremes of their reproductive life are less likely to be actively pursuing a pregnancy. It might be expected that these women would show less concern about future fertility and be more concerned about reducing the risk of another ectopic pregnancy.

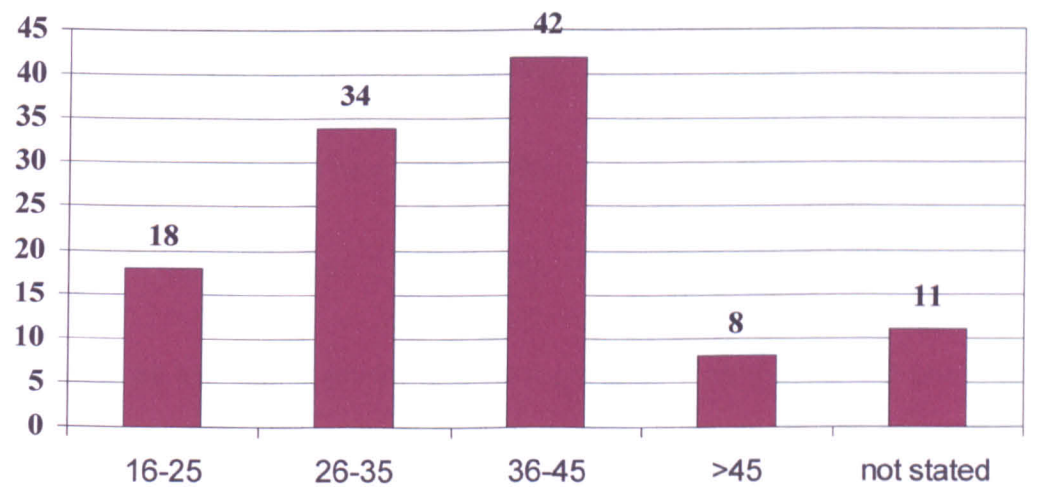


Figure 9.6 age of respondents

b) Results of Conjoint Analysis

- ***The base model***

This examined the basic attributes of the Conjoint Analysis - the need for further operation and the future pregnancy - in isolation. It does not look for any effect of the past experiences of the respondents on the responses they give. Not surprisingly, respondents valued the next pregnancy being correctly sited and did not wish to have a further ectopic pregnancy or a second operative procedure. An attribute with a negative coefficient is an attribute the respondent would prefer to avoid, whilst a positive coefficient denotes a favourable attribute. The possibility of a further ectopic pregnancy has a greater negative value than the possibility of a second general anaesthetic – ie the respondents were slightly more concerned about another ectopic than a second anaesthetic.

Attribute	**Coefficient**	**t-statistic**
further operation	-0.0908	-15.8
intrauterine next	0.0588	16.9
ectopic next	-0.1169	-16.7

As would be expected, having the next pregnancy in the correct place has a positive coefficient – this is a desirable outcome, but the effect is about half that of the other two attributes, so, approximately speaking, a 10% chance of the

pregnancy being in the right place is valued equally to a 5% chance of a second ectopic pregnancy or a further operation.

The t-statistics are taken directly from the ALOGIT package values of + or -2 will indicate a significance at 5% on a Two Tailed Test.

- **The full model**

This then introduces the variables that the respondents bring with them - employment, pregnancy history, and age.

Firslty, the effect of each characteristic on the base coefficient is described. The base coefficient is described for a woman who is seen neither in the context of management of miscarriage or ectopic pregnancy, has not had a previous general anaesthetic, is either self-employed or a student, has had no children and is aged between 16 and 25. The difference between the baseline coefficient and the coefficient for any other given variable describes the effect of changing that variable on the responses given. This gives an indication of how important different influences are on the woman's choice compared to a participant with the baseline characteristics (Tables 9.1, 9.2 and 9.3).

The variable *source of questionnaire* was tested in isolation. Women who were questioned whilst being treated for an ectopic pregnancy always felt more strongly than others; they felt more strongly that they would want an intra-uterine pregnancy on the next occasion, and that they would not want a second operation or another ectopic pregnancy.

	2nd operation	next intrauterine	next ectopic
ectopic	-0.1382	0.0764	-0.1823
other	-0.1251	0.0458	-0.1504

Table 9.1 The effect of the different characteristics of participants on weight they attach to the possibility of a second operation being needed.

Second operation operation	**Attribute level**	**Coefficient**	**t-statistic**
	Base level	-0.1109	-4.7
Source of questionnaire	Treatment for ectopic pregnancy	-0.0131	-0.5
	Treatment for miscarriage	0.0080	0.4
	Previous general anaesthetic	0.0384	2.3
employment	mother	0.0274	1.2
	Part time	0.0210	1.0
	Full time	0.0010	0.1
Number of pregnancies	1	0.0106	0.4
	2	0.0190	0.9
	3 or more	0.0417	2.0
Age	26 to 35	-0.0258	-1.6
	36 to 45	-0.0509	-3.0
	Over 45	-0.0094	-0.4

Table 9.2 The effect of the different characteristics of participants on weight they attach to the next pregnancy being intra-uterine.

Next pregnancy intra-uterine	**Attribute level**	**Coefficient**	**t-statistic**
	Base level	0.0783	5.5
Source of questionnaire	Treatment for ectopic pregnancy	0.0306	2.0
	Treatment for miscarriage	0.0038	0.3
	Previous general anaesthetic	-0.0470	-4.7
employment	mother	0.0247	1.9
	Part time	0.0391	3.2
	Full time	0.0262	2.4
Number of pregnancies	1	-0.0580	-3.9
	2	-0.0502	-3.8
	3 or more	-0.0273	-2.1
Age	26 to 35	-0.0007	-0.1
	36 to 45	0.0049	0.5
	Over 45	-0.0534	-3.4

Table 9.3 The effect of the different characteristics of participants on weight they attach to the next pregnancy being ectopic.

Further ectopic pregnancy	Attribute level	Coefficient	t-statistic
	Base level	-0.1554	-5.3
Source of questionnaire	Treatment for ectopic pregnancy	-0.0319	-1.1
	Treatment for miscarriage	-0.0305	-1.3
	Previous general anaesthetic	0.0496	2.4
employment	mother	0.0064	0.2
	Part time	-0.0185	-0.7
	Full time	0.0004	0.0
Number of pregnancies	1	0.0714	2.4
	2	0.0816	3.0
	3 or more	0.0533	2.0
Age	26 to 35	-0.0668	-3.3
	36 to 45	-0.0127	-0.6
	Over 45	0.0453	1.5

9.2.3 Discussion

This was a first attempt at designing a conjoint analysis and at this stage I hoped to explore its potential of discovering what women want from their management whilst gaining experience of the design process and use of this type of questionnaire. The fact that these results confirmed that women do make different decisions based on their past experiences and current life situation is a bonus and suggests that the development of this as a tool for assessing the decision making process in clinical care an exciting prospect.

With thanks to Mr. G. Whelan and Dr. A. Fowkes, Institute of Transport Studies, University of Leeds, for their help in the analysis of the Conjoint Analysis.

9.3 Salpingectomy versus Salpingotomy – a Pilot Trial to Compare Reproductive Outcome.

9.3.1 Method

When surgery was first used in the management of ectopic pregnancy, the aim was to save the woman's life by the cessation of the bleeding. This necessitated the removal of the fallopian tube along with the ectopic pregnancy. From the 1970's onwards, with earlier diagnosis, there was a move towards more conservative surgery with preservation of the fallopian tube, in the hope that this would improve the reproductive outcome. In their paper reviewing the management of ectopic pregnancy, Yao and Tulandi concluded that *"conservative surgery may provide a subsequent intrauterine pregnancy rate that is at least as comparable to or possibly higher than that after radical surgery. Unfortunately, the recurrent ectopic pregnancy rate also may be higher after conservative surgery."* (Yao and Tulandi, 1997) Their review looked at nine retrospective studies, commenting that to determine the optimum treatment a trial randomising women to either conservative surgery – salpingotomy, or radical surgery – salpingectomy, would be needed. Such a trial has not yet been performed.

I wished to examine the feasibility of such a trial and designed a pilot trial with a view to following women up post-operatively to determine the site of their next pregnancy. If the pilot trial proved to be successful, our aim was to design a large scale, multi-centre trial.

Inclusion criteria

- Haemodynamically stable patients with their first ectopic pregnancy.
- The ectopic pregnancy must be unruptured at the preliminary laparoscopy.
- A healthy contra-lateral fallopian tube at the preliminary laparoscopy.
- Written informed consent must be obtained.

Exclusion criteria

- Patients with a cornual ectopic pregnancy must not be entered into the trial
- A fimbrial ectopic pregnancy (those feasible to being milked free of the fallopian tube
- An unhealthy contra-lateral tube (as defined by the presence of adhesions, visible tubal damage, nodularity and inability to inspect the fimbrial end of the tube).

Women with a suspected ectopic pregnancy were recruited to the trial prior to going to theatre. Once the ectopic pregnancy was confirmed, a telephone randomisation line was contacted, resulting in the patient being randomised to either salpingotomy or salpingectomy. A postal questionnaire was to be sent out twelve months later to determine the number and site of pregnancies conceived.

9.3.2 Results

Recruitment required a detailed explanation of the aims of the trial:

1. with salpingotomy the hope was that there would be a greater chance of a conception, as both tubes were preserved, but that this might be at the expense a greater risk of a further ectopic pregnancy

2. with salpingectomy the chance of a pregnancy in the future might be reduced as only one tube was preserved, but the risk of a second ectopic pregnancy might be less.

Recruitment was between June and December 1999. In that time there were 47 ectopic pregnancies. Two cases were not analysed because their case notes were lost and it was not possible to verify the inclusion criteria or treatment given. Of the 45 women remaining, 40 were not recruited. In 37 their history and/or the findings from past laparoscopies clearly excluded them. The reasons are shown in Table 9.4.

Three women would have been suitable for the trial, but were not recruited. All other women either had a pre-operative or intra-operative exclusion factor, or did not wish to be randomised as they had a treatment preference pre-operatively. These women who did not wish to be randomised, fell into one of two groups; those with a prior history of subfertility chose salpingotomy, those with no history of subfertility chose salpingectomy.

Five women were successfully recruited, but only one randomised (Table 9.5). Two were not randomised because of a failure in the randomisation line, one because of contra-lateral tubal damage and the other the surgeon misunderstood the aims of the trial.

Table 9.4 Reasons why women were not randomised to the trial of surgical management of ectopic pregnancy. More detail can be found in *appendix 14* where each patient is given with details of why they could not, or preferred not to be, randomised.

Reasons for exclusion	number	
PID/tubal damage/past sterilisation	9	
Patient requests salpingectomy	9	
Patient requests salpingotomy	6	
Family complete	2	
Ruptured ectopic	2	
Haemodynamically unstable	2	
Unicornuate system	1	
Previous ectopic pregnancy	1	
Ectopic pregnancy not found	1	
Cornual ectopic	1	
Refused randomisation	1	
Failed recruitment	4	3 no discussion 1 paranoid schizophrenic

Table 9.5 Women successfully recruited to the trial

number	D.O.B	randomised	failure	Haemodynamically stable	first ectopic pregnancy	Fimbrial ectopic	ruptured	Pelvic inflammatory disease	suitable
956095	27.11.66	yes		yes	yes	no	no	no	yes
958114	30.12.65	no	line failure	yes	yes	no	no	no	yes
904065	2.1.79	no	line failure	yes	yes	no	no	no	yes
848796	12.3.72	no	left tubal disease	yes	yes	no	no	yes	no
477143	5.2.63	no	surgeon did not randomise	yes	yes	no	no	no	yes

In summary, there were 47 ectopic pregnancies over the seven month period of the trial, it was possible to analyse the records of 45. Only seven women were suitable for randomisation during this time but only one was randomised. This was a great disappointment!

When designing the trial it was estimated that approximately 800 women would need to be recruited. The number of patients was dictated by the assumption that

to demonstrate a 10% improvement in subsequent fertility is of clinical significance. Based on the evidence of the Yao and Tulandi (1997) review the subsequent fertility rate, with conservative surgery, was taken to be 57%. In order to demonstrate a 10% difference (with an 80% probability and 5% level of significance) 388 patients per trial arm would be needed.

9.3.3 Discussion

My attempts to recruit for the pilot trial of salpingectomy and salpingotomy were unsuccessful because either women were unwilling to be randomised or they were not clinically suitable. The recruitment required an explanation of the reasons for a trial – the desire to increase future fertility as much as possible whilst being aware of the possibility that tubal preservation might increase the risk of future ectopic pregnancy. If women had no prior history of infertility, they preferred to have radical surgery, apparently fearing the possibility of a future ectopic pregnancy above their fear of infertility. Those women who had conceived an ectopic pregnancy against a background of infertility chose conservative surgery, wishing to maximise their chances of achieving an intra-uterine pregnancy in the future. Their analysis of the situation is supported by the literature – women with a history of infertility prior to their ectopic pregnancy are least likely to achieve a subsequent intra-uterine pregnancy. The exceptions to this are the women who became pregnant through assisted conception who chose bilateral salpingectomy. They have accepted that natural conception is not an option for them and perceive a greater chance of successful assisted conception (and reduce the chance of ectopic implantation of an assisted conception) if as much of their tubes as possible have been removed.

A pragmatic approach to a trial comparing radical and conservative surgery for ectopic pregnancy – accepting that patients will choose their treatment, rather than agree to randomisation – would be inappropriate. The group most likely to choose conservative surgery is least likely to achieve an intra-uterine pregnancy and so a comparison with those choosing radical surgery would not be valid. From my experience, it would not seem possible to compare patient choices for surgical management.

9.4 Summary

Whilst my attempt at Conjoint Analysis was limited in what it showed, it did demonstrate that women do attach different weight to various outcomes. It is this very variation that meant ROCET failed – what was seen as a result in the Conjoint Analysis lead to a failure to recruit in ROCET ie women make choices when offered options, and those choices will differ according to her life experiences.

This is why tools, such as conjoint analysis, that provide a way of measuring how much patients will trade the different advantages and disadvantages when choosing one treatment above another are interesting.

The ROCET pilot suggests that concerns about future fertility are not the only influence, and the fear of another ectopic pregnancy leads women, who have not been concerned about their fertility in the past, to trade a possible increase in the intra-uterine pregnancy rate for a reduced risk of another ectopic pregnancy.

Whilst I failed to shed any light on whether or not conservative management offers any advantages to women with an ectopic pregnancy, what is clear is that women can make decisions about what is "best" for them. "Best" might not be what the doctor considers to be most advantageous, but women can make decisions about what treatment addresses their own fears and aspirations for their own future pregnancies when they are given information and choice. Any protocol for the management of ectopic pregnancy should include a choice of management options and advice on when each option is appropriate. The protocol I wrote for use in the Early Pregnancy Unit in Leeds includes guidance on the management options that can be considered when an ectopic pregnancy is diagnosed (*Appendix 14*).

Conclusions

Epidemiology of Ectopic Pregnancy

- There is a world-wide increase in the recorded incidence of ectopic pregnancy. Several factors account for this increase.
    - Better diagnostic tools leads to an increase in the number of ectopic pregnancies being detected.
    - Changes in patterns of sexual behaviour – for example a greater number of sexual partners, increases in the time between first intercourse and first pregnancy, greater spacing between pregnancies – means more women are either exposed to Chlamydia and have the opportunity to develop pelvic damage as a result of this exposure prior to conception.
    - Changes in reproductive practices, both the introduction of assisted conception techniques and the use of contraceptives that reduce the incidence of intra-uterine, but not extra-uterine pregnancies have an impact on the number of pregnancies that implant outside the endometrial cavity.

As ectopic pregnancy has a significant associated mortality and morbidity, it is good that a greater number of ectopic pregnancies are detected. However, if increased detection leads to an increase in therapeutic procedures in women who would have previously never known that they had an ectopic pregnancy, that in turn have an associated morbidity and mortality, this is not desirable. It is as important to recognise when methods, other than surgery, would be more appropriate. As diagnostic methods improve detection, it is imperative that

management protocols are developed to ensure *safe* treatment, with full consideration to medical and conservative management options

Reducing mortality and morbidity associated with ectopic pregnancy.

There are two important components to this.

- Increase awareness of pelvic infection particularly with *Chlamydia* both to reduce the incidence of infection, and to prompt rapid and effective treatment when infection has occurred.
- Increase awareness of ectopic pregnancy amongst both patients and health care workers.

Those countries that appear to have reduced the incidence of ectopic pregnancy have done so by tackling *Chlamydia* and the sequelae of this infection. This requires, firstly, population-wide knowledge of prevention of the infection, but secondly the importance of rapid treatment and screening for the asymptomatic infections. Prevention of chlamydial tubal disease will reduce the number of ectopic pregnancies that occur in the long-term.

If an ectopic pregnancy occurs, early presentation widens the management options and reduces the risk of major haemorrhage before diagnosis and treatment. A wider general awareness of ectopic pregnancy and direct access to Early Pregnancy Units for women in early pregnancy would reduce some of the obstacles to early presentation. It is also important to increase awareness amongst health care professionals, so that the diagnosis is considered, particularly in General Practice and emergency medicine, where the possibility of pregnancy is not as high on the agenda as in gynaecology.

As recurrence is a complication of ectopic pregnancy, it is important that women are instructed to have an early scan when they next become pregnant, even when they are asymptomatic. They should have unrestricted, direct access to Early Pregnancy Units for this.

Early Pregnancy Units allow organisation of services and expertise, facilitating rapid access to ultrasound and allow standards of diagnosis and management to be set. Protocols can set these standards and can be used as the basis to audit practice and ensure that these standards are met. They are the best place to deliver management choices to women.

Diagnosis of ectopic pregnancy.

Laparoscopy has been considered the gold standard for the diagnosis of ectopic pregnancy, as it allows direct visualisation of the ectopic itself. It is a management intervention in its own right; it is not 100% sensitive and has its own associated mortality and morbidity. If laparoscopy were required in the management of all ectopic pregnancies, it would be inappropriate to offer this in combination with either medical or expectant management, as this would expose the patient to the risks of two management options. If an ectopic pregnancy is diagnosed by laparoscopy it should be managed surgically.

In reality, diagnosis is reached by a combination of clinical findings with ultrasound and biochemical (largely hCG levels, but progesterone has a similar role). None of these three are adequately accurate in isolation, and even together often resulting diagnostic uncertainty

- Clinical findings are neither sensitive, nor specific and can be misleading when taken in isolation
- Transvaginal ultrasound is most useful when it excludes ectopic pregnancy. Whilst it can confirm the presence of an ectopic pregnancy, when a fetal heart pulsation is found in the adenexum, it more often just sets the level of suspicion by finding an adnexal mass. Endometrial stripe thickness is of no value in predicting ectopic pregnancy. Adnexal masses and fluid in the Pouch of Douglas both increase the probability of an empty uterus representing an ectopic pregnancy.
- Biochemical testing - single hCG levels are of limited value. Their sensitivity can be increased at the expense of specificity by reducing the discriminatory zone. Paired levels, 48 hours apart, are the optimum method of using hCG estimations but ectopic pregnancies can give a normal rise. hCG estimations are only meaningful in the presence of an ultrasound scan when an intrauterine pregnancy (viable or non viable) is not found.

If a laparoscopy is not performed, the woman being managed non-surgically, a histological diagnosis is not reached. In many cases an ectopic pregnancy would appear highly likely, in others there would be more doubt. A label of trophoblast of uncertain location might be used, but these women should always be thoroughly followed up as for an ectopic pregnancy, in the index and subsequent pregnancies.

An ideal diagnostic test would differentiate between ectopic pregnancy, normal early pregnancy and failing intrauterine pregnancy, and would achieve this at the first time of testing, it would reach diagnosis at an early stage, reducing the risk of cardiovascular compromise and would result in a reduction in unnecessary laparoscopies.

The role of fetal fibronectin in early pregnancy

The role of fetal fibronectin has been studied extensively in the latter stages of pregnancy, with premature labour being the main indication for its use. In this case a positive result not conclusive, but a negative result is reassuring, with there being a low chance of ensuing labour. Fetal fibronectin, as a predictor of premature labour, is available commercially, and is used world-wide in the prediction of premature labour. These commercially available kits use the antibody directed against the FDC-6 epitope, which is considered unique to the onco-fetal form of fibronectin.

To date, two papers have been published which use this same assay to detect fetal fibronectin in early pregnancy. It was used at the time of acute presentation, and although some differences between uncomplicated and complicated early pregnancy were found, the differences were not useful in diagnosis.

I set out to see if fetal fibronectin might be useful as a predictive test to discriminate between normal and complicated early pregnancy, firstly to improve the detection of ectopic pregnancy and secondly to increase the

therapeutic options available to women in whom an ectopic pregnancy has been diagnosed by reaching a diagnosis at an early stage.

Whilst the assay for fetal fibronectin is in wide use, my work shows either it does not specifically detect the onco-fetal form of fibronectin, or the onco-fetal form of fibronectin is found more widely than has been assumed before. Whilst I found higher levels in normal early pregnancy of less than 9 weeks, and that the assay was consistently positive, to varying degrees, when an ectopic pregnancy was found, it is not possible to say whether this reflects differing levels of fetal fibronectin, or is merely a feature of contamination with maternal blood. Nor does it differentiate between ectopic pregnancy and other pregnancies, as the assay was positive in at least a proportion of all pregnancy groups.

Whether or not fetal fibronectin is useful in differentiating the complications of early pregnancy has not been answered. This would require an assay that was not positive in the presence of maternal blood. I attempted to acquire the antibody used in the work of Feinburg and Wang (1994), without success.

The assay, itself, also proved problematic. If it had seemed that this assay might prove useful in differentiating the problems of early pregnancy it would have been important to explore these problems further. However, by the stage that the extent of the problem was apparent, it was also clear that any test using this antibody to detect fetal fibronectin would not be a useful diagnostic tool.

As different early pregnancy diagnoses did result in differences in the levels of fetal fibronectin detected, it is possible that fetal fibronectin may yet prove

useful, if an appropriate assay is used, probably in combination with other markers.

Management of Ectopic Pregnancy

The primary objective in the managing of ectopic pregnancy is that the treatment used is safe i.e. that it avoids maternal death and minimizes morbidity, either from the complications of ectopic pregnancy or from the complications of treatment. Whilst ectopic pregnancy remains an important cause of maternal death, it is an uncommon complication, and most women who are faced with ectopic pregnancy will be more concerned with the associated morbidity. Ectopic pregnancy is associated with reduced subsequent fertility, recurrence of ectopic pregnancy in the future and persistence of ectopic pregnancy after treatment. The morbidity associated with the method of treatment must also be considered.

Surgical Management

Laparoscopic management has been conclusively shown to offer benefits over laparotomy to the patient, and should be considered the gold-standard for surgical management. These are short term benefits – with reduced blood loss, analgesic requirements and hospital stay. In the long-term, fertility and recurrence of ectopic pregnancy are similar for the two methods. There is a higher risk of persistent ectopic pregnancy with conservative laparoscopic management of ectopic pregnancy than with laparotomy.

When salpingectomy is compared with salpingotomy, there is no clear advantage of one procedure over the other, with similar long-term fertility and recurrent ectopic pregnancy rates, but there is a higher rate of persistent ectopic pregnancy.

Medical Management

Medical management predominantly uses methotrexate. It avoids the operative complications of surgical management and the recognised side-effects of therapy can be greatly reduced by single dose therapy. To be able to use medical management it must be possible to reach a diagnosis of ectopic pregnancy without resorting to laparoscopy, otherwise medical management will result in the patient being exposed to the potential complications of both treatments. Local infiltration with methotrexate, either laparoscopically or under ultrasound guidance, is to be discouraged as it has a lower success rate, whilst exposing the patient to similar systemic levels of the drug.

The only factor that has been consistently shown to predict the outcome of medical management is the hCG level. If a cut off of 2,000miu/ml (3^{rd} IS) is chosen, this not only has a 93% chance of success, but is also ties in with the discriminatory zone for an intra-uterine gestation sac on transvaginal ultrasound. Paired hCG levels should be used, as a sub-optimal rise gives further support to a non-viable pregnancy – to over-treat a miscarriage with methotrexate is acceptable, to miss a viable intra-uterine pregnancy and give methotrexate is not. Herein may lie the factor determining the success or not of medical management, it is not so much the actual level of hCG that determines

the success, or not, of medical treatment, but the rate of division of trophoblast reflected in the rate of change of hCG levels. Perhaps those ectopic pregnancies that can be successfully treated at higher hCG levels are those where the rate of change of hCG levels is low, many of which might be failing anyway.

Expectant Management

It would appear that the natural history of ectopic pregnancy is to resolve in around 50% of cases. This is, however, at a high cost, with those women with failed expectant management frequently requiring emergency surgery; it is not an option that is suitable to offer to every woman. It appears to be most successful when the initial level of hCG is <2000mi/ml and the paired level 48 hours later is seen to fall.

All methods of management seem to have similar rates of subsequent intra-uterine pregnancy. The conservative treatments all appear to have similar rates of recurrent ectopic pregnancy, and this is higher than with radical surgery.

It should be remembered that persistent ectopic pregnancy is a potential complication of all management of ectopic pregnancy. In any case which is managed conservatively (conservative surgical, medical or expectant management), hCG levels should be tracked to non-pregnant levels.

Each of the treatment options seem to result in similar subsequent fertility rates. Whilst the primary aim is to ensure the woman is safe, there are a substantial number of occasions when there would be more than one appropriate treatment

option available to a woman. Women value choice and discussion of their choices, but also, my work demonstrates that they are able to weigh the implications of those choices in light of their own circumstances.

Future work.

Although the assay side of this thesis produced disappointing results, there was enough there to encourage me to think that there will be biochemical markers for early pregnancy problems, particularly ectopic pregnancy. Since I am now working in an early pregnancy unit, I am keen to continue this work by assessing different methods of sample collection and analysis. Although HVS sampling had a lower positive rate, it does have some advantages with the possibility of self testing. Other markers of trophoblast activity should be studied, particularly the cytokines and growth factors.

I do not feel that this chapter is yet closed.

References

Aboud E. (1997) **A five-year review of ectopic pregnancy.** Clin Exp Obst Gynecol; 24:127-9

Aboud E. Chaliha C. (1998) **Nine year survey of 138 ectopic pregnancies.** Archives of Gynecology and Obstetrics; 261(2):83-7

[a]Ankum W.M., Van der Veen F., Hamerlynck J.V.T.H., Lammes F.B. (1993) Laparoscopy: a dispensable tool in the diagnosis of ectopic pregnancy. Hum Reprod; 8(8):1301-06

[b]Ankum W.M., Van der Veen F., Hamerlynck J.V.T.H., Lammes F.B. (1993) **Transvaginal sonography and human chorionic gonadotrophin measurements in suspected ectopic pregnancy: a detailed analysis of a diagnostic approach.** Hum Reprod; 8(8):1307-11

[a]Anonymous. (1995) **Ectopic pregnancy – United States 1990-1992.** Morbidity and mortality Weekly Report; 44(3): 46-8

[b]Anonymous. (1995) **Assisted reproductive technology in the United States and Canada: 1993 results generated form the American Society for Reproductive Medicine/Society for Assisted Reproductive Technology registry.** Fertil Steril; 64(1): 13-21

Atrash H.K., Strauss L.T., Kendrick J.S., Skjeldestad F.E., Ahn Y.W. (1997) **The relation between induced abortion and ectopic pregnancy.** Obstet Gynecol; 89(4): 512-8

Atri M., Bret P.M., Tulandi T., Senterman M.K. (1992) **Ectopic pregnancy: evolution after treatment with transvaginal methotrexate.** Radiology; 185:749-53

Arora R., Rathore A.M., Habeebullah S., Oumachigui A. (1998) **Ectopic pregnancy – changing trends.** J Indian Med Ass; 96(2): 53-4

Bajekal N.R., Michel M.Z., Li T.C. (2000) **Audit standards in ectopic pregnancy.** J Obstet Gynaecol; 20(2):119-125

Banerje S., Aslam N., Woelfer B., Lawrence A., Elson J., Jurkovic D. (2001) **Expectant management of early pregnancies of unknown location: a prospective evaluation of methods to predict spontaneous resolution of pregnancy.** Br J Obstet Gynaecol; 108(2):158-63

Barlow R.E., Cooke I.D., Odukoya O., Heatley M.K., Jenkins J., Narayansingh G., Ramsewak S.S., Eley A. (2001) **The prevalence of Chlamydia trachomatis in fresh tissue specimens from patients with ectopic pregnancy or tubal factor infertility as determined by PCR and in-situ hybridisation.** J Med Micro; 50(10):902-8

Ben-Arie A., Goldschmit R., Dgani R., Hazan Y., Ben-Hur H.,Open M., Hagay Z. (2001) **Trophoblastic peritoneal implants after laparoscopic treatment of ectopic pregnancy.** Eu J Obstet Gynecol; 96(1):113-5

Ben-Shlomo I., Eliyahu S., Yanai N., Shalev E. (1997) **Methotrexate as a possible cause of ovarian cysts formation: experience with women treated for ectopic pregnancies.** Fertil Steril; 67(4):786-8

Beral V. (1975) **An epidemiological study of recent trends in ectopic pregnancy.** Br J Obstet Gynaecol; 82:775-782

Bernoux A., Job-Spira N., Germain E., Coste J., Bouyer J. (2000) **Ferility outcome after ectopic pregnancy and use of an intrauterine device at the time of the index ectopic pregnancy.** Human Reproduction; 15(5): 1173-7

Bigrigg M.A. and Read M.D. (1991) **Management of women referred to an early pregnancy assessment unit: care and cost effectiveness.** Br Med J; 302:577-9

Bittar R.E., Yamasaki A.A., Sasaki S., Zugaib M. (1996) **Cervical fetal fibronectin in patients at increased risk for preterm delivery.** Am J Obstet Gynecol; 175(1):178-81

Block W.A. Jr, Wolf G.C., Best R.G. (1998) **Chromosomal abnormalities in ectopic pregnancy chorionic villi.** J Society Gynecologic Investigation; 5(6):324-6

Borsi L., Carnemolla B., Castellani P., Rosellini C., Vecchio D., Allemanni G., Chang S.E., Taylor-Papadimitriou J., Pande H., Zardi L. (1987) **Monoclonal antibodies in the analysis of fibronectin isoforms generated by alternative splicing of mRNA precursors in normal and transformed human cells.** Journal of Cell Biology; 104(3):595-600

[a]Bouyer J., Rachou E., Germain E., Fernandez H., Coste J., Pouly J.L., Job-Spira N. (2000) **Risk factors for extrauterine pregnancy in women using an intrauteine device.** Fertil Steril; 74(5):899-908

[b]Bouyer J., Job-Spira N., Pouly J.L., Coste J., Germain E., Fernandez H. (2000) **Fertility following radical, conservative surgical or medical treatment for tubal pregnancy: a population-based study.** Br J Obstet Gynaecol; 107:714-21

Bradley E. and Hamilton-Fairley D. (1998) **Managing miscarriage in early assessment pregnancy units.** Hospital Medicine; 59(6):451-6

Bradley W.G., Fiske C.E., Filly R.A. (1982) **The double decidual ring sign of early intrauterine pregnancy: use in exclusion of ectopic pregnancy.** Radiology; 143:223-226

Braithwaite J.M., Economides D.L. (1997) **Acceptability by patients of transvaginal sonography in the elective assessment of the first trimester fetus.** Ultrasound Obstet Gynecol; 9:91-3

Braunstein G.D., Rasor J., Adler D., Danzer H., Wade M.E. (1976) **Serum human chorionic gonadotrophin levels throughout normal pregnancy.** Am J Obstet Gynecol; 126:678-81

Bruhat M.A., Manhes H., Mage G., Pouly J.L. (1980) **Treatment of ectopic pregnancy by means of laparoscopy.** Fertil Steril; 33:411-4

Buck R.J., Joubert S.M., Norman R.J. (1988) **Serum progesterone in the diagnosis of ectopic pregnancy: a valuable test?** Fertil Steril; 50:752-55

Buster J.E., Carson S.A. (1997) **Medical management of ectopic pregnancy.** In *Problems in Early Pregnancy, Eds.* Grudzinskas J.G. and O'Brien P.M.S., RCOG Press, London, pages 187-199

[a]Cacciatore B., Tiitinen A., Stenman U-H., Ylöstalo P. (1990) **Normal early pregnancy: serum hCG levels and vaginal ultrasonography findings.** Br J Obstet Gynaecol; 97:899-903

[b]Cacciatore B., Stenman U-H., Ylöstalo P. (1990) **Diagnosis of ectopic pregnancy by vaginal ultrasonography in combination with a discriminatory serum hCG level of 1000IU/l.** Br J Obstet Gynaecol; 97:904-908

Cagnacci A, Landi S, Volpe A. (1999) **Rhythmic variation in the rate of ectopic pregnancy throughout the year.** Am J Obstet Gynecol; 180(5): 1067-71

Carnemolla B., Balza E., Siri A., Zardi L., Nicotra M.R., Bigotti A., Natali P.G. (1989) **A tumor-associated fibronectin isoform generated by alternative splicing of messenger RNA precursors.** Journal of Cell Biology; 108(3):1139-48

Castles A., Adams E.K., Melvin C.L., Kelsch C., Boulton M.L. (1999) **Effects of smoking during pregnancy. Five meta-analyses.** Am J Preventive Medicine; 16(3):208-15

Centres for Disease Control. (1995) **Ectopic pregnancy: United States 1990-1992.** Mor Mortal Wkly Rep CDC Surveill Summ; 44:46-48

Chien P.F.W., Khan K.S., Ogston S., Owen P. (1997) **The diagnostic accuracy of cervico-vaginal fetal fibronectin in predicting preterm delivery: an overview.** Br J Obstet Gynaecol; 104:436-444

Chuileannain F.N., Bell R., Brennecke S. (1998) **Cervicovaginal fetal fibronectin testing in threatened preterm labour –translating research findings into clinical practice.** Aust NZ J Obstet Gynaecol; 38(4):399-402

Coste J., Job-Spira N., Aublet-Cuvelier B., Germain E., Glowaczower E., Fernandez H., Pouly J-L. (1994) **Incidence of ectopic pregnancy. First results of a population-based register in France.** Hum Reprod; 9(4):742-5

[a]Coste J., Bouyer J., Germain E., Ughetto S., Pouly J-L., Job-Spira N. (2000) **Recent declining trend in ectopic pregnancy in France: evidence of two clinicoepidemiologic entities.** Fertil Steril; 74(5): 881-886

[b] Coste J., Fernandez H., Joyé N, Benifla J-L., Girard S., Marpeau L., Job-Spira N. (2000) **Role of chromosome abnormalities in ectopic pregnancy.** Fertil Steril; 74(6): 1259-60

Crane J.M., Armson B.A., Dodds L., Feinberg R.F., Kennedy W., Kirkland S.A. (1999) **Risk scoring, fetal fibronectin and bacterial vaginosis to predict preterm delivery.** Obstet Gynecol; 93(4):517-22

Dart R.G., Kaplan B., Varaklis K. (1999) **Predictive value of history and physical examination in patients with suspected ectopic pregnancy.** Annals of Emergency Medicine; 33(3):283-90

Daya S. (1987) **Human chorionic gonadotropin increase in normal early pregnancy.** Am J Obstet Gynecol; 156(2):286-90

Dimitry E.S. and Reid W. (1993) **Ectopic pregnancy: review of diagnosis and management.** Contemp Rev Obstet Gynaecol; 5:520

Dias Pereira G., Hajenius P.J., Mol B.W.J., Ankum W.M., Hemrika D.J., Bossuyt P.M.M., van der Veen F. (1999) **Fertility outcome after systemic methotrexate and laparoscopic salpingostomy for tubal pregnancy.** The Lancet; 353:724-5

Dorfman S.F. (1983) **Deaths from ectopic pregnancy, United States 1979 to 1980.** Obstet Gynecol; 62(3):334-8

Dorfman S.F., Grimes D.A., Cates W. Jr, Binkin N.J., Kafrissen M.E., O'Reilly K.R. (1984) **Ectopic pregnancy mortality, United States 1979 to 1980: clinical aspects.** Obstet Gynecol; 64(3):386-90

Duthie S.J., Ghosh A., Ma H.K. (1989) **Maternal mortality in Hong Kong.** Br J Obstet Gynaecol; 96(1):4-8

Dwarakanath L.S., Mascarenhas L., Penketh R.J.A., Newton J.R. (1996) **Persistent ectopic pregnancy following conservative surgery for tubal pregnancy.** Br J Obstet Gynaecol; 103:1021-24

Egger M., Low N., Davey Smith G., Lindblom B., Herrmann B. (1998) **Screening for chlamydia infections and the risk of ectopic pregnancy in a county in Sweden: ecological analysis.** Br Med J; 316: 1776-90

Ego A., Subtil D., Cosson M., Legoueff F., Houfflin-Debarge V., Querleu D. (2001) **Survival analysis of fertility after ectopic pregnancy.** Fertil Steril; 75(3):560-566

Eriksen N.L., Parisi V.M., Daoust S., Flamm B., Garite T.J., Cox S.M. (1992) **Fetal fibronectin: a method for detecting the presence of amniotic fluid.** Obstet Gynecol; 80(3 pt1):451-4

Feinberg R.F., Wang C-L. (1994) **Monoclonal antibody FDC-6 exhibits binding to human plasma fibronectin: a caveat for cervicovaginal oncofetal testing.** Am J Obstet Gynecol; 171:1302-8

Feinberg R.F., Kliman H.J., Bedian V., Monzon-Bardonaba F., Menzin A.W., Wang C-L. (1995) **Monoclonal antibody X18A4 identifies an oncofetal fibronectin epitope distinct from the FDC-6 binding site.** Am J Obstet Gynecol; 172:1526-36

Fernandez H., Rainhorn J.D., Papiernik E., Bellet D., Frydman R. (1988) **Spontaneous resolution of ectopic pregnancy.** Fertil Steril; 71:171

Fernandez H., Bourget P., Ville Y., Lelaidier C., Frydman R. (1994) **Treatment of unruptured tubal pregnancy with methotrexate: pharmacokinetic analysis of local versus intramuscular administration.** Fertil Steril; 62:943-7

Fernandez H., Pauthier S., Doumerc S., Lelaidier C., Oliveness F., Ville Y., Frydman R. (1995) **Ultrasound-guided injection of methotrexate versus laparoscopic salpingectomy in ectopic pregnancy.** Fertil Steril; 63(1):25-9

[a]Fernandez H., Marchal L., Vincent Y. (1998) **Fertility after radical surgery for tubal pregnancy.** Fertil Steril; 70(4):680-6

[b]Fernandez H., Yves Vincent S.C., Pauthier S., Audibert F., Frydman R. (1998) **Randomized trial of conservative laparoscopic treatment and methotrexate administration in ectopic pregnancy and subsequent fertility.** Human Reproduction; 13(11):3239-43

Frank H.G., Malekzadeh F., Kertschanska S., Crescimanno C., Castellucci M., Lang I., Desoye G., Kaufmann P. (1994) **Immunohistochemistry of two different types of placental fibrinoid.** Acta Anatomica; 150(1):55-68

Garite T.J., Casal D., Garcia-Alonso A., Kreaden U., Jimenez G., Ayala J.A., Reimbold T. (1996) **Fetal fibronectin: a new tool for the prediction of successful induction of labour.** Am J Obstet Gynecol; 175(6):1516-21

Giuliani A., Panzitt T., Schoell W., Urdl W. (1998) **Severe bleeding from peritoneal implants of trophoblastic tissue after laparoscopic salpingostomy for ectopic pregnancy.** Fertil Steril; 70(2):369-70

Glock J.L., Johnson J.V., Brumsted J.R. (1994) **Efficacy and safety of single-dose systemic methotrexate in the treatment of ectopic pregnancy.** Fertil Steril; 62:716-21

Goddijin M., van der Veen F., Schuring-Blom G.H., Ankum W.M., Leschot N.J. (1996) **Cytogenetic characteristics of ectopic pregnancy.** Hum Reprod; 11(12): 2769-71

Goepfert A.R., Goldenberg R.L., Mercer B., Iams J., Meis P.,Moawad A., Thom E., VanDorsten P., Caritas S., Thurnau G., Miodovnik M., Dombrowski M., Roberts J.M., McNellis D. (2000) **The preterm prediction study: quantitative fetal fibronectin values and the prediction of spontaneous preterm birth.** Am J Obstet Gynecol; 183(6):1480-3

Goldner T.E. Lawson H.W., Xia Z. Atrash H.K. (1993) **Surveillance for ectopic pregnancy 1970-89.** Morbidity & Mortality Weekly Report. CDC Surveillance Summaries; 42(6):73-85

Goldenberg R.L., Mercer B.M., Meis P.J., Copper R.L., Das A., McNellis D. (1996) **The preterm prediction study: fetal fibronectin testing and spontaneous preterm birth.** Obstet Gynecol; 87 (5 pt 1):643-4

Goldenberg R.L., Mercer B.M., Iams J.D., Moawad A.H., Meis P.J., Das A. McNellis D., Miodovnik M., Menard M.K., Caritis S.N., Thurnau G.R., Bottoms S.F. (1997) **The preterm prediction study: patterns of cervicovaginal fetal fibronectin as predictors of spontaneous preterm delivery.** Am J Obstet Gynecol; 117(1):8-12

Graczykowski J.W. and Mishell D.R. (1997) **Methotrexate prophylaxis is for persistent ectopic pregnancy after conservative treatment by salpingostomy.** Obstet Gynecol; 89:51-54

Gross Z., Rodriguez J.D., Stalnaker B.L. (1995) **Ectopic pregnancy: non-surgical, outpatient evaluation and single-dose methotrexate treatment.** J Reprod Med; 40:371-4

Hahlin M., Wallin A., Sjoblom P., Lindblom B. (1990) **Single progesterone assays for early recognition of abnormal pregnancy.** Hum Reprod; 5:622-26

Hajenius P.J., Engelsbel S., Mol B.W.J., van der Veen F., Ankum W.M., Bossuyt P.M.M. Hemrika D.J., Lammes F.B. (1997) **Randomised trial of systemic methotrexate versus laparoscopic salpingostomy in tubal pregnancy.** Lancet; 350:774-79

Hajenius P.J., Mol B.W.J., Bossuyt P.M.M., Ankum W.M., van der Veen F. (2000) **Interventions for ectopic pregnancy.** The Cochrane Library; 2

Hately W., Case J., Campbell S. (1995) **Establishing the death of an embryo by ultrasound: report of a public inquiry with recommendations.** Ultrasound Obstet Gynecol; 5:353-7

Heath V.C.F., Daskalakis G., Zagaliki A., Carvalho M., Nicolaides K.H. (2000) **Cervicovaginal fibronectin and cervical length at 23 weeks of gestation: relative risk of early preterm delivery.** Br J Obstet Gynaecol; 107:1276-81

Hellemans P., Gerris J., Verdonk P. (2000) **Fetal Fibronectin detection for prediction of preterm birth in low risk women.** Br J Obstet Gynaecol 1995; 102:207-212

Hillis S.D., Owens L.M., Marchbanks P.A., Amsterdam L.F., Mac Kenzie W.R. (1997) **Recurrent chlamydial infections increase the risks of hospitalization for ectopic pregnancy and pelvic inflammatory disease.** Am J Obstet Gynecol; 176(1 pt 1): 103-7

HMSO (1996) **Report on the confidential enquiries into maternal deaths in the United Kingdom 1991-1993.** London

Honore L.H. (1979) **A significant association between spontaneous abortion and tubal ectopic pregnancy.** Fertil Steril; 32(4):401-2

Hoppe D.E., Bekkar B.E., Nager C.W. (1994) **Single-dose systemic methotrexate for the treatment of persistent ectopic pregnancy after conservative surgery.** Obstet Gynecol; 83:51-54

Horrigan T.J., Fanning J.D.O., Marcotte M.P. (1997) **Methotrexate pneumonitis after systemic treatment for ectopic pregnancy.** Am J Obstet Gynecol; 176(3):714-5

Isaacs J.D., McGehee R.P., Cowan B.D. (1996) **Life-threatening neutropenia following methotrexate treatment of ectopic pregnancy: a report of two cases.** Obstet Gynecol; 88(4 Pt 2):694-6

Job-Spira N., Bouyer J., Pouly J-L., Germain E., Coste J., Aublet-Cuvelier B., Fernandez H. (1996) **Fertility after ectopic pregnancy: first results of population-based cohort study in France.** Hum Reprod; 11:99-104

Joffe G.M., Jaques D., Bemis-Heys R. Burton R., Skram B. Shelburne P. (1999) **Impact of fetal fibronectin assay on admissions for preterm labour.** Am J Obstet Gynecol; 180(3 pt 1):581-6

Kadar N., DeVore G., Romero R. (1981) **Discriminatory hCG zone: its use in the sonographic evaluation for ectopic pregnancy.** Obstet Gynecol; 58:156-61

Kamwendo F., Forslin L., Bodin L., Danielsson D. (2000) **Epidemiology of ectopic pregnancy during a 28 tear period and the role of pelvic inflammatory disease.** Sexually Transmitted Infections; 76(1):28-32

Kaufman R.H., Adam E., Hatch E.E., Noller K., Herbst A.L., Palmer J.R., Hoover R.N. (2000) **Continued follow-up of pregnancy outcomes in diethylstilbestrol-exposed offspring.** Obstet Gynecol; 96(4):483-9

Kendrick J.S., Tierney E.F., Lawson H.W., Strauss L.T., Klein L., Atrash H.K. (1996) **Previous cesarean delivery and the risk of ectopic pregnancy.** Obstet Gynecol; 87(2): 297-301

Kline J., Stein Z., Susser M. 1989 **Conception to birth – epidemiology of prenatal development. Monographs in epidemiology and biostatistics**. Vol 14, OUP, Oxford

Kupferminc M.J., Peaceman A.M., Wigton T.R., Rehnberg K.A., Socol M.L. (1994) **Fetal fibronectin levels are elevated in maternal plasma and amniotic fluid of patients with severe preeclampsia.** In: Proceedings of the forty-first annual meeting of the Society for Gynecologic Investigation:161

Landorff P., Thorburn J., Hahlin M., Kallfelt B., Lindblom B. (1991) **Laparoscopic surgery in ectopic pregnancy. A randomised trial versus laparotomy.** Acta Obstet Gynecol Scand; 70:343-8

Lecuru F., Camette S., Viens-Bitker C., Chasset S., Leonard F., Taurelle R. (2001) **Hospital resources used for ectopic pregnancy treatment by laparoscopy and methotrexate.** J Soc Laparoendoscopic Surgeons; 5(2):117-22

Leeson S.C., Maresh M.J.A., Martindale E.A., Mahmood T., Muotune A., Hawkes N., Baldwin K.J. (1996) **Detection of fetal fibronectin as a predictor of preterm delivery in high risk asymptomatic pregnancies.** Br J Obstet Gynaecol; 103:48-53

Leibman A.J., Kruse B., McSweeney M.B. (1988) **Comparison with transabdominal sonography in the diagnosis of pelvic masses.** Am J Rad; 151:89-92

Lemus J.F. (2000) **Ectopic pregnancy: an update.** Current Opinion in Obstetrics and Gynaecology; 12(5):369-375

Lesny P., Killick S.R., Robinson J., Maguiness S.D. (1999) **Transcervical embryo transfer as a risk factor for ectopic pregnancy.** Fertil Steril; 72(2): 305-9

Levgur M., Tsai T., Kang K., Feldman j., Kory L.A. (2000) **Endometrial stripe thickness in tubal and intrauterine pregnancies.** Fertil Steril; 74(5):889-891

Lipscomb G.H., Bran D., McCord M.L., Portera J.C., Ling F.W. (1998) **Analysis of three hundred fifteen ectopic pregnancies treated with single-dose methotrexate.** Am J Obstet Gynecol; 178(6):1354-8

Lipscomb G.H., McCord M.L., Stovall T.G., Huff G., Portera S.G., Ling F.W. (1999) **Predictors of success of methotrexate treatment in women with tubal ectopic pregnancies.** N Eng J Med; 341(26):1974-8

Lipscomb G.H., Stovall T.G., Ling F.W. (2000) **Nonsurgical treatment of ectopic pregnancy.** N Engl J Med; 343(18):1325-9

Lockwood C.J., Senyei A.E., Dische M.R., Casal D., Shah K.D., Thung S.N., Jones L. Deligdisch L., Garite T.J. (1991) **Fetal fibronectin in cervical and vaginal secretions as a predictor of preterm delivery.** N Engl J Med; 325:669-674

Lockwood C.J., Moscarelli R.D., Wein R., Lynch L., Lapinski R.H., Ghidini A. (1994)**Low concentrations of vaginal fetal fibronectin as a predictor of deliveries occurring after 41 weeks.** Am J Obstet Gynecol; 171(1):1-4

Luciano A.A., Roy G., Solima E. (2001) **Ectopic pregnancy from surgical emergency to medical management.** Annals of New York Academy of Sciences; 943:235-54

Lund J.J. (1955) **Early ectopic pregnancy.** J Obstet Gynaecol Br Emp; 62:70-5

Lukes A.S., Thorp J.M., Eucker B., Pahel-Short L. (1997) **Predictors of positivity for fetal fibronectin in patients with symptoms of preterm labor.** Am J Obstet Gynecol; 176(3):639-641

Mäkinen J. (1989) **Increase in ectopic pregnancy in Finland – combination of time and cohort effects.** Obstet Gynecol; 73(1):21-4

Mäkinen J. (1996) **Ectopic pregnancy falls in Finland.** Lancet; 348: 129-130

Mäkinen J., Rantala M., Vanha-Kamppa O. (1998) **A link between the epidemic of ectopic pregnancy and the "baby-boom" cohort.** Am J Epidem; 148(4):369-74

Malak T.M., Sizmur F., Bell S.C., Taylor D.J. (1996) **Fetal fibronectin in cervicovaginal secretions as a predictor of preterm birth.** Br J Obstet Gynaecol; 103:648-653

Marcus S.F. and Brisden P. (1995) **Analysis of the incidence and risk factors associated with ectopic pregnancy following in-vitro fertilisation and embryo transfer.** Hum Reprod; 10: 199-203

Marcus S.F., Macnamee M., Brisden P. (1995) **The prediction of ectopic pregnancy after in-vitro fertilisation and embryo transfer.** Hum Reprod; 10(8):2156-8

Matsuura H., Hakomori S. (1985) **The oncofetal domain of fibronectin defined by monoclonal antibody FDC-6: its presence in fibronectins from fetal and tumor tissues and its absence in those from normal adult tissues and plasma.** Proceedings of the National Academy of Sciences of the United States of America; 82(19):6517-21

Matsuura H., Takio K., Titani K., Greene T., Levery S.B., Salyan M.E., Hakomori S. (1988) **The oncofetal structure of human fibronectin defined by monoclonal antibody FDC-6. Unique structural requirement for the antigenic specificity provided by a glycosylhexapeptide.** Journal of Biological Chemistry; 263(7):3314-22

Mehta T.S., Levine D., Beckwith B. (1997) **Treatment of ectopic pregnancy: is a human chorionic gonadotrophin level of 2,000 miu/ml a reasonable threshold?** Radiology; 205:569-573

Mehta T.S., Levine D., McArdle C.R. (1999) **Lack of sensitivity of endometrial thickness in predicting the presence of an ectopic pregnancy.** J Ultrasound Medicine; 18(2):117-22

[a]Mol B.W.J., Ankum W.M., van der Veen F., Hogerzeil H.V., Hajenius P.J., Hemrika D.J., Engelsbel S., Bossuyt P.M.M. (1997) **Diagnosis of ectopic**

pregnancy after in vitro fertilisation and embryo transfer. Fertil Steril; 68(6):1027-32

[b]Mol B.W.J., Hajenius P.J., Engelsbel S., Ankum W.M., Hemrika D.J., van der Veen F., Bossuyt P.M.M. (1997) **Is conservative surgery for tubal pregnancy preferable to salpingectomy? An economic analysis.** Br J Obstet Gynaecol; 104:834-39

[a]Mol B.W.J., Hajenius P.J., Engelsbel S., Ankum W.M., van der Veen F., Hemrika D.J., Bossuyt P.M.M. (1998) **Serum human chorionic gonadotrophin measurement in the diagnosis of ectopic pregnancy when transvaginal sonography is inconclusive.** Fertil Steril; 70(5):972-81

[b]Mol B.W.J., Matthijsse H.C., TingaD.J., Huynh T., Hajenius P.J., Ankum W.M., Bossuyt P.M.M., van der Veen F. (1998) **Fertility after conservative and radical surgery for tubal pregnancy.** Hum Reprod; 13(7): 1804-9

[a]Mol B.W.J., Hajenius P.J., Engelsbel S., Ankum W.M., van der Veen F., Hemrika D.J., Bossuyt P.M.M. (1999) **Should patients who are suspected of having an ectopic pregnancy undergo physical examination?** Fertil Steril; 71(1):155-7

[b]Mol B.W.J., Hajenius P.J., Engelsbel S., Ankum W.M., van der Veen F., Hemrika D.J., Bossuyt P.M.M. (1999) **Can noninvasive diagnostic tool predict tubal rupture or active bleeding in patients with tubal pregnancy?** Fertil Steril; 71(1):167-73

[c]Mol B.W.J., Hajenius P.J., Engelsbel S., Ankum W.M., Hemrika D.J., van der Veen F., Bossuyt P.M.M. (1999) **Treatment of tubal pregnancy in The Netherlands: an economic comparison of systemic methotrexate administration and laparoscopic salpingostomy.** Am J Obstet Gynecol; 181(4):945-51

[d]Mol B.W., van der Veen F., Bossuyt P.M. (1999) **Implementation of probabilistic decision rules improves the predictive values of algorithms**

in the diagnostic management of ectopic pregnancy. Hum Reprod; 14(11):2855-62

Morrison J.C., Albert J.R., McLaughlin B.N., Whitworth N.S., Roberts W.E., Martin R.W. (1993) **Oncofetal fibronectin in patients with false labor as a predictor of preterm delivery.** Am J Obstet Gynecol; 168:538-542

Murphy A.A., Nager C.W., Wujek J.J., Kettel L.M. Torp V.A., Chin H.G. (1992) **Operative laparoscopy versus laparotomy for the management of ectopic pregnancy: a prospective trial.** Feril Steril; 57:1180-5

Nageote M.P., Casal D., Senyei A.E. (1994) **Fetal fibronectin in patients at increased risk for premature birth.** Am J Obstet Gynecol; 170(1 pt 1):20-5

Ness R.B., McLaughlin M.T., Heine R.P., Bass D.C., Mortimer L. (1998) **Fetal fibronectin to discriminate between ectopic and intrauterine pregnancies.** Am J Obstet Gynecol; 179:697-702

[a]Nieuwkerk P.T., Hajenius P.J., Ankum W.M., van der Veen F., Wijker W., Bossuyt P.M.M. (1998) **Systemic methotrexate therapy versus laparoscopic salpingostomy in patients with tubal pregnancy. Part 1. Impact on patients' health-related quality of life.** Fertil Steril; 70(3):511-517

[b]Nieuwkerk P.T., Hajenius P.J., van der Veen F., Ankum W.M., Wijker W., Bossuyt P.M.M. (1998) **Systemic methotrexate therapy versus laparoscopic salpingostomy in patients with tubal pregnancy. Part 11. Patient preferences for systemic methotrexate.** Fertil Steril; 70(3):518-522

Nisell H., Hagskog K., Westgren M. (1996) **Assessment of fetal fibronectin in cervical secretion in cases of equivocal rupture of the membranes at term.** Acta Obstet Gynecol Scand; 75(2):132-4

Nowacek G.E., Meyer W.R., McMahon M.J., Thorp J.R., Wells S.R. (1999) **Diagnostic value of cervical fetal fibronectin in detecting extrauterine pregnancy.** Ferti Steril; 72(2):302-4

Nyberg D.A., Laing F.C., Filly R.A., Uri-Symmons M., Jeffrey R.B.Jr. (1983) **Ultrasonographic differentiation of the gestation sac of early intrauterine pregnancy from the pseudogestational sac of ectopic pregnancy.** Radiology; 146:755-759

Nyberg D.A, Mack L.A., Laing F.C., Jeffrey R.B. (1988) **Early pregnancy complications:endovagianal sonographic findings correlated with human chorionic gonadotropin levels.** Radiology; 167(3):619-22

O'Leary P.C., Boyne P., Flett P.T., Beilby J., James I. (1991) **Longitudinal assessment of changes in reproductive hormones during normal pregnancy.** Clin Chem; 37:667-72

O'Leary P., Nichols C., Feddema P., Lam T., Aitken M. (1996) **Serum progesterone and human chorionic gonadotrophin measurements in the evaluation of ectopic pregnancy.** Aust NZ Obstet Gynaecol; 36(3):319-23

Olofsson J.I., Poromaa I.S., Ottander U., Kjellberg L., Damber M.G. (2001) **Clinical and pregnancy outcome following ectopic pregnancy; a prospective study comparing expectancy, surgery and systemic methotrexate treatment.** Acta Obstet Gynecol Scan; 80(8):744-9

Ong S., Wingfield M. (1999) **Increasing incidence of ectopic pregnancy: is it iatrogenic?** Irish Medical Journal; 92(5): 364-5

Orr P.H., Brown R. (1998) **Incidence of ectopic pregnancy and sexually transmitted disease in the Canadian Central Artic.** International Journal of Circumpolar Health; 57 suppl 1: 127-34

Ory H.W. (1981) **Ectopic pregnancy and intrauterine contraceptive devices: new perspectives. The Women's Health Study.** Obstet Gynecol; 57(2):137-44

Ory S.J., Nnadj E., Herrmann R., O'Brien P.S., Melton L.J. (1993) **Fertility after ectopic pregnancy.** Fertil Steril; 60:231-5

Paidas M.J., Taylor R.N., Schwartzman H, Saleh A.A., Alvarez M., Lockwood C.J. (1994) **Third trimester fetal fibronectin (fFN) levels are associated with the development of preeclampsia (PE)** In: Proceedings of the forty-first annual meeting of the Society for Gynecologic Investigation: 390

Peaceman A.M., Andrews W.W., Thorp J.M., Cliver S.P., Lukes A., Iams J.D., Coultrip L., Erisken N., Holbrook R.H., Elliot J., Ingardia C., Pietrantoni M. (1997) **Fetal fibronectin as a predictor of preterm birth in patients with symptoms: a multicenter trial.** Am J Obstet Gynecol; 177(1):13-18

Perdu M., Camus E., Rozenberg P., Goffinet F., Chastang C., Philippe H-J., Nisand I. (1998) **Treating ectopic pregnancy with the combination of mifepristone and methotrexate: A phase II nonrandomized study.** Am J Obstet Gynecol; 179(3):640-3

Peterson H.B., Xia Z., Hughes J.M., Wilcox L.S., Tylor L.R., Trussell J. (1997) **The risk of ectopic pregnancy after tubal sterilisation. U.S. Collaborative Review of Sterilisation Working Group.** N Eng J Med; 336(11): 762-7

Pisarska M.D., Carson S.A., Buster J.E. (1998) **Ectopic pregnancy.** Lancet; 351:1115-20

Pittaway D.E., Reish R.L., Wentz A.C. (1985) **Doubling times of human chorionic gonadotropin increase in early viable intrauterine pregnancies.** Am J Obstet Gynecol; 132(3):299-302

Pons J.C., Goujard J., Derbanne C., Tournaire M. (1988) **[Outcome of pregnancy in patients exposed in utero to diethylstilbestrol. Survey by the National College of French Gynecologists and Obstetricians].** Journal de Gynecologie, Obstetrique et Biologie de la Reproduction; 17(3):307-16

Pouly J.L., Chapron C., Manhes H., Canis M., Wattiez A., Bruhat M-A. (1991) **Multifactorial analysis of fertility after conservative laparoscopic treatment of ectopic pregnancy in a series of 223 patients.** Fertil Steril; 56:453-60

Quan M. (1994) **Pelvic inflammatory disease: diagnosis and management.** J Am Board of Family Practice; 7(2):110-23

Rajkhowa M., Glass M.R., Rutherford A.J., Balen A.H., Sharma V., Cuckle H.S. (2000) **Trends in the incidence of ectopic pregnancy in England and Wales from 1966 to 1996.** Br J Obstet Gynaecol; 107:369-74

RCOG Press. **Why Mother's Die. Report on the confidential enquiries into maternal deaths in the United Kingdom 1997-1999.** London 2001

Regan L. (1997) **Sporadic and recurrent miscarriage** *in Problems in Early Pregnancy, Eds.* Grudzinskas J.G. and O'Brien P.M.S., RCOG Press, London, pages 31-52

Ribic-Pucelj M, Tomazevic T., Vogler A., Meden-Vrtovec H. (1995) **Risk factors for ectopic pregnancy after in vitro fertilisation and embryo transfer.** J Assist Reprod Genetics; 12(9): 594-8

Rossing M.A., Daling J.R., Voigt L.F., Stergachis A.S., Weiss N.S. (1993) **Current use of an intrauterine device and risk of tubal pregnancy.** Epidemiology; 4(3):252-8

Rubin G.L., Peterson H.B., Dorfman S.F., Layde P.M., Maze J.M., Ory H.W., Cates W. Jr. (1983) **Ectopic pregnancy in the United States 1970 through 1978.** J Am Med Ass; 249(13): 1725-9

Rukosuev V.S. (1992) **Immunofluorescent localization of collagen types I, III, IV, V, fibronectin, laminin, enactin and heparan sulphate proteoglycan in human immature placenta.** Experienta; 48(3):285-7

Ryan M. and Hughes J. (1997) **Using conjoint analysis to assess women's preferences for miscarriage management.** Health Economics; 6:261-73

Ryan M., McIntosh E., Shackley P. (1998) **Using conjoint analysis to elicit the views of health service users: an application to the patient health card.** Health Expectations; 1:117-29

Sandvei R., Ulstein M., Wollen A.L. (1987) **Ferility following ectopic pregnancy with special reference to previous use of an intra-uterine contraceptive device (IUCD).** Acta Obstet Gynecol Scand; 66(2):131-5

San Miguel F., Ryan M., McIntosh E. (1997) **Methodological issues in the use of conjoint analysis in health care: an application to women's preferences for the management of menorrhagia.** Health Economics Research Unit Discussion Paper; 06/97, University of Aberdeen

Saraj A.J., Wilcox J.G., Najmabadi S., Stein S.M., Johnson M.B., Paulson R.J. (1998) **Resolution of hormonal markers of ectopic gestation: a randomized trial comparing single-dose intramuscular methotrexate with salpingostomy.** Obstet Gynecol; 92(6):989-94

Schiff E., Shalev E., Bustan M., Tsabari A., Mashiach S., Weiner E. (1992) **Pharmacokinetics of methotrexate after local tubal injection for conservative treatment of ectopic pregnancy.** Fertil Steril; 57:688-90

Schneider J., Berger C.J., Catell C. (1977) **Maternal mortality due to ectopic pregnancy. A review of 102 deaths.** Obstet Gynecol; 49(5):557-61

Schoenfeld A., Mashiach R., Vardy M., Ovadia J. (1992) **Methotrexate pneumonitis in nonsurgical treatment of ectopic pregnancy.** Obstet Gynecol; 80 (3 Pt 2):520-1

Seifer D.B., Gutmann J.N., Doyle M.B., Jones E.E., Diamond M.P., DeCherney A.H. (1990) **Persistent ectopic pregnancy following linear salpingostomy.** Obstet Gynecol; 76:1121-5

Seifer D.B. (1997) **Persistent ectopic pregnancy: an argument for heightened vigilance and patient compliance.** Fertil Steril; 68:402-4

Shalev E., Peleg D., Tsabari A., Romano S., Bustan M. (1995) **Spontaneous resolution of ectopic tubal pregnancy: natural history.** Fertil Steril; 63(1):15-19

Shapiro H.I., Adler D.H. (1973) **Excision of an ectopic pregnancy through the laparoscope.** Am J Obstet Gynecol; 117:290-1

Shepherd R.W., Patton P.E., Novy M.J., Burry K.A. (1990) **Serial βhCG measurements in early pregnancy detection of ectopic pregnancy.** Obstet Gynecol; 3(1):417-20

Shinagawa S., Katagiri S., Noro S., Nishihira M. (1983) **An autopsy study of 306 cases of maternal death in Japan.** Acta Obstet Gynecol Japonica; 35(2):194-200

Simms I., Rogers P.A., Nicoll A. (1997) **The influence of demographic change and cumulative risk of pelvic inflammatory disease on the incidence of ectopic pregnancy.** Epidemiology and Infection; 119(1): 49-52

Sivin I. (1991) **Dose- and age-dependent ectopic pregnancy risks with intrauterine contraception.** Obstet Gynecol; 78(2):291-8

Skjeldestad F.E. (1997) **How effectively do copper intrauterine devices prevent ectopic pregnancy?** Acta Obstet Gynecol; 76(6):684-90

[a]Skjeldestad F.E., Kendrick J.S., Atrash H.K., Daltveit A.K. (1997) **Increasing incidence of ectopic pregnancy in one Norwegian county – a population based study, 1970-1993.** Acta Obstet Gynecol Scand; 76(2): 159-65

[b]Skjeldestad F.E., Gargiullo P.M., Kendrick J.S. (1997) **Multiple induced abortions as a risk factor for ectopic pregnancy. A prospective study.** Acta Obstet Gynecol Scand; 76(7): 691-6

Sobane A.A. (2000) **Factors influencing reproductive performance following previous ectopic pregnancy.** Saudi Medical Journal; 21(12):1130-4

[a]Sowter M.C., Farquhar C.M., Petrie K.J., Gudex G. (2001) **A randomised trial comparing single dose systemic methotrexate and laparoscopic surgery for the treatment of unruptured tubal pregnancy.** Br J Obstet Gynaecol; 108(2):192-203

[b]Sowter M.C., Farquhar C.M., Gudex G. (2001) An **economic evaluation of single dose systemic methotrexate and laparoscopic surgery for the treatment of unruptured ectopic pregnancy.** Br J Obstet Gynaecol; 108(2):204-12

Spandorfer S.D., Barnhart K.T. (1996) **Endometrial stripe thickness as a predictor of ectopic pregnancy.** Fertil Steril; 66(3):474-7

Stromme W.B. (1953) **Salpingostomy for tubal pregnancy: report of a successful case.** Obstet Gynecol; 87:757

Stromme W.B. (1973) **Conservative surgery for ectopic pregnancy. A twenty year review.** Obstet Gynecol; 41(2):215-23

Storeide O., Veholmen M., Eide M., Bergsjo P., Sandvei R. (1997) **The incidence of ectopic pregnancy in Horaland County, Norway 1976-1993.** Acta Obstet Gynecol Scan; 76(4): 345-9

Stovall T.G., Ling F.W., Gray L.A., Carson S.A., Buster J.E. (1991) **Methotrexate treatment of unruptured ectopic pregnancy: a report of 100 cases.** Obstet Gynecol; 77:749-53

[a]Stovall T.G., Ling F.W. (1993) **Ectopic pregnancy. Diagnostic and therapeutic algorithms minimizing surgical intervention.** J Reprod Med; 38(10):807-12

[b]Stovall T.G., Ling F.W. (1993) **Single-dose methotrexate: an expanded clinical trial.** Am J Obstet Gynecol; 168:1759-65

Strandell A., Thorburn J., Hamberger L. (1999) **Risk factors for ectopic pregnancy in assisted conception.** Fertil Steril; 71(2):282-6

Sultana C.J., Easley K., Collins R.L. (1992) **Outcome of laparoscopic versus traditional surgery for ectopic pregnancies.** Fertil Steril; 57:28-9

Tanaka T., Hayashi H., Kutsuzawa T., Fujimoto S., Ichinoe K. (1982) **Treatment of interstitial ectopic pregnancy with methotrexate: a report of a successful case.** Fertil Steril; 37:851-2

Tawfiq A., Agameya A-F., Claman P. (2000) **Predictors of treatment failure for ectopic pregnancy treated with single-dose methotrexate.** Fertil Steril; 74(5):877-80

The Stationary Office. (1998) **Why Mother's Die. Report on the confidential enquiries into maternal deaths in the United Kingdom 1994-1996.** London

Timor-Tritsch I.E., Yeh M.N., Peisner D.B. (1989) **The use of transvaginal ultrasonography in the diagnosis of ectopic pregnancy.** Obstet Gynecol; 161:157-61

Tulandi T. and Guralnick M. (1991) **Treatment of tubal ectopic pregnancy by salpingotomy with or without tubal suturing and salpingectomy.** Fertil Steril; 55:53-5

Turner M.J., Flannelly G.M., Wingfield M., Rasmussen M.J., Ryan R., Cullen S., Maguire R., Stronge J.M. (1991) **The miscarriage clinic: an audit of the first year.** Br J Obstet Gynaecol; 98:306-8

Urbach D.R. and Cohen M.M. (1999) **Is perforation of the appendix a risk factor for tubal infertility and ectopic pregnancy? An appraisal of the evidence.** Canadian J Surgery; 42(2):101-8

[a]Vermesh M. (1989) **Conservative management of ectopic pregnancy.** Fertil Steril; 51(4):559-67

[b]Vermesh M., Silva P.D., Rosen G.F., Stein A.L., Fossum G.T., Sauer M.V. (1989) **Management of unruptured ectopic gestation by linear salpingostomy: a prospective, randomised clinical trial of laparoscopy versus laparotomy.** Obstet Gynecol; 73:400-4

Walker G.J., Ashley D.E., McCaw A.M., Bernard G.W. (1986) **Maternal Mortality in Jamaica.** Lancet; 1(8479):486-8

Walker J.J. and Shillito J. (1997) **Early pregnancy assessment units: service and organisational aspects.** In *Problems in Early Pregnancy: Advances in Diagnosis and Management, Eds.* Grudzinskas J.G. and O'Brien P.M.S., RCOG Press, London, pages 160-173

Weston M. (2001) **The first trimester** In *Clinical Ultrasound Volume 3: A Comprehensive Text – Ultrasound in Obstetrics and Gynaecology, 2nd edition* ed. Meire H, Cosgrove DO, Dewbury K, Farrant P; Harcourt Health Sciences, Philadelphia, pages 153-187

Wren J. and Craven B. (1999) **A cost-effectiveness study of changing medical practice in early pregnancy.** Clinical Performance and Quality Health Care; 7(4):172-7

Wollen A.L. Flood P.R., Sandvei R., Steier J.A. (1984) **Morphological changes in tubal mucosa associated with use of intrauterine contraceptive devices.** Br J Obs Gynaecol; 91(11):1123-8

Xiong X., Buekens P., Wollast E. (1995) **IUD use and the risk of ectopic pregnancy: a meta-analysis of case-control studies.** Contraception; 52(1): 23-34

Yamada T., Isemura M., Yamaguchi Y., Munakata H., Hayashi N., Kyogoku M. (1987) **Immunohistochemical localisation of fibronectin in the human placentas at their different stages of maturation.** Histochemistry; 86:579-584

Yao M. and Tulandi T. (1997) **Current status of surgical and nonsurgical management of ectopic pregnancy.** Fertil Steril; 67 (3):421-33

Yeko T.R., Gomil M.W., Hughes L.H., Rodi A., Bustan S.E. Sauer M.V. (1987) **Timely diagnosis of early ectopic pregnancy using a single blood progesterone measurement.** Fertil Steril; 48:1048-50

Ylöstalo P., Cacciatore B., Koskimies A., Kääriäinen M., Lehtovitra P., Mäkelä P., Siegberg R., Stenman U-H., Tenhunen A., Ylikorkala O. (1991) **Conservative treatment of ectopic pregnancy.** Annals New York Academy Sciences; XI:516-23

Ylöstalo P., Cacciatore B., Sjoberg J., Kääriäinen M., Tenhunen A., Stenman U-H. (1992) **Expectant management of ectopic pregnancy.** Obstet Gynecol; 80(3 pt 1):345-8

Zegers-Hochschild F., Altieri E., Fabres C., Fernádez E., Mackenna A., Orihuela P. (1994) **Predictive value of human chorionic gonadotrophin in the outcome of early pregnancy after in-vitro fertilisation and spontaneous conception.** Hum Reprod; 9(8):1550-5

Zhang J., Thomas A.G., Leybovich E. (1997) **Vaginal douching and adverse health effects: a meta-analysis.** Am J Public Health; 87(7):1207-11

HOSPITAL SURVEY OF EARLY PREGNANCY UNITS

Thankyou for taking time to complete this questionnaire

Name and address of Hospital

- **Does your hospital have an Early Pregnancy Assessment Unit (ie provision for women with problems in early pregnancy to be assessed without an inpatient admission)?**

yes / no *please ring*

1. If your hospital does have an EARLY PREGNANCY UNIT:

- **please indicate when your Early Pregnancy Unit is open and the times that ultrasound scanning is available within the Early Pregnancy Unit:**

Day	Time Open	Time Scanning Available
Monday		
Tuesday		
Wednesday		
Thursday		
Friday		
Saturday		
Sunday		

2. Thinking about ultrasound assessment in all units

➢ **If :**

- **either your unit does not have an Early Pregnancy Unit,**
- **or, for units with an Early Pregnancy Unit, at times when this unit is closed,**

please indicate when you would expect to have access to ultrasound assessment:
(eg scanning in the main ultrasound department, scanning on the ward which is dependent on whether an appropriately trained member of staff being on call)

day	Time scanning *always* available	Time scanning *might* be available
Monday		
Tuesday		
Wednesday		
Thursday		
Friday		
Saturday		
Sunday		

➢ **Does your unit have access to trans-vaginal ultra-sound scanning?**

Please tick the box closest to your situation

Yes – whenever indicated	
Yes – limited access	
No	

3. Thinking about ectopic pregnancy

- **If a diagnosis of ectopic pregnancy is suspected in an asymptomatic patient, please indicate which of the following might be considered in your unit.**
  Tick as many options as necessary

	Not available	Single use	Serial use
Ultrasound			
serum βhCG level			
Urine βhCG			
serum progesterone level			

- **Does your unit have a written protocol for the diagnosis and management of ectopic pregnancy?**

yes / no *please circle*

If your unit does have a written protocol, please could you enclose a copy.

- **If an *asymptomatic* woman has a suspected ectopic pregnancy, but further review is indicated before a diagnostic procedure, how would she be managed in your unit:**

As an in-patient	
As an out-patient	

4. Medical Management of Ectopic Pregnancy

- **Does your unit ever manage confirmed ectopic pregnancy medically?**

yes / no *please circle*

- **If yes, please indicate the method/s used:**

Local methotrexate	
Systemic methotrexate	
Other local agent	Please specify
Other systemic agent	Please specify

5. Surgical Management of Ectopic Pregnancy

The next question is about the laparoscopic management, <u>not diagnosis</u>, of ectopic pregnancy

➢ **Does your unit manage confirmed ectopic pregnancies laparoscopically?**

Yes – if appropriate, always	
Yes – if appropriate, sometimes	
no	

- **If yes, please indicate which doctors, in your unit, are able to manage ectopic pregnancies laparoscopically**

	Number in unit	Number managing ectopic pregnancy laparoscopically
Consultants		
Middle grades		

- **If your unit manages ectopic pregnancy laparoscopically, but is not able to do so on every appropriate occasion, please indicate why:**
  (you may tick more than one)

Appropriately trained staff not always available	
Facilities only available in normal working hours	
Facilities only available out of normal working hours	

➢ **During the surgical diagnosis or management of ectopic pregnancy, is it the policy of your unit to record the state of the patients *<u>affected</u>* tube?**

yes / no *please circle*

➢ **During the surgical diagnosis or management of ectopic pregnancy, is it the policy of your unit to record the state of the patients *<u>unaffected</u>* tube?**

yes / no *please circle*

If yes:

- **Would these findings be routinely discussed with the patient after the operation?**

yes / no *please circle*

- **Would the implications of these findings, with regard to her future fertility, be routinely discussed with her?**

Yes – post-operatively	
Yes – at an out-patient	
no	

6. Follow-up after an Ectopic Pregnancy

➢ **If a woman has had an ectopic pregnancy, how long would you advise her to wait before trying for another pregnancy?**

No wait	
After next period	
Specified time	Please indicate how long _____

➢ **Do you offer a follow-up out-patient appointment for women who have had an ectopic pregnancy?**

yes / no *please circle*

➢ **Do you offer an early pregnancy ultrasound scan, to women who have had an ectopic pregnancy, in their next pregnancy?**

yes / no *please circle*

➢ **Is counselling offered to women who have had an ectopic pregnancy**

yes / no *please circle*

- **If you have answered yes, please state who does the counselling (eg Early Pregnancy Unit nurse, psychologist etc)**

_____

- ***Is this person trained in counselling?***

yes / no *please circle*

- **Does your unit have information leaflets for patients who have had an ectopic pregnancy?**

Yes – produced by the unit	
Yes – produced by an external agency	Who?_ _ _ _ _ _ _ _ _ _ _ _
no	

- **Are there support groups available to women in your area who have had ectopic pregnancies?**

yes / no *please circle*

- **If yes, please state the name(s) of this (these) support groups:**

	local / national
	local / national
	local / national
	local / national

- **Is it the policy of your unit to pass on information about support groups to patients who have had an ectopic pregnancy?**

yes / no *please circle*

- **Are you aware of the existence of:**

The Miscarriage Association? yes / no

The Ectopic Pregnancy Trust? yes / no

please circle

7. Research into Problems in Early Pregnancy

- **Would your unit be interested in taking part in a trial looking at**

Ectopic pregnancy yes / no

Miscarriage yes / no

please circle

- **If you have answered yes to either of these, please could you identify a person we could contact in your unit**

Research Questionnaire

The Ectopic Pregnancy Trust c/o Hillingdon Hospital, Maternity Unit
Pield Heath Road Uxbridge, Middlesex, UB8 3NN

Registered Charity No 1071811 Telephone No: 01895 238025

1. PERSONAL DETAILS

Name:

Address:
(your name and address are useful for us to contact you in the future. Please do not complete if you wish to remain anonymous)

Date of Birth.

Ethnic Origin:

(not place of birth, but the ethnic group to which you belong)

- Black African ☐
- Black Afro-Caribbean ☐
- Black Other ☐
- European ☐
- Indian ☐
- Pakistani ☐
- Bangladesh ☐
- Oriental ☐
- Mediterranean ☐
- White/Other ☐

Other, please specify

Do you smoke:

- Yes ☐
- No ☐
- Given Up ☐

Do you know anyone else personally who has had an ectopic pregnancy?

- No ☐
- Mother ☐
- Daughter ☐
- Sister ☐
- Other Blood Relative ☐
- Other Relative ☐
- Friend ☐

Have you suffered from or received treatment for any of the following conditions prior to your 1st Ectopic Pregnancy?

(If you have received fertility treatment, it may be necessary to contact you at a later stage in relation to the type of treatment you may have had)

- Pelvic Infection ☐
- Endometriosis ☐
- Had a Coil (IUCD) ☐
- Used the Mini Pill ☐
- Chlamydia ☐
- Caesarean Section ☐
- Appendicitis ☐
- Abortion ☐
- Miscarriage ☐
- Abdominal Surgery ☐
- Tubal Surgery ☐
- Fertility Treatment ☐
- D & C ☐
- Sterilisation ☐

2. PREGNANCIES YOU HAVE HAD

How many pregnancies have you had?

Type of Pregnancy	Total	No. Before 1st Ectopic	No. After 1st Ectopic
Live Births			
Ectopics			
Miscarriages			
Still Births			
Terminations			

If you have had more than one ectopic pregnancy please list them in date order

- 1st Date: _____
- 2nd Date: _____
- 3rd Date: _____
- 4th Date: _____

3. EXPERIENCES OF YOUR 1ST ECTOPIC PREGNANCY

The following questions are about your experience of your 1st Ectopic Pregnancy. If you have had more than one Ectopic Pregnancy then please complete a separate sheet for each one. Additional sheets can be obtained from The Ectopic Pregnancy Trust.

Before your 1st ectopic pregnancy did you know what an ectopic pregnancy was?

Yes ☐ No ☐

What symptoms did you have when you were first seen by a Health Care Professional?

You may tick more than one answer.

- Abdominal Pain ☐
- Vaginal Bleeding ☐
- Bowel Problems ☐
- Feeling Faint ☐
- Vomiting ☐
- Pain in the Shoulder ☐
- Feeling Unwell ☐
- Fainting ☐
- Late period ☐
- To report being pregnant ☐
- To have scan because of previous ectopic ☐
- Scan following IVF or other infertility treatment ☐
- Sudden Collapse ☐

Please give details of any other symptoms you had?

By which Health Care Professional were you first seen?

- GP ☐
- Midwife ☐
- Practice Nurse ☐
- Casualty doctor ☐
- Gynaecology doctor ☐
- Emergency Admission with collapse - don't know ☐
- Don't know ☐
- Other (please specify) ☐

Did you know/or suspect you were pregnant when you were first seen by a Health Care Professional?

- Knew I was pregnant ☐
- Suspected I was pregnant ☐
- Did not know ☐

Were you asked if you were/or could be pregnant? Yes ☐ No ☐

Was a pregnancy test done at this time? Yes ☐ No ☐

If you knew you were pregnant did you inform anyone? Yes ☐ No ☐
If yes, who?

Did you suspect it was an ectopic pregnancy? Yes ☐ No ☐

If it was the hospital you attended first, which department were you seen in?

- A & E/Casualty ☐
- Early Pregnancy Unit ☐
- Antenatal Clinic ☐
- Gynaecology ☐

Which hospital did you attend?

What colour best describes the bleeding you had?

- Bright Red ☐
- Dark Red ☐
- Prune Juice ☐
- Other ☐

What was the initial diagnosis?

- Ectopic Pregnancy ☐
- Suspected Ectopic ☐
- Womb Infection ☐
- Gastro Problems ☐
- Food Poisoning ☐
- Appendicitis ☐
- Irritable Bowel Syndrome ☐
- Possible Miscarriage ☐
- Ovarian Cysts ☐
- Menstrual Disturbance ☐
- Normal Pregnancy ☐
- Treated for Miscarriage and recalled ☐
- Treated for Miscarriage and not recalled ☐
- Other (please specify) ☐

Who first suspected your ectopic pregnancy?

- GP ☐
- Midwife ☐
- Practice Nurse ☐
- Casualty doctor ☐
- Gynaecology doctor ☐
- Other (please specify) ☐

How many weeks pregnant were you when diagnosed with your ectopic pregnancy?

3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 ☐ 11 ☐ 12 ☐
More than 12 weeks ☐
Don't Know ☐

At what stage of your pregnancy did your symptoms first appear?

3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 ☐ 11 ☐ 12 ☐
More than 12 weeks ☐
Don't Know ☐

What tests were carried out and by whom?

GP
- Urine Pregnancy Test ☐
- Single Blood Preg. Test ☐
- Serial Blood Preg. Tests ☐
- Internal ☐
- None ☐

HOSPITAL
- Urine Pregnancy Test ☐
- Single Blood Preg. Test ☐
- Serial Blood Preg. Tests ☐
- Internal ☐
- Abdominal ultra-sound scan ☐
- Vaginal (internal) ultra-sound scan ☐
- None ☐

Please state how many times you visited your GP and/or Hospital before your ectopic pregnancy was considered?

GP _____

Hospital _____

Were you seen in or referred to an Early Pregnancy Unit?

- Yes ☐
- No ☐

4. AFTER THE DIAGNOSIS

Once diagnosed, was ectopic pregnancy fully explained to you?

- Yes ☐
- No ☐

If you were given any information, how was this given to you?

- Verbally ☐
- Written ☐

Were you given any options as to the treatment of your ectopic pregnancy?

(Not all treatments are available in every hospital)

(You may tick more than one answer)

- None ☐
- Collapsed - Urgent surgery required ☐

SURGERY
- Keyhole ☐
- Abdominal Incision ☐
- Removal of tube ☐
- To keep tube ☐

MEDICAL
- Methotrexate ☐
- Wait and see if ectopic would settle without treatment ☐

What treatment did you actually receive for your Ectopic pregnancy?

- Don't Know ☐

SURGERY
- Keyhole ☐
- Abdominal Incision ☐
- Removal of tube ☐
- To keep tube ☐

MEDICAL
- Methotrexate ☐
- Wait and see if ectopic would settle without treatment ☐

Did your tube rupture?

Yes ☐
No ☐
Don't Know ☐

Was your tube removed?

No ☐
Partially removed ☐
Removed Completely ☐
Don't Know ☐

Which tube was affected?

Right ☐
Left ☐
Don't Know ☐

Do you feel you were given an adequate explanation of the treatment?

Yes ☐
No ☐
Don't Know ☐

5. AFTER YOUR TREATMENT

Were you informed of the risks of future ectopics?

Yes ☐ No ☐

Were you advised to have an early scan when you next became pregnant to check it was in the right place?

Yes ☐
No ☐
Don't know ☐

Did the health professional who looked after you, give you information about local or national support groups?

Yes ☐
No ☐

Were you given any written information about ectopic pregnancies prior to leaving the hospital?

Yes ☐ No ☐
(If yes, from which organisation)

6. PREGNANCIES YOU HAD AFTER THIS ECTOPIC

Please read all the options before deciding which one is to your situation.

NO
My family is complete ☐
To scared to try again ☐
Having difficulty conceiving ☐
To soon after ectopic ☐

YES - I have conceived naturally:-

Number of Children = ___

Number of Miscarriages = ___

Number of Ectopics = ___

YES - I have needed assisted conception, ie IVF:-

Number of Children = ___

Number of Miscarriages = ___

Number of Ectopics = ___

Have you suffered from any medical problems since having your ectopic that you did not have before and that you feel could be associated with your ectopic pregnancy?

Yes ☐ No ☐
(If yes, please give details)

HOW HAS THE ECTOPIC PREGNANCY TRUST HELPED YOU?

If you contacted the Trust please indicate the ways in which they helped you?

Provided you with written information which you did not have ☐
Offered support over the telephone? ☐
Put you in touch with someone else who had had an Ectopic Pregnancy ☐

Do you think there is a need for the Ectopic Pregnancy Trust and if so what facilities should they provide?

Information Line ☐
Support Groups Locally ☐
Information ☐
Research ☐
One to One Contact with other women who have had Ectopics ☐

Other (please specify)

Would you be interested in becoming a member of The Ectopic Pregnancy Trust?

Yes ☐ (Please send me an application form)
No ☐

Would you have any objection to us contacting you in the future should we require any further information in relation to the answers you have given in this questionnaire?

YES ☐ NO ☐

7. HOW HAS THE ECTOPIC PREGNANCY AFFECTED YOUR LIFE

Please list the ten most important changes to your quality of life and wellbeing that have resulted from your ectopic pregnancy. Please start with the most important changes and continue on a separate sheet, if necessary

Areas you might consider are:-

a) Physical changes - eg abdominal pain.
b) Emotional changes - eg worries about becoming pregnant again.
c) Effect on your family - eg sexual relationship with your partner.

MAY WE TAKE THIS OPPORTUNITY OF THANKING YOU FOR COMPLETING THIS QUESTIONNAIRE AND SHOULD YOU HAVE ANY QUESTIONS RELATING TO IT THEN PLEASE CONTACT OUR OFFICE. BY COMPILING THE DATA GIVEN IN THIS QUESTIONNAIRE IT IS HOPED THAT WE CAN HELP TO DIAGNOSE ECTOPIC PREGNANCIES EARLIER AND MAKE ADVANCES IN THE TREATMENT AND MANAGEMENT OF ECTOPIC PREGNANCIES

Samples tested on more than one occasion, with date of testing.

number	Samples tested on more than one occasion, fFN mcg/ml against date tested										
	19/11/98	17/12/98	14/1/99	28/1/99	3/6/99	1/7/99	15/7/99	29/7/99	12/11/99	28/1/00	15/6/00
33423				0.26							0.16
104902				<0.05							<0.05
111111			0.085					0.07			
111254									<0.05		<0.05
241132										0	<0.05
317629				0.23				0.23			
374314				>1							0.825
381493			0.495					0.445			0.405
397099					0.13	0.245		0.295	0.215		
407680							0.23	0.2			
429131					0.42	0.63		0.445			
470749				0.065				0.06			0.07
493960					0.215	0.52		0.31			
524214				0.08				0.09			
560626					0.75	0.2		0.21			
567373				0.185							0.105
640240				<0.05							0.405
667849					<0.05						<0.05
674183										<0.05	<0.05
680294			0.765					0.75			0.66
698413			0.075					0.085			
702552				0.675				0.9			
750781										<0.05	<0.05
758313			0.155					0.145			
772111			0.145	0.125				0.175			
773649				>1							>1
796819				0.715				0.825			

number	Samples tested on more than one occasion, fFN mcg/ml against date tested										
	19/11/98	17/12/98	14/1/99	28/1/99	3/6/99	1/7/99	15/7/99	29/7/99	12/11/99	28/1/00	15/6/00
824588										0.06	0.11
836706							0.735	0.555			
857265										<0.05	<0.05
878917			0	<0.05							
880451							0.165	0.15			
931596			0.145					0.16			
932822		0.115						0.1			
941059			<0.05	<0.05							
941901				0.11				0.09			
943658				0.7				0.75			
944017			<0.05	<0.05							
945764			0	<0.05							
945906			<0.05	<0.05							<0.05
947432			0.375					0.51			
948454				>1							>1
948459				<0.05							<0.05
948541					0.12	0.28					
952540					0.05	0.165		0.15			
952556					0.185	0.27		0.275			
960087							0.925	>1			
963022										<0.05	<0.05
Plasma samples - tested in duplicate											
13149						0.76				>1	
										0.975	
958370						0.5				0.48	
										0.45	
958384						0.475				0.585	
										0.55	
958421						0.39				0.51	
										0.52	

Samples tested in duplicate at a single assay run

number	date	value 1 (absorbance nm)	value 2 (absorbance nm)
960087	29/07/99	0.735	0.724
952556	29/07/99	0.215	0.207
952540	29/07/99	0.139	0.133
947432	29/07/99	0.352	0.355
943658	29/07/99	0.5	0.506
941901	29/07/99	0.102	0.104
932822	29/07/99	0.109	0.108
880451	29/07/99	0.139	0.137
796819	29/07/99	0.54	0.564
772111	29/07/99	0.152	0.156
702552	29/07/99	0.568	0.626
698413	29/07/99	0.088	0.105
560626	29/07/99	0.162	0.185
524214	29/07/99	0.103	0.101
493960	29/07/99	0.231	0.232
429131	29/07/99	0.308	0.321
407680	29/07/99	0.185	0.173
397099	29/07/99	0.163	0.289
312629	29/07/99	0.185	0.18
111111	29/07/99	0.086	0.091
968644	15/06/00	0.949	1.005
965716	15/06/00	0.053	0.066
952487	15/06/00	0.067	0.066
946242	15/06/00	0.073	0.075
934248	15/06/00	0.086	0.079
910823	15/06/00	0.067	0.066
903126	15/06/00	0.331	0.337
871831	15/06/00	0.129	0.126
713745	15/06/00	0.346	0.358
646157	15/06/00	0.125	0.149
619048	15/06/00	0.117	0.098
582071	15/06/00	0.121	0.122
497569	15/06/00	0.472	0.436
331234	15/06/00	0.076	0.08

Plasma samples tested in duplicate at a single assay run

number	date	Value 1 (absorbance nm)	Value 2 (absorbance nm)
958421	28/01/00	0.145	0.147
958384	28/01/00	0.174	0.16
958370	28/01/00	0.14	0.127
913149	28/01/00	0.306	0.297

Samples from women attending the FCU.

unit number	date	gestation	fFN µg/ml
674036	13.1.99	5-6 weeks	0
435187	31.3.99	5-6 weeks	<0.05
491698	4.11.98	5-6 weeks	<0.05
238532	11.11.98	6-7 weeks	0
943655	11.11.98	6-7 weeks	0
871850	13.1.99	6-7 weeks	<0.05
941902	21.10.98	6-7 weeks	<0.05
941924	21.10.98	6-7 weeks	<0.05
943226	18.11.98	6-7 weeks	<0.05
702552	27.1.99	6-7 weeks	0.675
943650	18.11.98	6-7 weeks	1
945764	16.12.98	7-8 weeks	0
455223	17.3.99	7-8 weeks	<0.05
784545	18.11.98	7-8 weeks	<0.05
902756	17.3.99	7-8 weeks	<0.05
942658	4.11.98	7-8 weeks	<0.05
944017	18.11.98	7-8 weeks	<0.05
945907	16.12.98	7-8 weeks	<0.05
946641	16.12.98	7-8 weeks	<0.05
948459	27.1.99	7-8 weeks	<0.05
953175	31.3.99	7-8 weeks	<0.05
381493	13.1.99	7-8 weeks	0.495
243612	13.1.99	8-9 weeks	0
733059	14.7.99	8-9 weeks	0
959249	14.7.99	8-9 weeks	0
959250	14.7.99	8-9 weeks	0
445539	31.3.99	8-9 weeks	<0.05
493839	14.7.99	8-9 weeks	<0.05
528679	11.11.98	8-9 weeks	<0.05
544387	21.10.98	8-9 weeks	<0.05
547006	16.12.98	8-9 weeks	<0.05
601618	16.12.98	8-9 weeks	<0.05
611492	27.1.99	8-9 weeks	<0.05
667849	31.3.99	8-9 weeks	<0.05
671369	11.11.98	8-9 weeks	<0.05
771208	31.3.99	8-9 weeks	<0.05
942659	4.11.98	8-9 weeks	<0.05
943957	18.11.98	8-9 weeks	<0.05
947440	13.1.99	8-9 weeks	<0.05
947908	3.2.99	8-9 weeks	<0.05
948458	27.1.99	8-9 weeks	<0.05
959244	14.7.99	8-9 weeks	<0.05
890416	18.11.98	8-9 weeks	1

unit number	date	gestation	fFN µg/ml
840368	17.3.99	9-10 weeks	0
878917	13.1.99	9-10 weeks	0
111119	3.2.99	9-10 weeks	<0.05
306308	16.12.98	9-10 weeks	<0.05
629887	3.2.99	9-10 weeks	<0.05
733823	4.11.98	9-10 weeks	<0.05
863524	13.1.99	9-10 weeks	<0.05
927226	17.3.99	9-10 weeks	<0.05
948511	3.2.99	9-10 weeks	<0.05
948542	3.2.99	9-10 weeks	<0.05
951762	17.3.99	9-10 weeks	<0.05
470749	21.10.98	9-10 weeks	0.065
698413	13.1.99	9-10 weeks	0.075
932822	11.11.98	9-10 weeks	0.115
680294	16.12.98	9-10 weeks	0.765
773649	27.1.99	9-10 weeks	1
948454	27.1.99	9-10 weeks	1
951765	17.3.99	9-10 weeks	1
951817	17.3.99	9-10 weeks	1
751062	14.7.99	10-11 weeks	0
794306	27.1.99	10-11 weeks	0
804054	31.3.99	10-11 weeks	0
941289	21.10.99	10-11 weeks	0
578361	3.2.99	10-11 weeks	<0.05
945906	16.12.98	10-11 weeks	<0.05
946640	16.12.98	10-11 weeks	<0.05
948512	3.2.99	10-11 weeks	<0.05
948513	3.2.99	10-11 weeks	<0.05
959248	14.7.99	10-11 weeks	<0.05
941901	21.10.98	10-11 weeks	0.11
943658	11.11.98	10-11 weeks	0.7
959247	14.7.99	11-12 weeks	0
353114	17.3.99	11-12 weeks	<0.05
947445	13.1.99	11-12 weeks	<0.05
948456	27.1.99	11-12 weeks	<0.05
948510	3.2.99	11-12 weeks	<0.05
951818	17.3.99	11-12 weeks	<0.05
947443	13.1.999	11-12 weeks IUCD in situ	<0.05
650626	3.2.99	11-12 weeks	0.075
374314	21.10.98	11-12 weeks	1
560408	16.12.98	12-13 weeks	<0.05
951764	17.3.99	12-13 weeks	<0.05
856525	18.11.98	13-14 weeks	<0.05
943656	11.11.98	13-14 weeks	<0.05

unit number	date	gestation	fFN µg/ml
952540	31.3.99	13-14 weeks	0.05
952556	31.3.99	13-14 weeks	0.185
692315	3.2.99	14-15 weeks	0
544450	31.3.99	14-15 weeks	<0.05
959245	14.7.99	15-16 weeks	0

Samples from women attending the recurrent miscarriage clinic

number	date	gestation	outcome	absorbance nm	fFN mg/ml
554699	15/06/99	3 - 4	miscarriage – FH not seen	0	0
111114	29/12/98	4 - 5	miscarriage – FH not seen	0.018	<0.05
949908	15/03/99	4 - 5	ongoing	0.036	<0.05
772566	14/12/98	4 - 5	missed FH seen prior to loss	0.013	<0.05
927417	19/10/99	4 - 5	ongoing	0.003	<0.05
948758	27/04/99	4 - 5	ongoing	0.023	<0.05
752238	12/01/98	4 - 5	miscarriage – FH not seen	0	0
848172	08/02/99	4 - 5	ongoing	0.012	<0.05
878675	02/11/99	4 - 5	ongoing	0.014	<0.05
941055	22/02/99	4 - 5	ongoing	0.036	<0.05
111254	26/07/99	4 - 5	ongoing	0.013	<0.05
772566	05/10/99	4 - 5	missed FH seen prior to loss	0.016	<0.05
948756	13/04/99	4 - 5	ongoing	0.009	<0.05
524127	02/08/99	4 - 5	ongoing	0	0
854108	06/07/99	4 - 5	ongoing	0.003	<0.05
949910	14/06/99	4 - 5	ongoing	0	0
949889	16/08/99	4 - 5	miscarriage – FH not seen	0.026	0.05
938876	21/10/99	5 - 6	miscarriage – FH not seen	0.026	0.05
111115	30/12/98	5 - 6	miscarriage – FH not seen	0.009	<0.05
771068	09/03/99	5 - 6	ongoing	0.038	<0.05
880451	05/07/99	5 - 6	ongoing	0.056	0.165
917067	07/12/98	5 - 6	miscarriage – FH not seen	0	0
511345	28/06/99	5 - 6	ongoing	0	0
432113	23/08/99	5 - 6	miscarriage – FH not seen	0.169	0.35
929722	17/08/99	5 - 6	ongoing	0.025	<0.05
946242	15/05/00	5 - 6	ongoing	0.073	<0.05
407680	12/07/99	5 - 6	ongoing	0.086	0.23
713745	13/02/00	5 - 6	miscarriage – FH not seen	0.346	0.2
943293	15/04/99	5 - 6	2nd sac collapsing, other ongoing	0.007	<0.05
329896	27/09/99	5 - 6	ongoing	0.005	<0.05
658206	23/08/99	5 - 6	ongoing	0	0
903126	14/02/00	5 - 6	ongoing	0.331	0.185
582473	26/04/99	5 - 6	ongoing	0.032	<0.05
646157	03/02/00	5 - 6	miscarriage – FH not seen	0.125	<0.05
935712	04/05/99	5 - 6	ongoing (anencephalic)	0	0
941059	07/12/98	5 - 6	missed FH seen prior to loss	0.008	<0.05
917067	14/06/99	5 - 6	ongoing	0	0
111113	26/11/98	5 - 6	miscarriage – FH not seen	0	0
358083	15/03/99	5 - 6	ongoing	0	0

number	date	gestation	outcome	absorbance nm	fFN mg/ml
773736	17/05/99	5 - 6	ongoing	0.085	0.1
949909	20/04/99	5 - 6	ongoing	0.013	<0.05
963022	06/12/00	5 - 6	missed FH seen prior to loss	0	0
33423	06/12/99	6 - 7	miscarriage – FH not seen	0.623	0.26
876548	02/02/99	6 - 7	ongoing	0.026	<0.05
241132	20/12/99	6 - 7	ectopic	0	<0.05
889695	13/04/99	6 - 7	ongoing	0.026	<0.05
935719	30/03/99	6 - 7	missed FH seen prior to loss	0.017	<0.05
952487	20/03/00	6 - 7	ongoing	0.067	<0.05
331234	20/03/00	6 - 7	ongoing	0.076	<0.05
968644	14/02/00	6 - 7	ongoing	0.949	0.785
945046	16/08/99	6 - 7	missed FH seen prior to loss	0	0
144541	29/03/99	6 - 7	ongoing	0.008	<0.05
144544	29/03/99	6 - 7	ongoing	0.08	<0.05
564234	13/12/99	6 - 7	ongoing	0.272	0.89
910823	04/05/00	6 - 7	ongoing	0.067	<0.05
861931	16/09/99	6 - 7	ectopic	0.015	<0.05
619048	27/04/00	> 7	ongoing	0.117	<0.05
965716	24/01/00	> 7	ongoing	0.053	0
857265	06/12/00	> 7	ongoing	0	0
567373	06/12/99	> 7	ongoing	0.041	0.105
934248	10/04/00	> 7	ongoing	0.086	<0.05
420725	16/08/99	> 7	ongoing	0.409	0.81
836706	05/07/99	> 7	ongoing	0.329	0.735
871831	21/02/00	> 7	missed FH seen prior to loss	0.129	<0.05
582071	16/03/00	> 7	ongoing	0.121	<0.05

Samples taken from women in which there was either diagnostic dilemma, or a diagnosis of miscarriage had been made

Group 1

number	date	source	gestation	outcome	fFN mg/ml
111111	11/12/98	EPU	empty uterus	ectopic	0.085
111141	21/08/99	EPU	empty uterus	ectopic	0.145
279294	15/12/98	EPU	empty uterus	ectopic	<0.05
293303	19/03/99	EPU	empty uterus	ectopic	<0.05
390717	18/08/99	EPU	empty uterus	ectopic	<0.05
455598	23/08/99	EPU	empty uterus	ectopic	<0.05
531846	21/10/99	EPU	empty uterus	ectopic	0.185
750781	28/01/00	EPU	empty uterus	ectopic	<0.05
758313	29/11/98	EPU	empty uterus	ectopic	0.155
788654	07/07/99	EPU	empty uterus	ectopic	<0.05
828446	03/02/99	EPU	empty uterus	ectopic	<0.05
848376	30/12/98	EPU	empty uterus	ectopic	<0.05
932829	03/07/99	EPU	empty uterus	ectopic	<0.05
945068	03/02/99	EPU	empty uterus	ectopic	<0.05
949892	08/02/99	EPU	empty uterus	ectopic	<0.05
955894	07/05/99	EPU	empty uterus	ectopic	<0.05
111117	17/03/99	EPU	empty uterus	negative laparoscopy	<0.05
397099	18/03/99	EPU	empty uterus	negative laparoscopy	0.13
429131	09/04/99	EPU	empty uterus	negative laparoscopy	0.215
949880	10/02/99	EPU	empty uterus	resolving trophoblast	<0.05
111131	22/04/99	EPU	empty uterus	ongoing	<0.05

Group 2

number	date	source	gestation	outcome	fFN mg/ml
291914	20/08/99	EPU	missed miscarriage	miscarriage	0.68
317629	04/11/98	FCU	missed miscarriage	miscarriage	0.23
524214	04/11/98	FCU	anembryonic pregnancy	miscarriage	0.08
726060	16/12/99	FCU	anembryonic pregnancy	miscarriage	<0.05
772111	13/01/99	FCU	anembryonic pregnancy	miscarriage	0.145
931596	26/11/98	FCU	anembryonic pregnancy	miscarriage	0.145
947432	13/01/99	FCU	anembryonic pregnancy	miscarriage	0.375
947461	03/02/99	FCU	missed miscarriage	miscarriage	<0.05
950032	17/03/99	FCU	missed miscarriage	miscarriage	<0.05
950051	17/03/99	FCU	missed miscarriage	miscarriage	0
960087	14/07/99	FCU	missed miscarriage	miscarriage	0.925
796819	04/11/98	FCU	empty uterus	complete	0.715
948541	03/02/99	FCU	empty uterus	complete	0.12

Levels of fFN found in plasma samples

number	source	outcome	Swab fFN µg/ml	diluted plasma fFN µg/ml
402070	FCU	TOP		0.7
460386	FCU	TOP		0.665
522935	FCU	TOP		0.41
658596	FCU	TOP		0.44
705765	FCU	TOP		0.213
736504	FCU	TOP		0.734
913149	FCU	TOP		0.76
958370	FCU	TOP		0.5
958384	FCU	TOP		0.475
958421	FCU	TOP		0.39
958423	FCU	TOP		0.54
958425	FCU	TOP		0.47
958428	FCU	TOP		0.705
958453	FCU	TOP		0.5
958524	FCU	TOP		0.375
493839	FCU	TOP	<0.05	0.49
733059	FCU	TOP	0	0.285
751062	FCU	TOP	0	0.285
788654	EPU	ectopic	<0.05	0.6
836706	RMC	ongoing	0.735	0.59
854108	RMC	ongoing	<0.05	0.426
880457	RMC	ongoing	0.165	0.285
932829	EPU	ectopic	<0.05	0.42
959244	FCU	TOP	<0.05	0.555
959245	FCU	TOP	0	0.44
959247	FCU	TOP	0	0.41
959248	FCU	TOP	<0.05	0.555
959249	FCU	TOP	0	0.28
959250	FCU	TOP	0	0.295
960087	EPU	missed	0.925	0.455

Levels of fFN found in non-pregnant subjects

sample number	sex of subject	fFN µg/ml
1	female	0.42
2	female	0.67
3	female	0.325
4	female	0.5
5	female	0.49
6	male	0.42
7	male	0.335

Levels of fFN found in colposcopy subjects

number	sample	visible blood staining	fFN µg/ml
039035	no loop		0
104902	no loop		<0.05
289576	LLETZ	yes	0.07
322396	no loop	yes	0
390789	LLETZ	yes	0.215
408705	no loop		<0.05
409782	no loop	yes	0
563693	LLETZ	yes	0.255
640240	no loop		0
640240	LLETZ	yes	0.5
674183	no loop		<0.05
719614	LLETZ	yes	0.165
824588	no loop	yes	0.11
887675	no loop		0
912536	no loop		0
968693	no loop		0

Levels of fFN found in blood stained samples

number	outcome	fFN mcg/ml
111111	ectopic	0.085
111141	ectopic	0.145
291914	missed miscarriage	0.68
544387	viable	<0.05
698413	viable	0.075
758313	ectopic	0.155
878917	viable	<0.05
903126	viable	0.185
929722	viable	<0.05
931596	missed miscarriage	0.145
943226	viable	<0.05
943293	viable	<0.05
944017	viable	<0.05
945068	ectopic	<0.05
947432	missed miscarriage	0.375
947908	viable	<0.05
948758	viable	<0.05
949880	ectopic	<0.05
949892	ectopic	<0.05
949908	viable	<0.05
955894	ectopic	<0.05
960087	missed miscarriage	0.925

Conjoint Analysis

Dear patient,

We would be most grateful to you if you would help us with a study about the treatment of ectopic pregnancies.

- This will mean filling out the following questionnaire while you wait to see a doctor.
- **You do not need to have had an ectopic pregnancy.**

Your care will under no circumstances be affected by your participation or absence of participation with this study.

What is an ectopic pregnancy?

- An ectopic pregnancy is a pregnancy that develops outside of the womb, usually in the fallopian tube.
- It cannot lead to a live-birth of a baby.
- It can cause a serious haemorrhage and treatment by surgery under a general anaesthetic is necessary.

This involves:

1. looking inside your tummy with a telescope (laparoscopy)
2. either

a. the fallopian tube that contains the ectopic pregnancy is removed

- a single operation
- 2 - 3 day hospital stay or

b. the fallopian tube is opened and the pregnancy removed from it.

- follow-up and, possibly a second operation a few days later if the pregnancy is not completely removed the first time.

Women who have had an ectopic pregnancy are more at risk of a further ectopic pregnancy than women who have never had an ectopic pregnancy.

- Some treatments for ectopic pregnancy increase this risk slightly, others reduce it slightly.
- Some treatments slightly reduce the chances of a normal pregnancy next time whereas others don't.

What is the purpose of this study?

We are looking to see what patients take into consideration when choosing between different treatments for ectopic pregnancy

- For the purpose of this study you have to **IMAGINE** that you have been diagnosed with an ectopic pregnancy and that you need surgery for it.
- You have to decide between option 1 and option 2. Consider the advantages and disadvantages and then choose the option that you would want most.
  - for example

	Option **A**	Option **B**
Stay in hospital	10 days	1 day
Surgery	yes	no
Recovery from treatment	3 months	1 week
Your choice		✓

- You have chosen **option B**

If you have not been able to finish your questionnaires before you have been called to see the doctor, could you please be kind enough to complete it once you have been seen by the doctor.

Thank you very much for your help

Appendix 13

Dilemma number 1	Option 1	Option 2
Chance of needing more than one operation for treatment	0%	0%
Chance of next pregnancy to be in the right place	40%	60%
Risk of a repeat ectopic	10%	20%
What option would **YOU** choose?		

Dilemma number 2	Option 1	Option 2
Chance of needing more than one operation for treatment	0%	5%
Chance of next pregnancy to be in the right place	40%	60%
Risk of a repeat ectopic	10%	10%
What option would **YOU** choose?		

Dilemma number 3	Option 1	Option 2
Chance of needing more than one operation for treatment	0%	0%
Chance of next pregnancy to be in the right place	40%	60%
Risk of a repeat ectopic	10%	10%
What option would **YOU** choose?		

Appendix 13

Dilemma number 4	Option 1	Option 2
Chance of needing more than one operation for treatment	0%	5%
Chance of next pregnancy to be in the right place	40%	60%
Risk of a repeat ectopic	10%	20%
What option would **YOU** choose?		

Dilemma number 5	Option 1	Option 2
Chance of needing more than one operation for treatment	0%	15%
Chance of next pregnancy to be in the right place	40%	60%
Risk of a repeat ectopic	10%	10%
What option would **YOU** choose?		

Dilemma number 6	Option 1	Option 2
Chance of needing more than one operation for treatment	0%	15%
Chance of next pregnancy to be in the right place	40%	60%
Risk of a repeat ectopic	10%	20%
What option would **YOU** choose?		

Appendix 13

Dilemma number 7	Option 1	Option 2
Chance of needing more than one operation for treatment	0%	5%
Chance of next pregnancy to be in the right place	40%	40%
Risk of a repeat ectopic	20%	10%
What option would **YOU** choose?		

Dilemma number 8	Option 1	Option 2
Chance of needing more than one operation for treatment	0%	5%
Chance of next pregnancy to be in the right place	40%	60%
Risk of a repeat ectopic	20%	10%
What option would **YOU** choose?		

Dilemma number 9	Option 1	Option 2
Chance of needing more than one operation for treatment	0%	5%
Chance of next pregnancy to be in the right place	40%	60%
Risk of a repeat ectopic	20%	20%
What option would **YOU** choose?		

Appendix 13

Dilemma number 10	Option 1	Option 2
Chance of needing more than one operation for treatment	0%	0%
Chance of next pregnancy to be in the right place	40%	60%
Risk of a repeat ectopic	10%	20%
What option would **YOU** choose?		

Dilemma number 11	Option 1	Option 2
Chance of needing more than one operation for treatment	0%	15%
Chance of next pregnancy to be in the right place	40%	40%
Risk of a repeat ectopic	20%	10%
What option would **YOU** choose?		

Dilemma number 12	Option 1	Option 2
Chance of needing more than one operation for treatment	0%	15%
Chance of next pregnancy to be in the right place	40%	60%
Risk of a repeat ectopic	20%	20%
What option would **YOU** choose?		

Appendix 13

Dilemma number 13	Option 1	Option 2
Chance of needing more than one operation for treatment	0%	5%
Chance of next pregnancy to be in the right place	60%	40%
Risk of a repeat ectopic	20%	10%
What option would **YOU** choose?		

Dilemma number 14	Option 1	Option 2
Chance of needing more than one operation for treatment	0%	5%
Chance of next pregnancy to be in the right place	60%	60%
Risk of a repeat ectopic	20%	10%
What option would **YOU** choose?		

Dilemma number 15	Option 1	Option 2
Chance of needing more than one operation for treatment	0%	15%
Chance of next pregnancy to be in the right place	60%	40%
Risk of a repeat ectopic	20%	10%
What option would **YOU** choose?		

Appendix 13

Dilemma number 16	Option 1	Option 2
Chance of needing more than one operation for treatment	0%	15%
Chance of next pregnancy to be in the right place	60%	60%
Risk of a repeat ectopic	10%	10%
What option would **YOU** choose?		

Dilemma number 17	Option 1	Option 2
Chance of needing more than one operation for treatment	0%	15%
Chance of next pregnancy to be in the right place	60%	60%
Risk of a repeat ectopic	20%	10%
What option would **YOU** choose?		

Dilemma number 18	Option 1	Option 2
Chance of needing more than one operation for treatment	5%	5%
Chance of next pregnancy to be in the right place	40%	60%
Risk of a repeat ectopic	10%	20%
What option would **YOU** choose?		

Appendix 13

Dilemma number 19	Option 1	Option 2
Chance of needing more than one operation for treatment	5%	15%
Chance of next pregnancy to be in the right place	40%	60%
Risk of a repeat ectopic	10%	10%
What option would **YOU** choose?		

Dilemma number 20	Option 1	Option 2
Chance of needing more than one operation for treatment	5%	15%
Chance of next pregnancy to be in the right place	40%	60%
Risk of a repeat ectopic	10%	20%
What option would **YOU** choose?		

Dilemma number 21	Option 1	Option 2
Chance of needing more than one operation for treatment	0%	0%
Chance of next pregnancy to be in the right place	40%	60%
Risk of a repeat ectopic	10%	20%
What option would **YOU** choose?		

Appendix 13

Dilemma number 22	Option 1	Option 2
Chance of needing more than one operation for treatment	5%	15%
Chance of next pregnancy to be in the right place	40%	40%
Risk of a repeat ectopic	20%	10%
What option would **YOU** choose?		

Dilemma number 23	Option 1	Option 2
Chance of needing more than one operation for treatment	5%	15%
Chance of next pregnancy to be in the right place	40%	60%
Risk of a repeat ectopic	20%	10%
What option would **YOU** choose?		

Dilemma number 24	Option 1	Option 2
Chance of needing more than one operation for treatment	5%	15%
Chance of next pregnancy to be in the right place	40%	60%
Risk of a repeat ectopic	20%	20%
What option would **YOU** choose?		

Appendix 13

Dilemma number 25	Option 1	Option 2
Chance of needing more than one operation for treatment	5%	15%
Chance of next pregnancy to be in the right place	60%	40%
Risk of a repeat ectopic	20%	10%
What option would **YOU** choose?		

Dilemma number 26	Option 1	Option 2
Chance of needing more than one operation for treatment	5%	15%
Chance of next pregnancy to be in the right place	60%	60%
Risk of a repeat ectopic	10%	20%
What option would **YOU** choose?		

Dilemma number 27	Option 1	Option 2
Chance of needing more than one operation for treatment	5%	15%
Chance of next pregnancy to be in the right place	60%	60%
Risk of a repeat ectopic	20%	10%
What option would **YOU** choose?		

Dilemma number 28	Option 1	Option 2
Chance of needing more than one operation for treatment	15%	15%
Chance of next pregnancy to be in the right place	40%	60%
Risk of a repeat ectopic	10%	20%
What option would **YOU** choose?		

- **How easy or difficult have you found this questionnaire**

Very easy ***1*** ***2*** ***3*** ***4*** ***5*** ***very difficult***

Please ring the number that indicates most closely, the lower numbers indicate that you found it easy, the higher numbers that you found it difficult

- And finally, please complete the questions overleaf to tell us about yourself.

PLEASE COULD YOU GIVE US SOME DETAILS ABOUT YOURSELF

Your Age ☐

For the following questions, please tick the correct box or fill in your answer.

- **Could you tell us about your plans for pregnancies in the future:**

	Family complete
	I would like to become pregnant now, or in the future
	Do not wish to have children

- **How many pregnancies have you had?**

	Live births
	Miscarriages
	Ectopic pregnancies
	Still births
	Termination of pregnancy

- **Have you any history of difficulty with conceiving?**

	No
	Yes

- **If you have had an ectopic pregnancy in the past, can you tell us how it was treated**

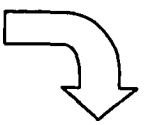
	Tube removed
	Tube saved
	Don't know

- **Do you know anyone who has had an ectopic pregnancy?**

	No
	yes

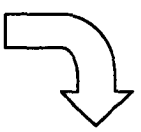
- **Have you ever had any operation under general anaesthetic?**

	No
	yes



- **if "yes", was this for a gynaecological reason?**

	No
	yes

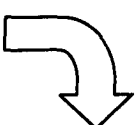


- if yes – what was the operation

	Scrape / D&C
	Hysteroscopy
	Laparoscopy
	sterilisation
	hysterectomy
	repair
	caesarean section
	other what_____

- **Do you work?**

	No
	yes



- If yes – how do you work

	Full time mother
	Self-employed
	Full time - 9 to 5
	Full time - shifts
	Part - time

Please give the questionnaire back to the person at the registration desk.

Thank you very much for your help.

Appendix 14

Reasons why women were not recruited to the ROCET Trial

number	D.O.B	discussed	Reason why patient was found unsuitable for or declined randomisation	Inclusion and exclusion criteria					
				cardiovascular stability stable	1st ectopic pregnancy	fimbrial – surgery not required	ruptured ectopic pregnancy	pelvic inflammatory disease	suitable for randomisation
60624	21.6.65	no	family complete	yes	yes	no	no	no	no
461434	20.8.59	no	ruptured ectopic	yes	yes	no	yes	no	no
545583	16.9.68	considered	known PID	yes	yes	no	no	yes	no
912341	11.10.63	yes	requested conservative	no	yes	no	yes	no	no
138802	22.1.68	yes	requested radical	yes	yes	no	no	no	yes
404780	12.3.77	yes	discussion not followed up	yes	yes	no	no	no	yes
649925	23.1.75	yes	didn't want randomising	yes	yes	no	no	yes	no
702860	14.3.72	no	unstable	no	yes	yes	no	no	no
788654	25.4.66	yes	requested radical	yes	yes	no	no	no	yes
932829	6.7.58	no	known PID	yes	yes	no	no	yes	no
878782	27.10.64	no	unicornuate uterus	yes	yes	no	yes	no	no
133802	22.1.68	yes	requested radical	yes	yes	no	no	no	yes
127787	4.7.66	yes	requested radical	yes	yes	no	no	no	yes
455598	21.6.76	no	previous ectopic	yes	no	no	no	yes	no

Appendix 13

number	D.O.B	discussed	Reason why patient was found unsuitable for or declined randomisation	Inclusion and exclusion criteria					
				cardiovascular stability stable	1st ectopic pregnancy	fimbrial – surgery not required	ruptured ectopic pregnancy	pelvic inflammatory disease	suitable for randomisation
941022	3.8.66	no	IVF, known PID – bilateral salpingectomy	yes	yes	no	no	yes	no
367682	14.8.69	yes	preferred salpingostomy	no	yes	no	no	no	yes
886023	25.8.65	no		yes	yes	no	no	no	yes
962921	25.4.77	no	no ectopic pregnancy	yes	yes	no EP		no	no
800691	24.1.57	no	ruptured ectopic	yes	yes	no	yes	no	no
861931	16.9.71	yes	requested radical	yes	yes	no	no	no	no
965680	6.5.74	yes	requested radical	yes	yes	no	no	no	Yes
946243	13.2.67	no	cornual ectopic, had requested radical	yes	yes	no	no	no	no
281244	28.1.64	no	sterilised	yes	yes	no	no	no	no
893085	24.1.60	yes	requested radical – pelvic ectopic	yes	yes	no EP			no
871511	3.2.64	yes	requested conservative	yes	yes	no	no	yes	no
668491	23.8.69	no	unilateral system	yes	no	no	no	yes	no
531846	5.11.71	yes	requested conservative	yes	yes	no	no	no	yes

Appendix 13

number	D.O.B	discussed	Reason why patient was found unsuitable for or declined randomisation	Inclusion and exclusion criteria					
				cardiovascular stability stable	1st ectopic pregnancy	fimbrial – surgery not required	ruptured ectopic pregnancy	pelvic inflammatory disease	suitable for randomisation
415627	5.6.79	considered	not appropriate - paranoid schizophrenic	yes	yes	no	no	yes	no
127015	29.12.70	yes	requested conservative	yes	no	no	yes	yes	no
739909	1.7.75	no		yes	yes	no	no	no	yes
701120	5.10.71	no	cornual ectopic	yes	yes	no	no	no	no
824588	26.6.62	yes	no further pregnancies desired	yes	yes	no	no	no	no
526009	29.1.67	no	previous sterilisation	yes	yes	no	no	yes	no
658814	17.11.76	no	tubal damage	yes	yes	no	no	yes	no
911638	22.9.72	no	tubal disease	yes	yes	no	no	yes	no
502020	12.8.63	no	chronic PID	no	yes	no	yes	yes	no
284755	16.7.71	no	known tubal disease	yes	yes	no	no	yes	no
630989	9.10.79	no	Haemodynamically unstable	no	yes	no	no	no	no

PID – pelvic inflammatory disease
IVF – in-vitro fertilisation

Ectopic Pregnancy Protocols

- Diagnosis is a combination of the clinical situation, ultrasound findings and biochemical parameters
- If the woman is cardiovascularly unstable she needs immediate action ie resuscitation and diagnostic laparoscopy. However a serum hCG level should be taken with the pre-operative bloods in case an ectopic pregnancy is not found.
- Most women who are being assessed with serial hCGs can be managed as outpatients if they are clinically stable. If there are worries about their clinical state they should be admitted. A woman who is being managed as an outpatient should be told to report any change in her symptoms – increase in pain, dizziness, fainting. She should be given the contact number of the EPU, or told to report to casualty out of normal hours.
- hCG levels should be known pre-operatively so that medical or conservative management may be discussed if appropriate. It might also prevent a false negative laparoscopy

- **Remember – whatever way an ectopic pregnancy is managed, the woman will be at high risk of another ectopic pregnancy (about 1 in 16 will have another ectopic pregnancy). She should be told to seek early review in her next pregnancy to confirm its location.**
- **The Ectopic Pregnancy Trust is a support group for women who have had an ectopic pregnancy. Tel. 0189 5238025**

Summary

Ultrasound scan cannot be reasonably expected to be helpful before 6 weeks amenorrhoea. If there are indications for investigation before 6 weeks amenorrhoea – that would either be symptoms or a past history of ectopic pregnancy – a baseline hCG should be taken and the timing of the first scan arranged in the light of this.

Procedure when a viable pregnancy cannot be confirmed

- Perform a pregnancy test. If positive she must remain under the care of the EPAU until the test becomes negative or a firm diagnosis is made.

A. With an empty uterus and cardio-vascular instability:

1. Needs diagnostic laparoscopy as soon as possible
2. Pre-op hCG to be taken but do not wait for the result

B. With an empty uterus and significant symptoms, particularly pain:

1. Admit
2. Alternate day hCG estimations
   - an abnormal rise in hCG over 48 hours would indicate a diagnostic laparoscopy is necessary
3. If hCG levels rise appropriately and the clinical situation is stable repeat ultrasound 1 week after first scan
4. If the patient's clinical picture is such that a diagnostic laparoscopy is indicated before the repeat scan 1 week later, repeat the scan early as demonstration of a viable intra-uterine pregnancy would avoid an unnecessary laparoscopy

C. With an empty uterus and minor or no symptoms + no other scan findings

1. Take hCG level
2. Arrange for her to be rescanned in 1 week
3. Explain what to look out for with ectopic pregnancy and give EPU number.
4. If the repeat ultrasound is consistent with ectopic pregnancy, a repeat hCG should then be taken to help plan management.

D. With an empty uterus and minor or no symptoms – adenexal mass/fluid in the POD

1. Take hCG level and repeat at 48 hours

2. If the level is rising, arrange for her to be rescanned in 1 week. If the level is plateauing or falling seek senior review and repeat hCG in a week.
3. Explain what to look out for with ectopic pregnancy and EPU number.
4. If hCG levels are >2000 miu/ml, senior review required

E. With an empty uterus following symptoms consistent with complete miscarriage

1. Repeat urine pregnancy test 10 days later in EPAU. If this is positive, serial serum hCG should be initiated.

F. If a gestation sac is found but viability is not confirmed

1. Repeat ultrasound in 1 week
2. hCG estimations are **not** indicated unless the sac is atypical and suggests the presence of a pseudosac.

Sometimes, the repeat scan is still inconclusive – this tends to occur if there has been an appropriate increase in sac size but no yolk sac/fetal pole has been seen but the sac is not large enough to diagnose a missed miscarriage. In these cases a further scan should be arranged

Remember – anti-D is required in rhesus negative women with ectopic pregnancy.

Background

Diagnosis

Diagnosis of ectopic pregnancy has three components

- clinical assessment
- ultrasound assessment
- biochemical assessment (ie largely hCG estimations)

No single component is likely to diagnose an ectopic pregnancy in isolation – the whole picture is more important.

- **Clinical assessment.**

History of vaginal bleeding and pain – particularly unilateral pain - might suggest ectopic pregnancy, but also can be misleading. Equally, asymptomatic women may have an ectopic pregnancy.

The date of the last menstrual period gives a guide to the gestation of the pregnancy. In assisted conceptions this date is likely to be reliable. In natural conceptions there is more scope for error in the gestational age, even with a reliable date of last menstrual period.

Vaginal examination should be undertaken when there is an indication, not automatically. Women with an ectopic pregnancy might have a pre-disposing chlamydial infection and screening for chlamydia could be indicated. Chlamydia may be asymptomatic and still cause tubal damage.

Cardiovascular instability should be taken seriously ie fainting, tachycardia, hypotension – women who die with ectopic pregnancy die of blood loss. In general this requires immediate action ie diagnostic laparoscopy.

- **Ultrasound assessment.**

The presence of an intra-uterine gestation sac excludes an ectopic pregnancy except:

1. ***with a heterotrophic pregnancy***, ie the presence of an ectopic pregnancy with a simultaneous intrauterine pregnancy. In spontaneous conceptions this occurs approximately once in 30,000 pregnancies. The current overall incidence of heterotrophic pregnancy is 1 in 7,000 - this indicates the impact of assisted conception on the incidence. Heterotrophic pregnancy is hard to diagnose, serum hCG levels are not helpful and ultrasound will only be diagnostic if an adenexal fetal heart pulsation/yolk sac is found on scan. It is something to be considered in a woman with persistent problems and an apparently normal intra-uterine pregnancy. In assisted conceptions the incidence of ectopic pregnancy, and heterotrophic pregnancy is higher than with natural conceptions. In assisted conceptions, the pregnancy is often monitored from a very early stage which is helpful for diagnosis.

2. ***with a pseudo-gestational sac***, this is the appearance of a gestational sac on ultrasound which is in reality a decidual cast and blood clot. A true gestation sac has a thick, bright rim, but the two can be mistaken. "Double ring sign" reliably predicts a gestation sac, but its absence does not exclude it.

An empty uterus or an "early gestation sac" (ie where a fetal pole or yolk sac is not seen) may represent an early viable intra-uterine pregnancy, a non-viable intra-uterine pregnancy, a complete or incomplete miscarriage or an ectopic pregnancy. A baseline hCG level should be taken and a repeat ultrasound arranged for a week later. Medical staff should see the patient.

An ectopic pregnancy can only be diagnosed with certainty by ultrasound if a fetal heart pulsation or a yolk sac is seen within the adenexa. This occurs in around 5% of ectopic pregnancies.

Ultrasound Finding	Likelihood ratio for ectopic pregnancy
Ectopic mass, no fluid in POD	3.6
Fluid in POD only	4.4
Ectopic Mass and fluid in POD	9.9

Mol et al, 1998

Adenexal masses may represent corpus lutea, corpus luteal cysts, ruptured corpus lutea or hydrosalpinges – in isolation, fluid in the Pouch of Douglas is more predictive of ectopic pregnancy than an adnexal mass. If an adenexal mass or fluid in the POD is found, the hCG levels should be tracked at 48 hour intervals and the scan repeated after a week if she remains asymptomatic.

If the ultrasound cannot be exclude an ectopic pregnancy, further diagnostic steps are required, this may not necessarily be a diagnostic laparoscopy at this stage, this will depend on the clinical and biochemical assessment of the woman. It is still more likely that this will not be an ectopic pregnancy.

- **Biochemical assessment**

hCG Currently, this means serum hCG estimations. Urine hCG (ie a pregnancy test) can confirm pregnancy but it is not quantifiable and, therefore, not useful in the further management of early pregnancy complications. If the urine test is positive and the serum negative, the serum result is the one to believe.

Paired hCG levels (ie levels taken two days apart) are more useful than an isolated level – isolated levels have little value.

- there is a wide variation of levels of hCG at any gestation
- in normal early pregnancy the levels double approximately every 48 hours
- however the levels can double over 48 hours in ectopic pregnancy also – so remember to think about the whole picture, Shepherd et al (1990)

found a normal doubling of hCG levels in the early stages in 64% of women who eventually had ectopic pregnancy. The doubling time increased as the women became more symptomatic – be suspicious if the levels double and nothing is found on ultrasound.

- If the ultrasound shows an intra-uterine sac, no further hCG levels are needed. If a fetal heart has not been seen, the scan will need to be repeated 1 week later to confirm viability, **not** the hCG.
- On trans-vaginal scan, an intra-uterine pregnancy (defined as either an intradecidual sign or the presence of a yolk sac or a fetal pole with cardiac activity) should be expected by a level of *2000 miu/ml. Mehta et al (1997) and Mol et al (1998) suggested 1500 miu/ml if fluid in the PoD or an adenexal mass was found or 2000 miu/ml with no suspicious ultrasound findings. If the hCG level has reached 2000 miu/ml and an intra-uterine pregnancy has not been found at ultrasound a senior doctor should be involved.

  * caution, normal pregnancies may not be apparent at higher levels and different laboratories use different assays giving different levels. Things are made more difficult by the different international standard used to measure hCG – when looking at the literature make sure you know which standard was used.
- an ectopic pregnancy might be missed at laparoscopy with very low levels of hCG, i.e. <500 miu/ml

Management Options

1. **Conservative management**

- If the hCG levels are falling no treatment may be required.
- This is more likely to be successful if the initial hCG level is low ie <2000 miu/ml.
- The trophoblast might invade a blood vessel and cause major haemorrhage even when the levels are falling. Therefore, the woman must be warned to report any suspicious symptoms. This applies until hCG levels have reached non-pregnant levels.
- She cannot be discharged from follow-up until hCGs have reached non-pregnant levels (ie<2miu/ml at SJUH, <5 miu/ml at LGI)). Once falling hCG levels have been demonstrated, weekly estimations are sufficient.
- hCG levels need to be checked weekly until they reach non-pregnant levels.

Management Options

2. Medical Management – methotrexate (single dose regime)

**This decision must be made by a senior SpR or consultant.

- Medical management can only be considered if the diagnosis of ectopic pregnancy can be reached without the need for laparoscopy. If she requires a general anaesthetic for diagnosis, a surgical procedure should be performed under that anaesthetic, and there is no place for laparoscopic infiltration of the ectopic pregnancy with methotrexate. Local methotrexate leads to similar systemic levels as systemic administration, this will expose the woman to the potential complications of both surgical and medical management)
- Medical management works best in ectopic pregnancies where the hCG level is less than 2000 miu/ml and/or the hCG levels are plateauing.
- The woman must be cardio-vascularly stable. The presence of pain does not contra-indicate the use of methotrexate if she is cardio-vascularly stable. However, if there were concerns about the degree of symptoms, it would be unwise to use medical management as it is action is not immediate.
- She must be willing to attend for hCG follow-up until levels are <2miu/ml
- Methotrexate should not be used in liver disease.
- A baseline haemoglobin should be taken before treatment. If there are any post-treatment symptoms/signs of cardiovascular instability, a drop in the haemoglobin level is a further sign of intra-abdominal blood loss.
- A dose of 50mg/m^2 is used. Pharmacy can work out the body surface area if you give them the patient's height in metres and weight in kilograms. The methotrexate is given as a single IM dose. The woman should be warned
  - her pain might increase in the first 2 - 4 days
  - she may experience vaginal bleeding
  - she must be willing to attend for follow-up blood tests until non-pregnant levels are reached
  - she may require a second dose of methotrexate if the levels do not fall appropriately
  - she should avoid strong sunlight in the first 48 hours (because of photosensitivity)
  - she should avoid foods such as beans and cabbage (in the first 48 hours because of flatulence)
  - she should avoid intercourse until hCG reaches non-pregnant levels
  - her hCG levels are likely to increase in the first few days

  Alopecia and neutropenia are not relevant in single dose regimes.
- Treatment should be given in the EPU and the woman may be allowed home afterwards unless symptoms or her circumstances would make it advisable for her to be admitted.
- hCG levels should be taken at 4 and 7 days post treatment. If the level at day 4 has risen, this should not cause concern, in fact would be expected. The

day 4 hCG level should not be acted upon. The level at day 7 should be 15% lower than the level at day 4.

- If levels are falling, repeat monitoring weekly until non-pregnant levels. If levels are not falling, a second dose of methotrexate may be required or consider surgery.
- If we expect an increase in pain after the administration of methotrexate, it can be difficult to know when to intervene. Surgery is required if there are any cardio-vascular signs ie tachycardia, hypotension, fainting. The patient should be reviewed by senior medical staff.
- The trophoblast might invade a blood vessel and cause major haemorrhage even when the levels are falling, therefore, the woman must be warned to report any suspicious symptoms until hCG levels have reached non-pregnant levels.
- The woman should be advised to wait for two periods before trying to become pregnant. This is because of methotrexate is a folate antagonist but there are not clear guidelines on this.

Contraindications to use of methotrexate

A viable intrauterine pregnancy has been confirmed
Clinically unstable or in severe pain
History of liver disease
Serum hCG more than 2000 miu/ml
Patient not willing to return for serum hCG monitoring

Management Options

3. Surgical Treatment

- A hCG level should be taken pre-operatively. Unless the patient is collapsed, the result should be known before she is taken to theatre. No randomised trial comparing salpingectomy (removal of the tube containing the ectopic pregnancy) with salpingotomy (removal of the ectopic pregnancy with preservation of the tube) has been successfully completed; therefore, it is not possible to say whether tubal preservation improves the chances of a successful intra-uterine pregnancy in the future. Review by Yao and Tulandi (1997) of the management of ectopic pregnancy suggest that conservative, in comparison to radical surgery, at best gives a small increase in the chance of an intra-uterine pregnancy in the future, however, the risk of a further ectopic pregnancy is increased.

  - Nine retrospective studies

	IUP	Recurrent EP
salpingectomy	49.3%	9.9%
salpingotomy	53.0%	14.8%

  - One prospective study

	IUP	Recurrent EP
salpingectomy	53.8%	7.7%
salpingotomy	60%	18.3%

- The RCOG guidelines for the surgical management of ectopic pregnancy recommend salpingectomy as the treatment of choice for a first ectopic pregnancy. This should be discussed with the woman pre-operatively so that her preferred treatment can guide surgical treatment.
- Laparoscopic management is the preferred route for the surgical management of ectopic pregnancy. It shortens hospital stay, and reduces pain and blood loss. It appears to make little difference to future pregnancy outcome. Persistent trophoblast is more likely with laparoscopic management.
- If salpingotomy is performed, whether as an open procedure or laparoscopically, persistent trophoblast is a possibility. hCGs should be tracked until they reach non-pregnant levels. If levels plateau or begin to rise again, methotrexate is indicated.
- If diagnostic laparoscopy is negative, a diagnosis has not been made. The woman should be followed up until
  1. an intra-uterine pregnancy is found on ultrasound
  2. the hCG levels return to non-pregnant levels
  3. it becomes apparent that an ectopic pregnancy was present but not visualised at laparoscopy. (This might be

because the ectopic pregnancy was too small to be visualised or it is located outside the tube). Treatment with methotrexate may be the best way of managing this situation.

References

Mehta T.S., Levine D., Beckwith B. **Treatment of ectopic pregnancy: is a human chorionic gonadotrophin level of 2,000 miu/ml a reasonable threshold?** Radiology 1997; 205:569-573

Mol B.W.J., Hajenius P.J., Engelsbel S., Ankum W.M., van der Veen F., Hemrika D.J., Bossuyt P.M.M. **Serum human chorionic gonadotrophin measurement in the diagnosis of ectopic pregnancy when transvaginal sonography is inconclusive.** Fertil Steril 1998; 70(5):972-81

Shepherd R.W., Patton P.E., Novy M.J., Burry K.A. **Serial βhCG measurements in early pregnancy detection of ectopic pregnancy.** Obstet Gynecol 1990; 3(1):417-20

Yao M. and Tulandi T. **Current status of surgical and nonsurgical management of ectopic pregnancy.** Fertil Steril 1997; 67 (3):421-33