9. Miscarriage Following Assisted Conception

A. H. Balen and J. L. Yovich

Miscarriage occurs in between 10% and 30% of all spontaneous pregnancies (Shoham et al. 1991). Infertility is also common, affecting about 30% of couples (Hull et al. 1985). The causes of infertility are multiple and diverse, yet some, for example endometriosis and the polycystic ovary syndrome, may also affect successful implantation and pregnancy outcome. With the development of the techniques of assisted conception it is now possible either to overcome or to circumvent the majority of problems presented by the subfertile couple. One of the main questions to have arisen from the various therapies available is: Do they increase the rate of miscarriage or fetal malformations? And if they are found to do so, is this secondary to the treatment or a reflection of the underlying fertility disorder?

We shall address these questions by examining both the influence on miscarriage of the drugs that are used in ovulation induction and the effect of the different techniques that are employed in assisted conception. We shall also include data from the first 1000 pregnancies in the in-vitro fertilisation (IVF) programme at the Hallam Medical Centre.

Miscarriage in the Infertile Couple

Couples attending the infertility clinic tend to be older than the average couple attending an antenatal clinic. They may have tried for a pregnancy for several years before seeking medical advice, and may then have attended both their general practitioner and gynaecologist for investigation and possibly simple treatments, prior to being referred for assisted conception. Women may also choose to delay starting a family, for example whilst establishing a career. Such a delay leads to a greater incidence of ovulatory dysfunction, endometriosis and the possibility of developing gynaecological pathology necessitating surgery, such as

ovarian cysts, fibroids and tubal damage. In our clinic the mean age of the women attending is 33 years (range 22–44).

In addition to the problem of becoming pregnant, the older woman has a high chance of miscarriage. In a recent series of 2730 sonographically confirmed pregnancies the overall first trimester spontaneous abortion rate was 14.6% (Brambati 1990). The incidence of abortion in those women under 35 was 6.4%, rising to 14.7% in women between 35 and 40, and to 23.1% in women over 40. The frequency of chromosomal abnormalities in this series was 82.7% and was greatest in the first 6–8 weeks (86.5%). There are extensive data that confirm a rising risk of chromosomal anomalies with maternal age (Penrose 1933; Trimble and Baird 1978; Hook et al. 1979; Hassold et al. 1980), and this accounts, in a large part, for the increasing miscarriage rate. If a pregnancy continues there appears to be no association between birth defects of unknown aetiology and advancing maternal age (Baird et al. 1991). These data were compiled from 26859 children with birth defects from 576 815 consecutive live births, in whom chromosomal abnormalities and defects of known aetiology (e.g., maternal illness (infection, diabetes, alcohol), teratogenic drugs etc.) had been excluded.

There has been disagreement concerning male factors in spontaneous abortion. Chromosomally abnormal spermatazoa that achieve fertilisation may result in a chromsomally abnormal abortus. Polyploidy should be excluded during IVF procedures as embryos are screened at the pronuclear stage. The uncertainty remains with respect to the influence of abnormal semen parameters severe enough to affect fertility. Some authors have described an adverse effect on pregnancy outcome (Furuhjelm et al. 1962; Joel 1966), whereas more recent reports have found no correlation between abortion and sperm count or motility (Steinberger et al. 1982; Lev-Gur et al. 1990). The use of donor sperm does not appear to have an adverse effect on miscarriage rate (Smith et al. 1981; Lev-Gur et al. 1990).

Apart from the considerations of parental age, the couple with secondary infertility often presents with a poor obstetric history, and with pregnancy losses prior to treatment in 70%–80% (Goldfarb et al 1968; Weir and Hendricks 1969; Hack et al. 1972).

Pregnancy Diagnosis

A major difference between spontaneous and assisted conception is the intensity of early pregnancy monitoring. Pregnancy can be diagnosed as early as 24 h after conception, with the measurement of early pregnancy factor. It is, however, human chorionic gonadotrophin (hCG) that is usually assayed. hCG can be measured in maternal serum and urine from between 8 and 11 days post-ovulation. It is, therefore, possible to determine the success of an assisted conception cycle in the late luteal phase, and so women may know whether they are pregnant before the expected commencement of menses. The usual practice after assisted conception treatements is to wait until day 16 following the day of ovulation or egg collection procedure.

With the advent of sensitive assays for hCG it has been possible to obtain a better idea of the incidence of pregnancy failure in both natural and assisted conceptions. In 1967, Hertig suggested that in natural cycles 85% of oocytes

fertilise, 70% of these implant, yet only 58% of these survive until the end of the second week and 16% of them are abnormal and abort shortly after this time. In a series of women trying to conceive, an elevated urinary hCG was found in 59.6% of 198 ovulatory cycles (Edmonds et al. 1982), yet 62% of conceptuses were lost by 12 weeks and most of the losses (92%) were subclinical. The overall fecundability was therefore 22%, which is similar to that expected for a normal population.

It should be remembered that hCG is usually given in most assisted conception regimens in order to mimic the mid-cycle luteinising hormone (LH) surge. This is required in order to initiate oocyte maturation prior to a timed oocyte collection procedure. The exogenous hCG should have been cleared from the circulation by 9–10 days after ovulation or oocyte retrieval (Jones et al. 1985), so hCG at a concentration of greater than 10 IU/l on luteal days 11–13 indicates a pregnancy (and one can be certain of the hCG had been less than 5 IU/l on days 9–10). Many regimens also include hCG for luteal support, administered in one or multiple doses either alone or in combination with a progestogen. In these cases pregnancy can only be diagnosed by a rising titre of hCG, which is usually measured 14–16 days after oocyte retrieval.

A preclinical, or biochemical, abortion occurs with a measurable hCG, usually less than 50 IU/l, which remains elevated for a few days only and results in a delay of menses of no more than 14 days (Jones et al. 1985). A clinical abortion occurs after the hCG has continued to rise to a time when an intrauterine gestation sac can be seen sonographically, either with or without a fetal pole or heart beat.

The Influence on Miscarriage of the Drugs used in Assisted Conception

Ovulatory failure accounts for 21% of cases of infertility (Hull et al. 1985). Over the last 30 years drug regimens of increasing complexity have evolved to induce ovulation. The drugs prescribed to anovulatory women are also used to induce multifollicular growth in women who ovulate normally. These women benefit from superovulation as the production of several oocytes increases the success of assisted conception therapies. The most commonly used preparations are the anti-oestrogens (e.g., clomiphene citrate), the gonadtrophins and gonadotrophin-releasing-hormone agonists. Information about the sequelae of the use of fertility drugs therefore chiefly refers to these three groups.

Anti-oestrogens

The most widely prescribed anti-oestrogen is clomiphene citrate (CC). Its use in ovulation induction was first reported in 1961 (Greenblatt et al. 1961) at a time when human pituitary, and menopausal urinary, gonadotrophins were also beginning to be extracted and standardised. Because of worries about ovarian cyst formation and the difficulties in monitoring the response to the drug, the use

of clomiphene was restricted to anovulatory women with a "moderately intact pituitary-ovarian axis" (Karow and Payne 1968).

In an early report of pregnancy outcome in a small number of women, Greenblatt found the incidence of spontaneous abortion to be 22% (Greenblatt et al. 1962). It was to be a few years before the results of larger series were published. Karow and Payne (1968) reported on a heterogeneous group of 410 infertile women, in whom a pregnancy rate of 39.8% was achieved. The spontaneous abortion rate was 19% and similar to that seen in infertility patients prior to the advent of the drug (Karow and Payne 1968). The incidence of twins was 8.6%, contributing to a premature delivery rate of 12%. There was no confirmation of an earlier theory that conception in the first treatment cycle resulted in an increased chance of miscarriage or multiple pregnancy. Also in 1968, a series of 2196 CC-induced pregnancies were reported (MacGregor et al. 1968), in which miscarriage rate was 17.6%, multiple pregnancy rate 10.2% and the incidence of congenital anomalies 2.5%. In a smaller series (160 pregnancies) a lower miscarriage rate of 10.8% was attributed to the use of various combined oestrogen-progestin preparations which were prescribed from the sixth to the twenty-second week of pregnancy (Goldfarb et al. 1968).

Although CC was found to achieve ovulation in about 90% of infertile women and pregnancy in 50%, the multiple pregnancy rate was sometimes as high as 50% (Gemzell 1967). In general the miscarriage rate has been found to be between 20% and 27%, the rate of multiple pregnancy 10%–15% and the incidence of congenital abnormalities about 2%–3% (Bishop 1970; Garcia et al. 1977; Adashi et al. 1979; Kurachi et al. 1983).

One series reported an overall miscarriage rate of 9.3%, yet a rate of 28.1% if conception occurred during the first cycle of treatment and as high as 70.0% if conception resulted after 7 cycles (Toshinobu et al. 1979). It is thought that prolonged usage of CC may have a deleterious effect on the endometrium, causing atrophy and implantation failure (Wall et al. 1964). The relatively high miscarriage rate during the first cycle of treatment that was seen in this study was postulated as being secondary to the release of "over ripe" oocytes after a prolonged period of anovulation (Toshinobu et al. 1979).

Interpreting data from the early use of CC is made difficult by the lack of uniformity in presenting details of maternal age and the cause of infertility. The monitoring of an individual's response to the drug was limited to urinary oestrogens or vaginal cytology, and often monitoring was omitted (Bishop 1970). Pregnancy diagnosis was not as advanced as we have described above and so it is difficult to compare miscarriage data between the different series.

Congenital Abnormalities with Clomiphene Citrate

The incidence of congenital abnormalities and physical development of infants born to mothers who had received CC has not been found to be different to the general population (Bishop 1970; Hack et al. 1972; Garcia et al. 1977; Adashi et al. 1979; Kurachi et al. 1983), yet concern was expressed by the finding of an increased frequency of chromosomal abnormalities after induced ovulation (Boué and Boué 1973), an effect that appeared to persist during the subsequent, non-stimulated cycle.

Following the report of two cases of neural tube defects following CC therapy

(Dyson and Kohler 1973), other isolated cases of congenital abnormalities appeared in the literature (Sandler 1973; Berman 1975; Singh 1978; Czeizel 1989). Others have felt that factors related to infertility itself may be to blame, rather than induction of ovulation (James 1974; Field and Kerr 1974; Ahlgren et al. 1976) and that babies born after ovulation induction are no more at risk of being malformed than if they were conceived spontaneously (Harlap 1976).

Whereas there continue to be reports that suggest a more than coincidental association between ovulation induction specifically using CC, and neural tube defects (Cornel et al. 1989), other reports are reassuring and suggest no evidence for this (Mills et al. 1990). Shoham recently reviewed 3751 births after CC therapy and found an overall incidence of major and minor malformations of 32.5 per 1000 births (Shoham et al. 1991), this figure being within the range found among the normal population (Harlap 1976).

Hypersecretion of Luteinising Hormone

It has been postulated that CC may either reduce the chance of conception in some women, and similarly increase the risk of miscarriage, by inducing an abnormal hormonal environment for the developing oocyte. CC causes an exaggerated early follicular phase release of both gonadotrophins and the resultant luteinising hormone (LH) is thought to have a deleterious effect (Shoham et al. 1990).

In recent years there has been increasing evidence that hypersecretion of luteinising hormone (LH) is deleterious both to fertility and pregnancy outcome (Stanger and Yovich 1985; Abdulwahid et al. 1985; Howles et al. 1986; Homburg et al. 1988). Treatment has therefore been tailored to try to correct the gonadotrophin abnormality.

LH has several functions in the control of the developing follicle: in the early follicular phase low levels of LH induce a change in function of the theca interstitial cells from progesterone to androgen production (Erickson et al. 1985). Follicle stimulating hormone (FSH) then promotes the conversion of androgen to oestradiol by the granulosa cells. Of equal importance is the role of LH in the suppression of the oocyte maturation inhibitor (OMI). The precise nature of OMI is uncertain; it is known that cyclic adenosine monophosphate (cAMP) activates OMI or is itself OMI (Downs 1990). The action of OMI is to maintain the meiotic arrest of the oocyte at the diplotene stage of prophase 1. By reducing cAMP in the oocyte, LH enables the reactivation of meiosis and hence the attainment of oocyte maturity prior to ovulation (Dekel et al. 1990). Inappropriate release of LH may profoundly affect this process such that the released egg is either unable to be fertilised (Homburg et al. 1988) or, if fertilised, miscarries (Regan et al. 1990).

Recently there has been debate about the predictive value of an elevated follicular phase LH for either conception or pregnancy outcome. It was first demonstrated in 1985 that oocytes obtained from women undergoing IVF who had a serum LH value greater than one standard deviation above the mean on the day of human chorionic gonadotrophin (hCG) administration had a significantly reduced rate of fertilisation and cleavage (Stanger and Yovich 1985). This relationship has subsequently been confirmed with urinary LH measurements in the Bourn Hall IVF programme (Howles et al. 1986) and in the ovulation

induction clinic at the Middlesex Hospital (Homburg et al. 1988). It has also been shown that not only are ovulation and fertilisation affected by high tonic LH levels but also miscarriage is more likely (Homburg et al. 1988).

The only syndrome to result in a tonic elevation of LH is the polycystic ovary syndrome (PCOS), and it is in women with this condition that CC may induce an exaggerated follicular phase LH rise (Shoham et al. 1990).

A study of women attending a clinic for those who had suffered recurrent miscarriage demonstrated that 82% had PCO (Sagle et al. 1988) and women attending this clinic were also found to have abnormalities in follicular phase LH secretion (Watson et al. 1989). A recent study of 193 women planning to become pregnant showed that mid-follicular phase LH levels of greater than 10 IU/l were associated with both a significant drop in conception rate (67%) and a major increase in miscarriage rate (65%), compared with those women with normal LH levels (88% and 12% respectively) (Regan et al. 1990).

There has been some disagreement on the effect of an elevated LH with one group suggesting no deleterious effect in IVF cycles (Thomas et al. 1989). In this study it was considered that only cycles that result in a pregnancy should be used to provide the normal range of LH concentrations and that by taking LH levels above the 75th centile no adverse effect on fertilisation or cleavage was detected. An effect on miscarriage was not addressed.

While the precise mechanism resulting in hypersecretion of LH in the PCOS is unclear (Conway et al. 1989) we are currently exploring a possible deficiency of a follicular peptide (different from inhibin, and termed "gonadotrophin surge attenuating factor") that has been found by others to suppress pituitary LH release (Fowler et al. 1989; Knight et al. 1990). Irrespective of the aetiology of LH hypersecretion, the therapeutic approach to ovulation induction in women with PCOS should be aimed at preventing inappropriate gonodotrophin levels.

To this end, recent work at the Middlesex Hospital has explored the use of oral Tamoxifen as an alternative regimen to CC, as this antiandrogen has been found to induce ovulation without increasing serum LH concentrations (MacDougall, unpublished data).

Ovulation Induction with Gonadotrophins

Women who do not respond to oral CC therapy may succeed in having ovulation induced with gonadotrophin therapy. The preparations available are either human menopausal gonadotrophin (hMG), which contains 75 IU of both LH and FSH, or "purified" FSH (which contains 75 IU of FSH and less than 1 IU of LH). It was thought that the use of the latter would benefit women with the PCOS by minimising circulating LH levels (Jones et al. 1985). However, these women are usually very senstive to both forms of treatment and the use of "purified" FSH confers no advantage (Homburg et al. 1990). Preparations of recombinant FSH are currently being evaluated and may have a role in future therapies. Whatever the preparation, the main problems with exogenous gonadotrophin therapy are multiple pregnancy and miscarriage (Wang and Gemzell 1980).

Pulsatile administration of luteinising hormone releasing hormone (LHRH) (Mason et al. 1984; Homburg et al. 1989) or FSH (Polson et al. 1987) results is a

more physiological response. Another advantage of pulsatile infusion regimens is the low multiple pregnancy rate (Shoham et al. 1990). The use of gonadotrophin releasing hormone analogues (GnRHa) to suppress endogenous gonadotrophins is of uncertain benefit in ovulation induction regimens (Homburg et al. 1990), although there may be a reduction of the miscarriage rate via the suppression of excess LH (Johnson and Pearce 1990).

As for the actual reported miscarriage rate after gonadotrophin-induced ovulation, this varies between 11.3% and 27.5% (Shoham et al. 1991), with an average of 18.8% in a total of 1340 pregnancies, from 6 separate series (Spadoni et al. 1974; Caspi et al. 1976; Schwartz et al. 1980; Kurachi et al. 1983; Lunenfeld et al. 1986; Brown 1986). Lunenfeld also reports an analysis of the abortion rates in both the first and subsequent treatment cycles and the first and subsequent pregnancies (Lunenfeld et al. 1981). In this study it was found that whereas the abortion rate was 28.8% in a first pregnancy, it was only 12.8% in a second pregnancy. This figure is similar to the 13% of women who aborted after a spontaneous conception that followed a successful gonadotrophin-induced pregnancy. There was no difference in the abortion rates of patients who became pregnant after the first or subsequent treatment cycles. This goes against a commonly proposed theory that women who are anovulatory release eggs of "poor quality" in their first ovulation induction cycle (Boué and Boué 1973).

Other groups have also found a higher miscarriage rate in the first gonadotrophin-induced pregnancy. One series demonstrated a reduction in miscarriage rate from 28.5% in first hMG pregnancies to 11.9% in those conceiving for a second time (Ben-Rafael et al. 1983); another series found these figures to be 33% and 9.8% respectively (Miyake et al. 1988). In contrast to these studies a more recent paper reported an overall spontaneous abortion rate in first treatment cycles of 24.2%, yet a 48% abortion rate in women whose first hMG pregnancy ended in a spontaneous abortion; this compared to an incidence of abortion of 6.7% if the first hMG-induced pregnancy was normal (Corsan and Kemmann 1990). This large study looked at 4113 treatment cycles in 996 women, of whom 350 achieved a total of 424 pregnancies. There were no differences in terms of age, weight, duration of infertility, parity or peak oestradiol levels. These data are in keeping with the knowledge that the risk of miscarriage following a natural conception is directly related to a woman's past obstetric history (Poland et al. 1977; Regan et al. 1989).

Various factors have been proposed in the aetiology of spontaneous abortion following gonadotrophin therapy, including an increased incidence of chromosomal abnormalities (Boué and Boué 1973), increased maternal age and obesity (Bohrer and Kemmann 1987), abnormal hormone patterns (Lam et al. 1989) and luteal phase deficiency (Olson et al. 1983). The ovarian hyperstimulation syndrome (OHSS) has also been implicated. This condition may occur when superovulation results in the development of 15 or more follicles and concomitant serum oestradiol levels of greater than 10 000 pmmol/l. There may then follow a range of endocrine, haematological and metabolic disturbances. Several groups have reported a higher than expected miscarriage rate when the OHSS has occurred (Hack et al. 1970; Caspi et al. 1976; Lunenfeld et al. 1981; Ben-Rafael et al. 1983). We have not found this to be the case at the Hallam Medical Centre, where the incidence of miscarriage in moderate to severely hyperstimulated women was 14.3% in a recent series (MacDougall et al. 1992).

Congenital Abnormalities after Gonadotrophin Treatment

An analysis of 7 studies that addressed the outcome of gonadotrophin-induced pregnancies concluded that this treatment results in the same incidence of congenital malformations expected for the general population (Shoham et al., 1991). These studies included a total of 1160 newborn infants, in whom the overall incidence of malformations was 54.3 per 1000 (21.6/1000 major and 32.7/1000 minor malformations) (Hack et al. 1970; Spadoni et al. 1974; Harlap 1976; Caspi et al. 1976; Kurachi et al. 1983; Lunenfeld et al. 1986).

Miscarriage after IVF and Related Procedures

Clomiphene or gonadotrophins used for induction of ovulation for either "natural" conception or insemination procedures are aimed to stimulate the development of one, two or at the most three ovulatory follicles. In in-vitro fertilisation (IVF) and other related methods of assisted conception, the usual aim is to achieve superovulation and multifollicular development, with at least 4 oocytes and often many more. However, the usual number of oocytes obtained is between 8 and 15 at the Hallam Medical Centre, with a mean number of 10 oocytes; occasionally 30 or more oocytes are collected. Both CC and the gonadotrophins are used, either singly or in combination, but in recent years there has been a move towards pituitary desensitisation with a gonadotrophin releasing hormone agonist (Porter et al. 1984). The reversible hypogonadotrophic hypogonadism produced permits unimpeded control over follicular development (Fleming et al. 1985) leading to improved pregnancy rates in IVF programmes (Rutherford et al. 1988; Frydman et al. 1988).

The suppression of endogenous LH by GnRH agonists is of particular relevance and advantage to the woman with the PCOS (Jacobs et al. 1987; Fleming and Coutts 1988). Thus many oocyte-containing follicles may develop in the sensitive polycystic ovary free from the adverse environment of high tonic LH levels. These oocytes appear to fertilise better than those from cycles without pituitary desensitisation (Fleming et al. 1988; Abdalla et al. 1990) suggesting that it is indeed the abnormal hormonal milieu, rather than the polycystic ovary itself, that is the problem for women with the PCOS.

Since the birth in 1978 of Louise Brown, the first baby born following in-vitro fertilisation and embryo transfer – in an unstimulated, "natural" cycle – many groups worldwide have reported their experience with IVF and related procedures. It is now possible to determine the rate of miscarriage from the publication of series with large numbers of pregnancies, both from individual clinics and collated national registers (Table 9.1).

It is important to note the criteria that are used both to diagnose pregnancy and to determine the gestational age at miscarriage, as these influence the interpretation of data from different series (Steer et al. 1989). Some groups record "biochemical" pregnancies and miscarriage separately, whilst others classify both together under the heading "miscarriage". The mean age of patients and the methods used to stimulate follicular growth are not always recorded. Up to 1989

Table 9.1. Analysis of multicentre studies on pregnancy outcome following various ovarian stimulation regimes for IVF–ET

Series	Time span	No. of cycles	Regimen	Pregnancies	Live births	Biochemical	Miscellaneous (%)
Trounson and Wood 1984	1979–82	874	CC/hMG	80	55	–	24 (30)
Seppala 1985	1978–84	10028	CC/hMG	1084	600+	–	324 (29.9)
Australian IVF Collab. 1985	1979–83	–	–	244	135	18%	50 (27)
Frydman et al. 1986	1981–84	1280	CC/hMG	142	100	15.5%	27 (19)
Andrews et al. 1986	1981–84	–	hMG/FSH	155	115	18%	23 (15)
Yovich and Matson 1988	1981–86	–	CC/hMG	205	139	9.7%	30 (14.6)
Cohen et al. 1988	1979–85	–	CC/FSH CC/hMG	2329	1456+	–	577 (24.8)
Sharma et al. 1988	1984–86	2232	CC/hMG	306	265	13.3%	26 (8.6%)
NPSU 1988	1979–87	–	CC/hMG	3247	1993	15%	1090 (33.6)
Corson et al. 1989	–	870	CC/hMG	242	187	–	39 (16.1)
Med Res Int 1989	1987	14647	–	1909	1858	–	472 (25%)
Total				9943	6903+	–	2682 (27%)

+ indicates ongoing pregnancies at time of publication

the most popular stimulation regimens were clomiphene citrate with either hCG or purified FSH, and there were also a small number of treatments performed in natural cycles.

The first large series was the World Collaborative Report compiled in 1984 by Seppala from the results of 200 groups worldwide. There was a miscarriage rate of 29.9% in the 1084 pregnancies reported and the 1.5% incidence of congenital anomalies was considered to be similar to that after natural conception. The Australian IVF Collaborative Group reported the results from 8 centres recording a miscarriage rate of 21% and a biochemical pregnancy rate of 18% (Australian IVF Collaborative Group 1985). When the "biochemical" pregnancies were excluded the spontaneous abortion rate was 27%, and this was greatest in older women, as expected after spontaneous conception. It was suggested that some causes of infertility may be associated with a high risk of spontaneous abortion and even premature delivery. The overall live-birth rate was 55% of all diagnosed pregnancies. Again the 1.1% incidence of major congenital abnormalities was equivalent to the Australian national average of 1.5%–2.0%.

Frydman et al. (1986) found that 34.5% of pregnancies conceived in their unit ended either as a biochemical pregnancy or a miscarriage, although with the exclusion of the former group the overall miscarriage rate of 22.5% is not very different from those reported for both fertile and infertile populations (Boué and Boué 1977; Weir and Hendricks 1969). Other authors concur with this finding and stress both the older age of treated women and the greater intensity of pregnancy monitoring, which leads to the detection of biochemical pregnancies and early

spontaneous abortions (Andrews et al. 1986; Yovich et al. 1988; Corson et al. 1989).

Early ultrasonography has also demonstrated the spontaneous absorption of a gestation sac in 11 of 42 twin pregnancies and in 5 of 13 sets of triplets (in which two were reduced to singleton pregnancies) (Corson et al. 1989). In another study, 140 pregnancies were scanned weekly from the fifth to the thirteenth week of conception (Tan et al. 1989). In the patients with one sac seen initially, 27% of the sacs disappeared; when there were two sacs, 25% disappeared; and with three sacs, 47% disappeared. The percentage of women who ended up with a viable pregnancy was 72%, 94% and 100% respectively for those initially with 1, 2 and 3 sacs.

The collaborative study by Cohen et al. (1988) looked at 2342 clinically detected pregnancies from 55 centres. With the exclusion of biochemical pregnancies, the miscarriage rate was 24.8% and was greatest in older women. The incidence of malformation was also higher in women of 34.7 years and older; this was 3.4% compared to an incidence of 2.7% in those under 32.9 years. The incidence of congenital malformations was also found to be higher in multiple births (3.6%) compared to singletons (2.5%). This is an interesting observation as the chance of a multiple pregnancy (Cohen et al. 1988) after IVF and its associated procedures is 19% (because of the usual transfer of 2 or more eggs/ embryos). The incidence of multiple pregnancy after natural conception is about 1%.

Two other large collaborative studies report the results of conceptions by both IVF and gamete intrafallopian transfer (GIFT) (National Perinatal Statistics Unit (NPSU) 1988; Medical Research International (MRInt) 1989). In 96 clinics in the United States in 1987 the miscarriage rate after IVF was 25% and after GIFT 24% (MRInt 1989). There was similarly little difference between the two procedures in Australia (22.9% for IVF and 24.7% for GIFT) (NPSU 1988). Again the incidence of miscarriage rose markedly with maternal age, being 14% in women under the age of 25 years and 40% in those over 40. This has been a consistent finding and many centres do not treat women over the age of 40 because of the reduced chance of achieving a pregnancy and the increased risk of miscarriage. This issue was addressed by Romeu et al. (1987) who actually found a surprisingly good response to ovulation induction and in-vitro fertilisation in older women, and also found that the abortion rate is only slightly higher than in the younger age group, at 60% overall (33.3% biochemical pregnancies and 26.6% clinical abortions). The incidence of chromosomal abnormalities is increased in this group of patients and so careful counselling and prenatal diagnosis is suggested.

The first 1000 pregnancies at the Hallam Medical Centre occurred as a result of treatment from 1984 to Feburary 1989. 680 pregnancies resulted in the birth of 901 live children (147 twins, 34 triplets and 2 sets of quadruplets). There were 52 ectopic pregnancies – an incidence of 5.2%, which is similar to the mean of 4.7% from other large series (Table 9.2). There were 13 cases of heterotopic pregnancy; in 7 of these there was a viable intrauterine pregnancy and the pregnancy progressed uneventfully after the ectopic pregnancy had been removed.

There were 80 biochemical pregnancies (8%) and 188 miscarriages (18.8%) resulting in an early pregnancy loss rate of 26.8%, excluding ectopic pregnancies. It is interesting that there is no difference between the mean age of the women

Table 9.2. Analysis of multicentre studies on the incidence of ectopic pregnancy and fetal congenital abnormality following treatment by IVF–ET

	Ectopic (%)	Congenital anomalies (%)
Trounson and Wood 1984	1.25	1.25
Seppala 1985	1.8	1.5
Australian IVF Collab. 1985	5	1.1
Frydman et al. 1986	2.1	2.6
Andrews et al. 1986	1.6	
Yovich and Matson 1988	7.8	
Cohen et al. 1988	5.2	3
Corson et al. 1989	5.8	
Med Res Int 1989	7	1.4
MRC 1990		2.9
Total	4.7	2

who miscarried (32.8 years (range 22–41)) and those who had successful pregnancies (32.1 years (range 22–44)). The primary diagnosis of sub-fertility was also the same in the two groups (Table 9.3) and this is similar to the experience of other centres. The mean gestation at the time of miscarriage was 9.75 weeks.

Luteal support was given in the form of 2 injections of hCG 2000 U, the first on the day of embryo transfer and the second three days later. We have since changed to the regimen of 5 daily intramuscular injections of Gestone 50 mg (Paines and Byrne UK) followed by hCG 1000 U on days 4, 7, 10 and 13 after oocyte recovery (Yovich et al 1991).

A variety of regimens are used in different centres for supporting the luteal phase of assisted conception cycles. Published reports of randomised controlled trials assessing the use of progesterone (P) (Leeton et al. 1985; Yovich et al. 1985; Trounson et al. 1986) or hCG (Yovich et al. 1984; Mahadevan et al. 1985; Buvat et al. 1990) fail to show significant improvements in pregnancy rates, although

Table 9.3. Analysis of multicentre studies of diagnostic categories of couples undergoing IVF-ET

	Tubal damage (%)	Endometriosis (%)	Male factor (%)	Immunological (%)	Unknown (%)	Other (%)
Trounson and Wood 1984	52	8	20		20	
Seppala 1985	78	8.7			13.1	
Frydman et al. 1986	90		12	3.2	2.5	
Cohen et al. 1988	67.9		3.5		11.9	16.7
Sharma et al. 1988	44.5	12.3	5.4	3.6	27.2	6.9
Corson et al. 1989	42	31	8	4	10	9
MRC 1990	65	6	8		11	8
Mean	62.8	13.2	9.5	3.6	12.2	10.2

there is usually a trend implying benefit. All of these studies have suffered by being too small and comprising heterogeneous populations of patients.

The study of Yovich et al. (1991), compared four groups: group 1 received no luteal support; group 2, hCG 1000 U given by intramuscular injection on days 4, 7, 10 and 13 of the luteal phase (the day of oocyte recovery being day 0); group 3, 50 mg progesterone in oil, given by intramuscular injection on days 0, 1, 2, 3 and 4; and group 4 being a combination of groups 2 and 3. 280 couples were randomised into the four groups during GIFT treatment cycles, although only 207 completed the treatment. Those in group 4 achieved the best pregnancy rate of 41.2%, compared to 27.5% in group 1, 34.6% in group 2 and 32.0% in group 3. These differences were not significant. However, the birth rates were significantly better in those women receiving luteal support (29.4% group 4, 26.0% group 3, 25.5% group 2) compared to those who received none (11.8%). Thus luteal support appears to reduce the miscarriage rate and improve the ongoing pregnancy rate.

Summary

In conclusion, we have found that the incidence of early pregnancy loss in our IVF practice differs little from that of other clinics. However, in contrast to the experience of others, and that expected for the general population, there was no difference in age between those women who miscarried and those who carried a pregnancy to term. When one accounts for the intensity of early pregnancy monitoring after assisted conception procedures, and hence the relatively frequent diagnosis of "biochemical" pregnancy, the overall spontaneous miscarriage rate is similar to that expected for the general population. Indeed it has been pointed out by Shoham et al. (1991) that as a mean age of under 30 is usually quoted for patients in studies of miscarriage after spontaneous conception, the abortion rate is treated, subfertile women might be "even lower than that of the so called normal population when adjusted for age". It is also encouraging to note that the drugs used in assisted conception regimens do not appear to adversely affect the incidence of congenital abnormalities.

References

Abdalla HI, Ahuja KK, Leonard T, Morris NN, Honour JW, Jacobs HS (1990) Comparative trial of luteinising hormone releasing hormone analogue/HMG and clomiphene citrate/HMG in an assisted conception programme. Fertil Steril 53:473–478

Abdulwahid NA, Adams J, Van der Spuy ZM, Jacobs HS (1985) Gonadotrophin control of follicular development. Clin Endocrinol 23:613–626

Adashi EY, Rock JA, Sapp KC, Martin EJ, Wentz AC, Jones GS (1979) Gestational outcome of clomiphene-related conceptions. Fertil Steril 31:620–626

Ahlgren M, Kallen B, Rannevik G (1976) Outcome of pregnancy after clomiphene therapy. Acta Obstet Gynecol Scand 55:371–375

Andrews MC, Muasher SJ, Levy D, Jones HW, Garcia JE, Rosenwaks Z, Jones GS, Acosta AA

(1986) An analysis of the obstetric outcome of 125 consecutive pregnancies conceived in vitro and resulting in 100 deliveries. Am J Obstet Gynecol 154:848–854
Australian IVF Collaborative Group (1985) High incidence of preterm births and early losses in pregnancy after IVF. Br Med J 291:1160–1163
Baird PA, Sadovnick AD, Yee IML (1991) Maternal age and birth defects: a population study. Lancet 337:527–530
Ben-Rafael Z, Dor J, Mashiach S, Blankstein J, Lunenfeld B, Serr DM (1983) Abortion rate in pregnancies following ovulation induced by human menopausal gonadotropin/human chorionic gonadotropin. Fertil Steril 39:157
Berman P (1975) Congenital abnormalities associated with maternal clomiphene ingestion. Lancet i:878
Bishop PMF (1970) Clomiphene. Br Med Bull 26:22–25
Bohrer M, Kemmann E (1987) Risk factors for spontaneous abortion in menotropin-treated women. Fertil Steril 48:571
Boué JG, Boué A (1973) Increased frequency of chromosomal anomalies in abortions after induced ovulation. Lancet i:679
Boué A, Boué J (1977) Le role des anomalies chromosomiques dans les echecs de la reproduction. J Gynecol Obstet Biol Reprod 6:5–21
Brambati B (1990) Fate of human pregnancies. In: Edwards RG (ed): Establishing a successful human pregnancy, Serono Symposia, vol. 66. Raven Press, NY, pp 269–281
Brown GB (1986) Gonadotropins. In: Insler V, Lunenfeld B (eds) Infertility: male and female. Churchill Livingstone, New York, pp 359–373
Buvat J, Marcolin G, Guittard C, Herbaut JC, Louvet AL, Dehaone JL (1990) Luteal support after LHRH agonist for IVF: superiority of human chorioinic gonadotropin over oral progesterone. Fertil Steril 53:490–494
Caspi E, Ronen J, Schreyer P, Goldberg MD (1976) The outcome of pregnancy after gonadotropin therapy. Br J Obstet Gynaecol 83:967–971
Cohen J, Mayaux MJ, Guihard-Moscato ML (1988) Pregnancy outcomes after in vitro fertilization: A collaborative study on 2342 pregnancies. Ann NY Acad Sci 541:1–6
Conway GS, Honour JW, Jacobs HS (1989) Heterogeneity of the polycystic ovary syndrome: clinical, endocrine and ultrasound features in 556 patients. Clin Endocrinol 30:459–470
Cornel MC, Kate LPT, Dukes MN, de Jong VD, Berg LTW, Meyboom RHB, Garbis H, Peters PW (1989) Ovulation induction and neural tube defects. Lancet i:1386
Corsan GH, Kemmann E (1990) Risk of a second consecutive first-trimester spontaneous abortion in women who conceive with menotropins. Fertil Steril 53:817–821
Corson SL, Dickey RP, Gocial B, Batzer FR, Eisenberg E, Huppert L, Maislin G (1989) Outcome in 242 in vitro fertilization-embryo replacement or gamete intrafallopian transfer-induced pregnancies. Fertil Steril 51:644–650
Czeizel A (1989) Ovulation induction and neural tube defects. Lancet i:167
Dekel N, Galiani D, Aberdam E (1990) Regulation of rat oocyte maturation: involvement of protein kinases. In: Bavister BD, Cummins J, Roldan ERS (eds) Fertilisation in mammals. Serono Symposia, Norwell, USA, pp 17–24
Downs SM (1990) Maintenance of meiotic arrest in mammalian oocytes. In: Bavister BD, Cummins & Roldan ERS (eds) Fertilisation in mammals. pp 5–16. Serono Symposia, Norwell, USA
Dyson JL, Kohler HG (1973) Anencephaly and ovulation stimulation. Lancet i:1256–1257
Edmonds DK, Lindsay KS, Miller JF, Williamson E, Wood PJ (1982) Early embryonic mortality in women. Fertil Steril 38:447–453
Erickson GF, Magoffin DA, Dyer CA, Hofeditz C (1985) The ovarian androgen producing cells: a review of structure/function relationships. Endo Rev 6:371–399
Field B, Kerr C (1974) Ovulation stimulation and defects of neural-tube closure. Lancet ii:1511
Fleming R, Haxton MJ, Hamilton MPR, McCune GS, Black WP, Macnaughton MC, Coutts JRT (1985) Successful treatment of infertile women with oligomenorrhoea using a combination of a luteinising hormone releasing hormone agonist and exogenous gonadotrophin. Br J Obstet Gynaecol 92:369–374
Fleming R, Jamieson ME, Hamilton MPR, Black WP, Macnaughton MC, Coutts JRT (1988) The use of gonadotrophin releasing hormone analogues in combination with exogenous gonadotropins in infertile women. Acta Endocrinol, suppl 288, 119:77–84
Fleming R, Coutts JRT (1988) luteinising hormone releasing hormone analogues for ovulation induction, with particular reference to polycystic ovary syndrome. In: Healy D (ed) Anti-Hormones in Clinical Gynaecology, Bailliere's Clin Obstet Gynaecol 2:677–688

Fowler PA, Messinis IE, Templeton AA (1989) Gonadotrophin surge-attenuating factor activity in human follicular fluid is different from inhibin. J Repro Fert, Abs series 4 no. 17
Frydman R, Belaisch-Allart JC, Fries N, Hazout A, Glissant A, Testart J (1986) An obstetric assessment of the first 100 births from the in vitro fertilization program at Clamont, France. Am J Obstet Gynecol 154:550–555
Frydman R, Fries N, Testart J et al. (1988) Luteinising hormone releasing hormone agonists in in-vitro fertilisation: different methods of utilization and comparison with previous ovulation stimulation treatments. Hum Reprod 3:559–561
Furuhjelm M, Jonson B, Lagergren CC (1962) The quality of human semen in spontaneous abortion. Int J Fertil 7:17–21
Garcia J, Jones GS, Wentz AC (1977) The use of clomiphene citrate. Fertil Steril 28:707–717
Gemzell CA (1967) Clomiphene induction of ovulation. In: Westlin B, Wiqvist N (eds). Fertility and sterility. Excerpta Medica Foundation, Amsterdam, p 43
Goldfarb AF, Morales A, Rakoff AE, Protos P (1968) Critical review of 160 clomiphene related pregnancies. Obstet Gynecol 31:342–345
Greenblatt RB, Barfield WE, Jungck EC, Ray AW (1961) Induction of ovulation with MRL–41. JAMA 178:101
Greenblatt RB, Roy S, Mahesh VB, Barfield W, Jungck EC (1962) Induction of ovulation. Am J Obstet Gynecol 84:900–907
Hack M, Brish M, Serr DM, Insler V, Lunenfeld B (1970) Outcome of pregnancy after induced ovulation. Follow-up of pregnancies and children born after gonadotropin therapy. JAMA 211:791–976
Hack M, Brish M, Serr DM, Insler V, Salomy M, Lunenfeld B (1972) Outcome of pregnancy after induced ovulation. JAMA 220:1329–1333
Harlap S (1976) Ovulation induction and congenital malformations. Lancet ii:961
Hassold T, Jacobs P, Kline J, Stein Z, Warburton D (1980) Effect of maternal age on autosomal trisomies. Ann Hum Genet 44:29–36
Hertig AT (1967) The overall problem in man. In Benirschke K (ed) Comparative aspects of reproductive failure. Springer-Verlag, NY, pp 11–41
Homburg R, Armar NA, Eshel A, Adams J, Jacobs HS (1988) Influence of serum luteinising hormone concentrations on ovulation, conception and early pregnancy loss in polycystic ovary syndrome. Br Med J 297:1024–1026
Homburg R, Eshel A, Armar NA, Tucker M, Mason PW, Adams J, Kilborn J, Sutherland IA, Jacobs HS (1989) One hundred pregnancies after treatment with pulsatile luteinising hormone releasing hormone to induce ovulation. Br Med J 298:809–812
Homburg R, Eshel A, Kilborn J, Adams J, Jacobs HS (1990) Combined luteinising hormone releasing hormone analogue and exogenous gonadotrophins for the treatment of infertility associated with polycystic ovaries. Hum Repro 5:32–35
Hook EB, Woodbury DF, Albright SG (1979) Rates of trisomy 18 in livebirths, stillbirths and at amniocentesis. Birth defects: original article series. New York: A. R. Liss, 15(5c):81–89
Howles CM, Macnamee MC, Edwards RG, Goswamy R, Steptoe PC (1986) Effect of high tonic levels of luteinising hormone on outcome of in-vitro fertilisation. Lancet i:521–522
Hull MGR (1990) Indications for assisted conception. In: Edwards RG (ed) Assisted Human Conception. Br Med Bull 46:580–595
Hull MGR, Glazener CMA, Kelly NJ et al. (1985) Population study of causes, treatment and outcome of infertility. Br Med J 291:1693–1697
Jacobs HS, Porter R, Eshel A, Craft I (1987) Profertility uses of luteinising hormone releasing hormone agonist analogues. In: Vickery BH, Nestor JJ (eds) LHRH and its Analogs. MTP Press Ltd, Lancaster, pp 303–322
James WH (1974) Anencephaly, ovulation stimulation and subfertility. Lancet ii:1353
Joel CA (1966) New etiologic aspects of habitual abortion and infertility with special reference to the male factor. Fertil Steril 17:374–379
Johnson P, Pearch JM (1990) Recurrent spontaneous abortion and polycystic ovarian disease: comparison of two regimens to induce ovulation. Br Med J 301:154–156
Jones GS, Acosta AA, Garcia JE, Bernadus RE, Rosenwaks Z (1985) The effect of follicle stimulating hormone without additional luteinising hormone on follicular stimulation and oocyte development in normal ovulatory women. Fertil Steril 43:696–702
Karow WG, Payne SA (1968) Pregnancy after clomiphene citrate treatment. Fertil Steril 19:351–362
Knight PG, Lacey M, Peter JLT, Whitehead SA (1990) Demonstration of a non-steroidal factor in human follicular fluid that attenuates the self-priming action of gonadotrophin-releasing hormone on pituitary gonadotropes. Biol Repro 42:613–618

Kurachi K, Aono T, Minagawa J, Miyake A (1983) Congenital malformations of newborn infants after clomiphene-induced ovulation. Fertil Steril 40:187–189

Lam S-Y, Baker HWG, Evans JH, Pepperell RJ (1989) Factors affecting fetal loss in induction of ovulation with gonadotrophins: increased abortion rates related to hormonal patterns in conceptual cycles. Am J Obstet Gynecol 160:621–629

Leeton J, Trounson A, Jessup D (1985) Support of the luteal phase in in vitro fertilization programs: result of a controlled trial with intramuscular Proluton. J In Vitro Fert Embryo Transfer 2: 166–171

Lev-Gur M, Rodriguez LJ, Smith KD, Steinberger E (1990) Risk factors for pregnancy loss apparent at conception in infertile couples. Int J Fert 35:51–57

Lunenfeld B, Serr DM, Mashiach S et al. (1981) Therapy with gonadotropins: Where are we today? Analysis of 2890 menotropin treatment cycles in 914 patients. In: Insler V, Bettendorf G (eds) Advances in diagnosis and treatment of infertility. Elsevier Inc, Amsterdam, pp 27–31

Lunenfeld B, Blankstein J, Kotev-Emet S, Kokia E, Geier A (1986) Drugs used in ovulation induction: safety of patients and offspring. Hum Reprod 1:435–439

MacDougall J, Tan SL, Jacobs HS (1992) Ovarian Hyperstimulation Syndrome after in-vitro fertilisation. Fertil Steril (in press).

MacGregor AH, Johnson JE, Bunde CA (1968) Further clinical experience with clomiphene citrate. Fertil Steril 19:616–622

Mahadevan MM, Leader A, Taylor PJ (1985) Effects of low dose human chorionic gonadotrophin on corpus luteum function after embryo transfer. J In Vitro Fert Embryo Transfer 2:190–194

Mason P, Adams J, Morris DV, Tucker M, Price J, Voulgaris Z, Van der Spuy ZM, Sutherland I, Chambers GR, White S, Wheeler MJ, Jacobs HS (1984) Induction of ovulation with pulsatile luteinising hormone releasing hormone. Br Med J 288:181–185

Medical Research International (1989) In vitro fertilization/embryo transfer in the United States: 1987 results from the National IVF-ET Registry. Fertil Steril 51:13–15

Mills JL, Simpson JL, Rhoads GG et al. (1990) Risk of neural tube defects in relation to maternal fertility and fertility drug use. Lancet 336:103–104

Miyake A, Kurachi H, Wakimoto H, Hirota K, Terakawa N, Aono T, Tanizawa O (1988) Second pregnancy with spontaneous ovulation following clomiphene- or gonadotropin-induced pregnancy. Eur J Obstet Gynecol Reprod Biol 27:1–5

National Perinatal Statistics Unit (NPSU) and the Fertility Society of Australia and New Zealand (1988) IVF and GIFT Pregnancies Australia and New Zealand, 1987. NPSU, 1988

Olson JL, Rebar RW, Schreiber JR, Vaitukaitis JL (1983) Shortened luteal phase after ovulation induction with human menopausal gonadotropin and human chorionic gonadotropin. Fertil Steril 39:284–289

Penrose LS (1933) The relative effects of maternal and paternal age in mongolism. J Genet 27:219–224

Poland BJ, Miller JR, Jones DC, Trimble BK (1977) Reproductive counselling in patients who have had a spontaneous abortion. Am J Obstet Gynecol 127:685–691

Polson DW, Mason HD, Saldahna MB, Franks S (1987) Ovulation of a single dominant follicle during treatment with low-dose pulsatile follicle stimulating hormone in women with polycystic ovary syndrome. Clin Endocrinol 26:205–212

Porter RN, Smith W, Craft IL, Abdulwahid NA, Jacobs HS (1984) Induction of ovulation for in-vitro fertilisation using buserelin and gonadotrophins. Lancet ii:1284–1285

Regan L, Braude PR, Trembath PL (1989) Influence of past reproductive performance on risk of spontaneous abortion. Br Med J 299:541–545

Regan L, Owen EJ, Jacobs HS (1990) Hypersecretion of luteinising hormone, infertility and miscarriage. Lancet ii:1141–1144

Romeu A, Muasher SJ, Acosta AA, Veeck LL, Diaz J, Jones GS, Jones HW, Rosenwaks Z (1987) Results of in vitro fertilization attempts in women 40 years of age and older: the Norfolk experience. Fertil Steril 47:130–136

Rutherford AJ, Subak-Sharpe RJ, Dawson MJ, Margara RA, Franks S, Winston RML (1988) Improvement of in-vitro fertilisation after treatment with buserelin, an agonist of luteinising hormone releasing hormone. Br Med J 296:1765–1768

Sagle M, Bishop K, Alexander FM, Michel M, Bonney RC, Beard RW, Franks S (1988) Recurrent early miscarriage and polycystic ovaries. Br Med J 297:1027–1028

Sandler B (1973) Anencephaly and ovulation stimulation. Lancet ii:379

Schwartz M, Jewelewicz R, Dyrenfurth I, Tropper P, Vande Wile RL (1980) The use of human menopausal and chorionic gonadotropins for ovulation induction. Am J Obstet Gynecol 138:801–806

Seppala M (1985) The World Collaborative Report on in vitro fertilization and embryo replacement: current state of the art in January 1984. Ann N Y Acad Sci 442:558–563
Sharma V, Riddle A, Mason BA, Pampiglione J, Campbell S (1988) An analysis of factors influencing the establishment of a clinical pregnancy in an ultrasound-based ambulatory in-vitro fertilisation program. Fertil Steril 49:468–478
Shoham Z, Borenstein R, Lunenfeld B, Pariente C (1990) Hormonal profiles following clomiphene citrate therapy in conception and nonconception cycles. Clin Endocrinol 33:271–278
Shoham Z, Zosmer A, Insler V (1991) Early miscarriage and fetal malformations after induction of ovulation (by clomiphene citrate and/or human menotropins), in vitro fertilization, and gamete intrafallopian transfer. Fertil Steril 55:1–11
Singh M (1978) Possible relationship between clomiphene and neural tube defects. J Ped 93:152
Smith KD, Rodriguez-Rigau LJ, Steinberger E (1981) The influence of ovulatory dysfunction and timing of insemination on the success of AID with fresh or cryopreserved semen. Fertil Steril 36:496–499
Spadoni LR, Cox DW, Smith DC (1974) Use of human menopausal gonadotropin for the induction of ovulation. Am J Obstet Gynecol 120:988–992
Stanger JD, Yovich JL (1985) Reduced in-vitro fertilisation of human oocyte from patients with raised basal luteinising hormone levels during the follicular phase. Br J Obstet Gynaecol 92:385–393
Steer C, Campbell S, Davies M, Mason B, Collins W (1989) Spontaneous abortion rates after natural and assisted conception. BMJ 299: 1317–1318
Steinberger E, Rodriguez-Rigau LJ, Smith KD (1982) Interaction of the two partners in the couple. In Menchini Fabris GF, Pasini W, Martini L (eds) Therapy in Andrology. Int Cong Ser 596: 21–29
Tan SL, Riddle A, Sharma V, Mason B, Campbell S (1989) The relation between the number of gestation sacs seen after IVF-ET and outcome of pregnancy. Proceedings of the XIIth Asian and Oceanic Congress of Obstetrics and Gynaecology
Thomas A, Okamoto S, O'Shea F, Maclachlan V, Besanko M, Healy D (1989) Do raised serum luteinising hormone levels during stimulation for in-vitro fertilisation predict outcome? Br J Obstet Gynaecol 96:1328–1332
Toshinobu T, Seiichiro F, Noriaki S, Kihyoe I (1979) Correlation between dosage or duration of clomid therapy and abortion rate. Int J Fert 24:193–197
Trimble BK, Baird PA (1978) Maternal age and Down syndrome. Age specific incidence rates by single year maternal age intervals. Am J Med Genet 1:1–5
Trounson A, Wood C (1984) In vitro fertilisation results, 1972–1982, at Monash University, Queen Victoria, and Epworth Medical Centres. J IVF-ET 1:42–47
Trounson A, Howlett D, Rogers P, Hoppen HO (1986) The effect of progesterone supplementation around the time of oocyte recovery in patients superovulated for in vitro fertilization. Fertil Steril 45:532–537
Wall JA, Franklin RR, Kaufman RH (1964) Reversal of benign and malignant endometrial changes with clomiphene. Am J Obstet Gynecol 88:1–7
Wang CF, Gemzell C (1980) The use of human gonadotrophins for the induction of ovulation in women with polycystic ovary syndrome. Clin Endocrinol 12: 479–486
Watson H, Hamilton-Fairly D, Kiddy D, Bray C, Armstrong P, Beard R, Bonrey R, Franks S (1989) Abnormalities of follicular phase luteinising hormone secretion in women with recurrent early miscarriage. J Endocrinol 123 suppl, Abstract 25
Weir WC, Hendricks CH (1969) The reproductive capacity of an infertile population. Fertil Steril 20:289–298
Yovich JL, Stanger JD, Yovich JM, Tuvik A (1984) Assessment and hormonal treatment of the luteal phase of IVF cycles. Aus N Z J Obstet Gynaecol 24:125
Yovich JL, McColm SC, Yovich JM, Matson PL (1985) Early luteal serum progesterone concentrations are higher in conception cycles. Fertil steril 44:185–191
Yovich JL, Matson PL (1988) Early pregnancy wastage after gamete manipulation. Br J Obstet Gynaecol 95:1120–1127
Yovich JL, Edirisinghe WR, Cummins JM (1991) Evaluation of luteal support therapy in a randomized controlled study within a gamete intrafallopian transfer program. Fertil Steril 55:131–139