4. Embryonic Loss: Clinical Perspectives

J.L. Yovich

Introduction

For women conceiving after prolonged periods of subfertility, the early diagnosis of pregnancy is welcomed with an overwhelming sense of achievement. However, such enthusiasm should be tempered by the knowledge that early pregnancy wastage is high (25%–30%) and includes a 5%–6% risk of ectopic pregnancy (Yovich and Matson 1988; National Perinatal Statistics Unit [NPSU] 1988). Furthermore, late pregnancy complications such as preterm delivery and low birthweight are increased mainly, but not entirely, due to the markedly increased risk of multiple pregnancies if ovarian stimulation or in vitro fertilization (IVF)-related therapies have been applied (NPSU 1988; Yovich et al. 1990). For these reasons subfertile couples should be counselled at an early stage so that they can receive the diagnosis of pregnancy with cautious optimism.

The underlying causes of pregnancy wastage are likely to be an extension of those same factors underlying implantation disorders, namely embryo quality and uterine receptivity. However, the further advanced the pregnancy, the more likely that additional complex maternal factors will operate and embryo-based factors will be less relevant. In addition, from the clinician's standpoint, two questions are prominent:

1. Is it possible to make an early or predictive diagnosis of pregnancy outcome?
2. What therapeutic options may be considered given the earlier diagnosis of an abnormal pregnancy or the prediction of early fetal loss?

Diagnosis of Pregnancy

The placental hormone human chorionic gonadotrophin (hCG) remains the most useful substance to test for the early diagnosis of pregnancy, although a number of other proteins can be considered, namely Schwangerschaftsprotein 1 (SP1)

Blighted Ovum (Anembryonic)

An intrauterine gestational sac is defined by ultrasound. However no clear fetal outline, fetal movements or fetal heart action is demonstrable within the sac which also needs to be differentiated from the pseudo-sac sometimes associated with ectopic pregnancies (Nyberg et al. 1983). The resolution of images from pelvic ultrasound is influenced by patient factors (e.g. the adverse effect of obesity), equipment characteristics (electronic phased array sector scanning preferred) and the scanning route (transvaginal technique may be preferable during early pregnancy, particularly for the retroverted uterus). The pregnancy may subsequently abort spontaneously or be evacuated electively following diagnosis.

Spontaneous Miscarriage

One or more viable fetuses are demonstrated within the gestational sac(s); i.e. fetal movements and/or heart action demonstrated but the pregnancy aborts before the 20th week.

Ectopic Pregnancy

Refers to any extrauterine pregnancy loss but the vast majority are intratubal. As previously noted this may be associated with an intrauterine pseudosac and increasingly, using transvaginal ultrasound, the intratubal pregnancy may be clearly defined, sometimes with a live fetus in situ. Occasionally combined intra- and extrauterine or heterotopic pregnancies will be diagnosed particularly in the high-risk situation of ovarian stimulation and/or IVF (Yovich et al. 1984, 1985b).

Other Early Pregnancy Losses

These include therapeutic pregnancy terminations, heterotopic pregnancies and hydatidiform molar pregnancies.

Advanced Pregnancies

Refers to those which advance beyond 20 weeks (dating is from LMP or adjusted LMP). Thereafter completed pregnancies are classified as births which are subcategorized as single or multiple, term or preterm, livebirths or stillbirths, perinatal losses (stillbirths and neonatal deaths) and normal or congenitally abnormal.

Histological confirmation of pregnancy will often but not always be obtained after pregnancy wastage. Preclinical pregnancies do not require curettage, improving ultrasound diagnostic skills means that suspected complete abortions or miscarriages may also not require curettage and many ectopics can now be treated by non-excision methods.

(Lenton et al. 1981), placental protein 14 (PP14) (Yovich et al. 1986a) and pregnancy-associated plasma protein A (PAPP-A) (Westergaard et al. 1983).

Beta-hCG is detectable between days 7 to 10 of the luteal phase in both spontaneous (Lenton and Woodward 1988) and IVF (Yovich et al. 1985a; Confino et al. 1986) conception cycles. However, many such cases may not show persisting rises nor reach the stage of either ultrasound (5th–8th week) or clinical (7th–10th week) diagnosis. Furthermore, hormone tests vary in both specificity and sensitivity hence laboratories must specify their reference standards (e.g. 25 mIU/ml beta-hCG detected by radioimmunoassay [RIA] set against the 2nd IS 61/6 equates with 52 mIU/ml on the first IRP 75/537). Increasingly, monoclonal enzyme-linked immunosorbent assays measuring colour or chemiluminescent endpoints are proving to have greater specificity and practical benefits than RIA, with coefficients of variation often under 5%.

However at this stage, for the aforementioned and other reasons there is a wide variation in the criteria applied for the diagnosis of pregnancy.

At PIVET, pregnancy diagnosis is based on the following criteria, arising from internal observations from more than 1600 clinically or histologically defined pregnancies and which is supported by independent observers (e.g. Lenton and Woodward 1988):

1. Quantitative serum beta-hCG $\geqslant$ 25 mIU/ml on or after day 16 of the luteal phase (dated from oocyte recovery or the day after LH surge)
2. Concomitant elevation of serum progesterone $\geqslant$ 31 nmol/litre and serum, oestradiol-17ß $\geqslant$ 620 pmol/litre
3. Beta-hCG continues to rise significantly on a further serum sample taken no less than 3 days later

If hCG injections have been used during the luteal phase, e.g. 1000 IU on days 4, 7, 10, and 13 (Yovich 1988), caution is required when interpreting the day 16 result. However the extensive experience at PIVET indicates that serum beta-hCG levels are almost never greater than 15 IU on samples collected 72 h or more after the injection and do not rise on the subsequent test if conception has not occurred.

Pregnancy Categories

Once pregnancy has been diagnosed, the following outcomes may occur:

Preclinical Pregnancy (Biochemical)

Any case which meets the above criteria for the diagnosis of pregnancy but does not reach completion of week 6, i.e. bleeding ensues when the beta-hCG level shows a fall, with subsequent levels <25 IU/ml. This may ensue after the completion of week 6 but if the event began at a prior stage and a clear sac is not demonstrable on ultrasound, it should still be categorized as a preclinical pregnancy loss.

Pregnancy Outcomes

From the outset it appeared that pregnancies generated in women of subfertile marriages were at greater risk of early wastage than the normally fertile population. At PIVET all pregnancies diagnosed were therefore registered and outcomes tabulated in order to assess the wastage rates and determine any underlying factors with a view to potential therapeutic considerations.

Materials and Methods

Following the referral of couples to PIVET for infertility over a 7-year period, 1657 pregnancies have ensued and completed their clinical outcome by May 1989. Following a clinical and investigative assessment according to a defined protocol (Yovich and Grudzinskas 1990), treatments have included reconstructive tubal microsurgery, specific treatments such as surgical or hormonal management of endometriosis, ovarian stimulation for disorders of ovulation and a range of procedures involving gamete handling/manipulation i.e. donor insemination (DI); intrauterine insemination of husband's washed, precapacitated sperm (AIH); and certain IVF-related procedures – gamete intrafallopian transfer (GIFT), traditional IVF and embryo transfer (IVF-ET), pronuclear stage tubal transfer (PROST) and tubal embryo stage transfer (TEST). The methods have been fully described (Yovich et al. 1989a, 1990) Yovich and Grudzinskas 1990) and variants have included ovum donation and IVF surrogacy. The vast majority of women having ovarian stimulation and gamete manipulation procedures (but only a small number of those having unstimulated cycles) had close hormonal and ultrasound tracking throughout the conception cycle so that the LH surge and ovulation days were precisely documented for subsequent dating.

Once pregnancy was diagnosed, a serum sample was obtained from women each week (dated from luteal day 16) through to week 12 and analysed for quantitative beta-hCG, oestradiol-17ß (E2) and progesterone (P4). Current assays are performed using the Amerlite (Amersham, UK) system, and have been adjusted to the appropriate reference levels for the previous double antibody RIA (Diagnostic Products Corporation, LA, USA). The inter-assay variation for the Amerlite hCG-60 assay gave the following results – low range (7–12 IU/litre): 6.5%, medium range (25–38 IU/litre): 4.2%, higher range (186–278 IU/litre): 4.3%. Selected serum samples have also been analyzed for SP1, PAPP-A and PP14 using RIAs by courtesy of J.G. Grudzinskas (Joint Academic Unit of Obstetrics, Gynaecology and Reproductive Physiology, London Hospital Medical College, London) and M. Chapman (Department of Obstetrics and Gynaecology, United Medical Schools [Guy's] London).

Results and Discussion

Pregnancy outcomes from the respective treatment programmes are show in Fig. 4.1. Of the total 1657 pregnancies diagnosed, 1145 (69.1%) progressed to births with the delivery of 1613 infants. Early pregnancy wastage ranged from a low

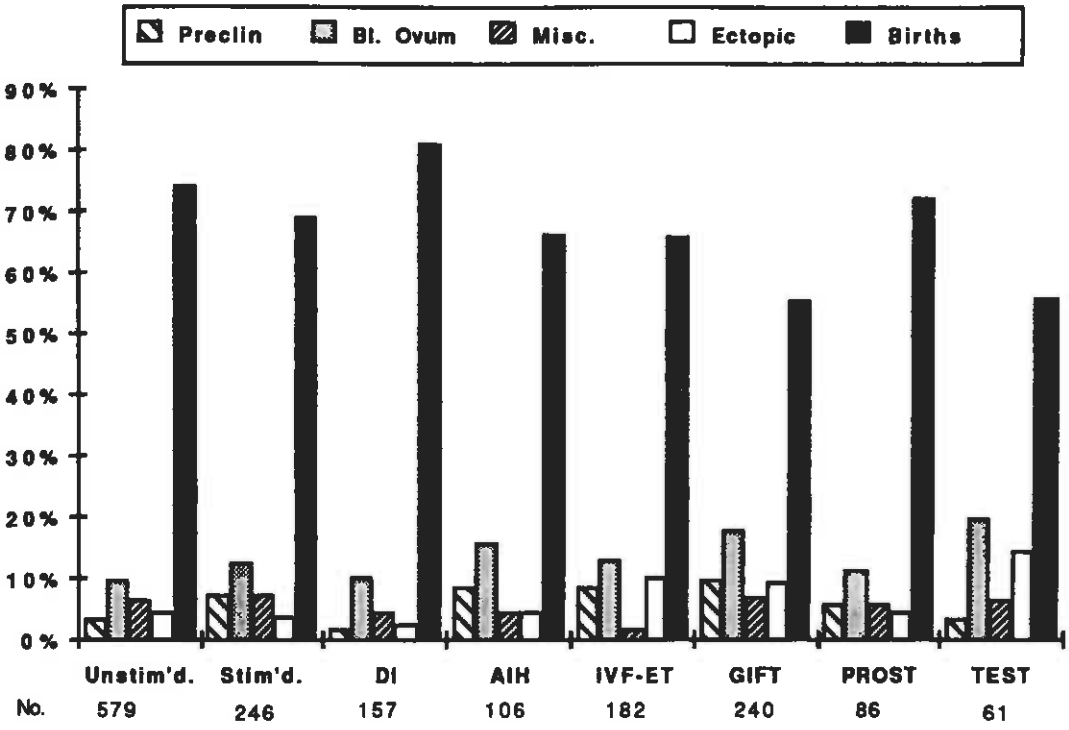

Fig. 4.1. Defined outcomes of 1657 pregnancies arising after various treatments for infertility over a 7-year period. Includes 5 heterotopic pregnancies categorized with ectopics, 12 therapeutic terminations categorized with spontaneous abortions and one hydatidiform mole categorized with blighted ovum pregnancies.

of 19% for DI to a high of 44.6% for GIFT. These findings are similar to a previous report from PIVET and are not related to age differences as the mean ages were similar in all programmes, ranging from 29.7 years in PROST to 32.7 years in GIFT (Yovich and Matson 1988). The better outcome for the DI programme may reflect the clear male-factor basis underlying the infertility (implying no female factor which might limit reproductive potential to conceive or carry a pregnancy) and the highly selected male gametes placed in the cervical canal (ensuring optimum embryo quality). With respect to the subcategories of pregnancy wastage the following interpretations can be made:

Preclinical Pregnancies

These comprised 6% (n=98) of all pregnancies and were highest in the GIFT programme. This latter finding was examined further and it was found that oligospermic patients treated by the modified GIFT protocol which involved transferring higher sperm numbers into the fallopian tubes (Matson et al. 1987) had early pregnancy wastage rates from combined preclinical and blighted ovum pregnancies of 56% (Yovich et al. 1989b). This finding is supported elsewhere (Rodriguez-Rigau 1989) and is likely to be due to polyspermic fertilization or other types of defective embryo which cannot be selected out in GIFT as with other IVF-related procedures. This is one of the reasons for developing the PROST and TEST procedures and regarding oligo/asthenospermia as contraindicated for GIFT.

The question of lingering exogenous hCG from luteal phase injections has been considered as a possible cause of false diagnosis of preclinical pregnancies in some patients. However, this is thought to be a rare phenomenon if it occurs and the finding of a 4% background rate of preclinical pregnancies in the unstimulated group (who also received no luteal phase injections of hCG) indicates that preclinical pregnancies are a real diagnostic category.

Blighted Ovum Pregnancies

This is the main category of early pregnancy wastage and ranged from 10% in women not receiving ovarian stimulation or having procedures involving gamete manipulation, to 20% for the TEST procedure. Previously we have commented on high blighted ovum pregnancy rates for AIH (Yovich and Matson 1988) and GIFT (see above) in relation to oligo/asthenospermia but this is unlikely to operate for TEST where embryos are preselected according to morphological criteria. Instead, the inclusion of post-cryopreservation embryos which may have suffered non-apparent damage, could explain the finding. With all IVF-related procedures it should be borne in mind that <25% of morphologically acceptable embryos have the capacity to implant even when maternal receptivity is optimal (Yovich et al. 1989a). It is likely that many IVF-generated embryos can begin the implantation process but not have the full capacity for normal post-implantation development.

Spontaneous Miscarriages

These comprised 6% (98 pregnancies) of outcomes and 32% of the combined group described in the past as "spontaneous abortions" (i.e. blighted ovum pregnancies and miscarriages; n=309). A high proportion of early miscarriages (6–12 weeks) were shown to have chromosomal aberrations on cytogenetic evaluation and later losses (12–20 weeks) were often multiple pregnancies.

Ectopics

Ectopic pregnancies were almost invariably tubal and comprised 6% (N=100) of outcomes. The rates were highest among patients with known or suspected tubal disease (Yovich 1990). In the TEST programme the highest rate of 14.8% was recorded and this was entirely among early cases included with past histories of fallopian tube reconstructions who failed to conceive spontaneously but had patency demonstrated in at least one tube (63 treatment cycles resulted in 23 pregnancies, 9 of which were ectopics [39%] with one arising after transcervical TEST). There was a similar background history of tubal disorders among the GIFT ectopics; as a result tubal transfer procedures are now totally contraindicated in any patient with any degree of tubal disease at PIVET. Ectopics are apparently an unavoidable problem in the IVF-ET group but may be minimized by careful uterine placement (Yovich et al. 1985c) which avoids deposition of embryos into the fallopian tubes where entrapment may occur if there are proximal endosalpingeal disorders or tubal dysfunction.

Heterotopic Pregnancies

Heterotopic pregnancies have occurred on five occasions. The hormonal data and abdominal ultrasound findings were misleading on each occasion by indicating parameters consistent with intrauterine pregnancy i.e. normal values for viable fetus and falling values for blighted ovum pregnancies. On an early occasion one woman presented in a state of clinical shock at 10 weeks with a ruptured tubal heterotopic pregnancy and subsequently miscarried her intrauterine twins almost 4 weeks later (Yovich et al. 1984). On each of the other occasions laparoscopy has been performed before the 9th week because of persisting vaginal bleeding (prune juice character) which did not cease following medroxyprogesterone acetate (MPA) therapy (see below). Persisting pelvic pain of a boring nature and localized to one iliac fossa has usually, but not always, been a supporting clinical symptom.

Hydatidiform Mole

This has occurred on only one occasion. The hormonal values were similar to the profile for blighted ovum (beta-hCG, E2 and P4 low and falling), the ultrasound features revealed the diagnostic snowstorm appearance and the histological findings after curettage indicated a degenerating hydatidiform mole.

Therapeutic Terminations

These have been performed on 12 occasions, almost invariably for genetic reasons following amniocentesis or chorionic villus sampling.

Late Pregnancy Outcomes

Data on large numbers of IVF-generated pregnancies indicates that the perinatal death rate is more than double that of the general community rates for singleton pregnancies and the risks are compounded by the high proportion of multiple pregnancies (NPSU 1988). The major problem is that of preterm delivery (12%–14% among IVF singleton pregnancies) and the problem is likely to be related to maternal factors rather than embryo characteristics or IVF techniques. The risk of singleton preterm delivery appears to be similar among subfertile patients regardless of the method of conception.

Multiple pregnancies are a consequence of ovarian stimulation and oocyte or embryo numbers transferred. IVF efficiency has improved in recent years due to improved ovarian stimulation methods; technical developments (e.g. in oocyte recovery and embryo transfer techniques); the introduction of tubal transfer procedures; increasing laboratory experience and expertise; and the use of luteal support regimens. Current data at PIVET indicates the risk of multiple pregnancy is 25%–30% when three embryos are transferred. This number is now set as the upper limit for oocytes and embryos. Pregnancy rates remain at 36% per treatment cycle with birthrates around 25% and it may well be time to consider further reductions in the maximum numbers transferred (Yovich et al. 1989a).

Fetal abnormality rates are not increased after fertility management (Yovich et al. 1988b) although one report suggests an increased incidence of spina bifida and transposition of the great vessels among IVF births and urinary tract malformations among GIFT births (NPSU 1988). Major recurrent abnormalities have not occurred among 1613 infants born following infertility treatments at PIVET.

Predicting Pregnancy Outcome

The evaluation of fetal wellbeing by a relatively simple serum test to reflect feto-placental function was inititally best achieved by human placental lactogen (hPL) estimations using RIA (Chard 1976). Low levels in the first trimester (>8 weeks)

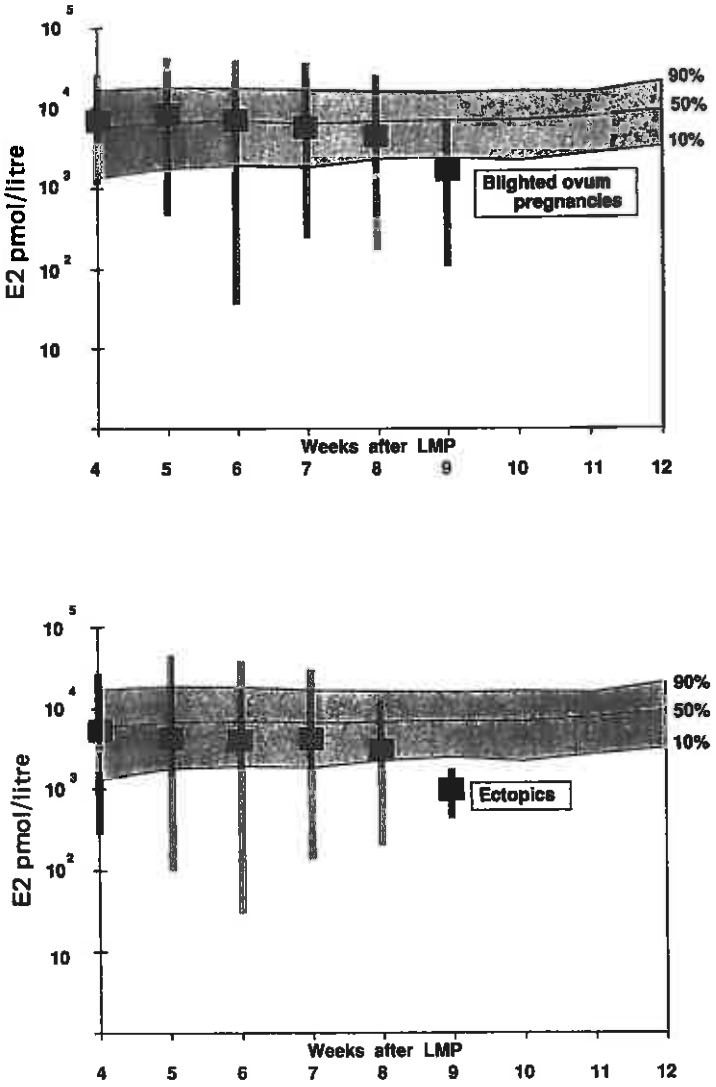

Fig. 4.2. Serial serum oestradiol-17ß (E2) estimations in women who had ovarian stimulation therapy, depicting profiles for normal singleton deliveries (shaded; n=100), tubal ectopic (n=52) and blighted ovum pregnancies (n=35). Filled boxes show observations around the mean and whiskers define the full range of observations at each week.

indicated a non-viable pregnancy and levels <4 μg/ml in late pregnancy indicated the fetus was at high risk from placental insufficiency leading to intrauterine growth retardation. However, clinicians were sceptical and preferred to place their confidence in the developing art of ultrasound at that time. Currently, there is a renewed interest in serum testing as a fine discriminator where ultrasound is at the limits of its diagnostic capacity (e.g. very early pregnancy) or as a screening test for time-consuming ultrasound examinations (e.g. genetic screening, the early detection of placental insufficiency) but mostly as a potential predictor of pregnancy outcome in both the early and late stages of pregnancy.

Early Pregnancy

Previous reports have addressed the question of the ability of placental hormone and protein measurements to provide a prognosis of pregnancy outcome (Yovich

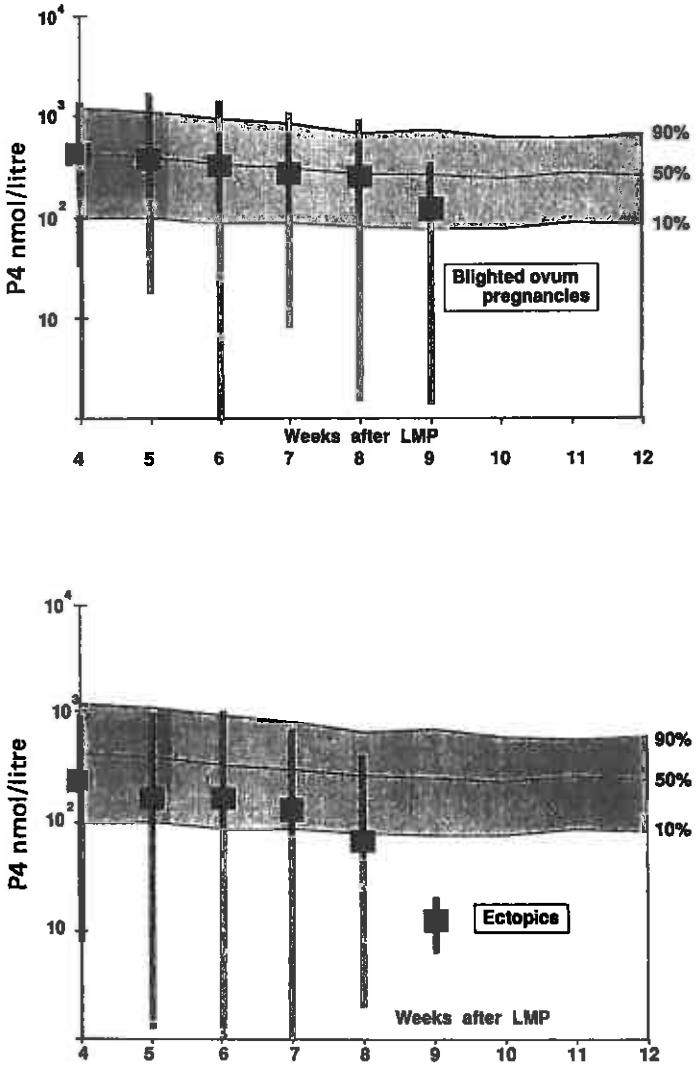

Fig. 4.3. Serial serum progesterone (P4) estimations in women who had ovarian stimulation therapy, depicting profiles for normal singleton deliveries (shaded; $n=100$), tubal ectopic ($n=52$) and blighted ovum pregnancies ($n=35$). Filled boxes show observations around the mean and whiskers define the full range of observations at each week.

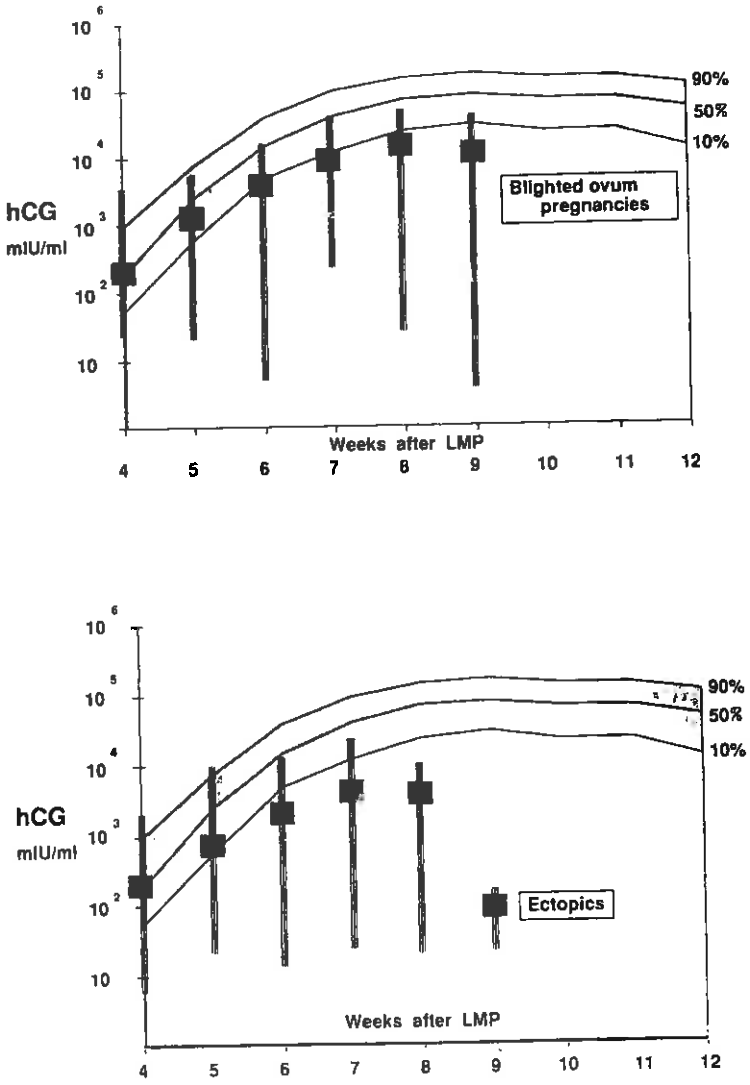

Fig. 4.4. Serial serum beta-hCG estimations in women who had ovarian stimulation therapy, depicting profiles for normal singleton deliveries (shaded; n=100), tubal ectopic (n=52) and blighted ovum pregnancies (n=35). Filled boxes show observations around the mean and whiskers define the full range of observations at each week.

et al. 1986a; 1986b). The most common clinical question concerns the differential diagnosis of spontaneous abortion and ectopic pregnancy. Serial estimations of E2 (Fig. 4.2), P4 (Fig. 4.3) and beta-hCG (Fig. 4.4) for 35 blighted ovum pregnancies and 50 ectopic pregnancies have been compared with the profiles from 100 normal singleton outcomes. All the cases had ovarian stimulation. In many patients the likelihood of pregnancy wastage was predictable at the time of pregnancy diagnosis by low levels of beta-hCG and sometimes low E2 and P4. For both ectopic and blighted ovum pregnancies, beta-hCG estimations provided the most sensitive indicator with significantly widening disparity from the norm with each advancing week. E2 and P4, whilst sometimes showing the same trend, did not become clearly diagnostic until a later stage when ultrasound information was also available. Furthermore, whilst ectopics tended to have lower beta-hCG levels, the profiles were not able to differentiate the two conditions until a late stage (8th and 9th week) when ectopic pregnancies almost

invariable showed very low E2 and P4 levels, particularly the latter. This data supports other reports suggesting that low P4 levels are indicative of ectopics (Matthews et al. 1986) but only from the 8th week. This is probably related to the stage at which the ovarian contribution to circulating P4 wanes, revealing low trophoblastic activity. Absence of a clear gestational sac in utero at 8 weeks usually means ectopic pregnancy but the diagnosis is not always clear if a pseudosac or degenerating gestational sac is present when laparoscopy will be required to make the definitive diagnosis. Some studies suggest that PAPP-A may be a useful differentiating marker (Sinosich 1988; Jacobs et al. 1990a) as levels tend to remain elevated until late with blighted ovum pregnancies but are very low or absent with ectopics. SP-1 exhibits a profile similar to beta-hCG in anembryonic pregnancies (Yovich et al. 1986a) without any specific advantages (except perhaps when hCG therapy is being used during early pregnancy) and PP14 did not appear to provide a useful prognostic test in that category of wastage.

Late Pregnancy

To date we have concentrated on early pregnancy outcomes in the studies at PIVET and have not recognized any obvious connection between early pregnancy hormonal profiles of beta-hCG, E2 or P4 and late pregnancy complications. Profiles of beta-hCG, SP-1 and PAPP-A have been analysed with respect to plurality and these indicate higher levels during the first trimester of twin and triplet pregnancies (Jacobs et al. 1990b). It appears unlikely that late pregnancy outcomes such as preterm parturition and placental insufficiency will be predicted from early pregnancy profiles of hormones and proteins derived from the ovary, trophoblast or decidua. However, direct fetal and placental assessment by biophysical measurements such as ultrasound, Doppler and perhaps nuclear magnetic resonance imaging techniques will make increasingly greater contributions.

Therapeutic Implications

The value of making predictive diagnoses is to improve the therapeutic options. These may be categorized as preventive (pre-pregnancy), early pregnancy therapies and late pregnancy therapeutic strategies.

Preventive

Preventive treatments are considered at PIVET for cases of recurrent abortion (three or more) and such cases require comprehensive investigations to exclude underlying disorders.

Genetic Causes

Detailed banded chromosome analysis of leucocytes is checked from both partners.

Anatomical Causes

The detection of anatomical defects involves careful clinical evaluation of the woman along with hysterography, laparoscopy and hysteroscopy to check for evidence of fibroids, cervical incompetence, DES uterus/cervix, active pelvic endometriosis, genital tract infections and uterine abnormalities. With respect to the latter, uterine synechiae, a septate uterus and possibly bicornuate uterine abnormalities may be relevant.

Infective Causes

Serological tests are performed for antibodies in the detection of syphilis, brucellosis, toxoplasmosis and rubella. Endocervical swabs are cultured for aerobic and anaerobic bacteria and specific investigations are performed to exclude infection with *cytomegalovirus, Chlamydia trachomatis,* herpes virus, *Listeria monocytogenes* and *Mycoplasma hominis*. Mycobacterium tuberculosis also requires consideration depending upon clinical features and the patient's demographic background.

Maternal Disorders

Tests are performed for systemic lupus erythematosus – lupus anticoagulant and/or cardiolipin antibody, ANF, C3 and C4; fasting blood sugar for diabetes; as well as screening for cardiovascular, renal and thyroid diseases. Other considerations such as exposure to anaesthetic gases, industrial chemicals and pesticides; the ingestion of antimetabolites and anticoagulants; and smoking/alcohol history may also be relevant in individual cases. Fertility assessments should include evaluation of the luteal phase (see below).

Immunotherapy by Paternal Lymphocytes

It has been suggested that the absence of an essential maternal immunoregulatory response to the genetically foreign fetus is the cause of at least some cases of recurrent miscarriage (Taylor and Faulk 1981). It has been speculated that immunizing the woman with her husband's prepared lymphocytes will stimulate the appropriate maternal response; one controlled study (Mowbray et al. 1985) has suggested that this approach might be valid. Certainly women who recurrently miscarry often have negative mixed lymphocyte reactivity (MLR) which is positive in most women who have successfully completed a pregnancy. This test is used to screen patients into a double-blind control trial at PIVET, which is part of a multicentre study. It is not possible at this stage to make a prediction but so far the majority of failed pregnancies after immunotherapy (when the protocol detail is revealed) have occurred in women receiving their own (control) cells.

Early Pregnancy Treatments

Studies reported during the sixties indicated that hormone support therapy was probably not effective (Shearman and Garrett 1963; Goldzieher 1964; Klopper

and MacNaughton 1965). Furthermore it was shown that 50%–60% of the fetuses obtained from women who experience spontaneous abortions have chromosomal abnormalities (Boué et al. 1975; Simpson 1980). However while the general rate of spontaneous abortions is considered to be 10%–15%, subfertile women who conceive are much more prone to abort their pregnancies (Lunenfeld and Insler 1978; Yovich and Matson 1988) and sometimes this was found to be caused by luteal phase defects (Jones 1976). In recent days two findings have influenced the current approach to hormone treatment during pregnancy. First, that pregnancies can be established and maintained in women without ovaries by simply providing exogenous oestradiol valerate and progesterone during the conception cycle and throughout the first trimester (Lutjen et al. 1984), and that high serum levels of progesterone should be maintained (Yovich et al. 1988a). Second, that after some ovarian stimulation treatments, the luteal phase may be severely shortened (Yovich et al. 1988a); this can be corrected by hCG injections to stimulate the corpus luteum or by using progesterone or the progestagen MPA.

Hormone Support Therapy

At PIVET, hormone support is provided for the following indications in the described regimens.

Ovarian Failure Pregnancies

Oral oestradiol valerate 2 mg t.d.s. is given in addition to Proluton 50 mg i.m.i. daily and progesterone pessaries (locally manufactured) 100 mg b.d. vaginally. (The ability of this current vaginal pessary to replace the injections altogether is being explored.) Placental production of E2 and P4 is usually, but not always adequate by the 8th week; the drug regimen is therefore continued to the 12th week and weaned over the ensuing fortnight.

Threatened Abortion

Women who present with fresh vaginal bleeding sufficient to cause staining (more than 3 cm on the underclothing) are offered MPA therapy within a trial testing its efficacy in reducing wastage from the spontaneous abortions of normal fetuses. Early data from this suggest a beneficial effect without causing the retention of abnormal fetuses or creating fetal abnormalities (Yovich et al. 1988b).

During the acute phase of bleeding, MPA tablets (Provera, Upjohn) are commenced 20 mg 4-hourly (120 mg/day) and women are advised to rest at home. As vaginal bleeding settles, the schedule is reduced to 20 mg q.i.d.; the patient can mobilize normally but should avoid coitus for 2 weeks. If beta-hCG levels remain elevated, MPA is continued and reviewed at the 8th week. With ultrasound confirmation of a viable pregnancy MPA is continued through to the 16th week and is weaned off over the ensuing fortnight. If ultrasound fails to confirm viability by the 8th week, the differential diagnosis of blighted ovum, missed abortion or ectopic pregnancy must be investigated.

Recurrent Abortion

In the belief that such cases may have a corpus luteum defect, hCG is used to maintain luteal activity and is usually supported by MPA. The regimen commences at the time of pregnancy diagnosis as follows:

5000 IU hCG i.m.i. twice weekly (e.g. Wed/Sun) to 10 weeks.
MPA 20 mg oral q.i.d. to 16 weeks, weaning over the ensuing fortnight.

In selecting MPA as the support progestagen for PIVET patients, we were influenced by previous observations that the drug did not cause significant congenital abnormalities and, in the case of virilization of one female infant amongst 170 newborn (Burstein and Wasserman 1964), only mild clitoral hypertrophy was noted. MPA is a substituted progesterone and therefore differs from the derivatives of the 19-nortestosterone group which have been used in the past and have been shown to have androgenic effects on the developing female fetus (Wilkins 1960). Female virilization has also been observed by the author associated with the use of both hydroxyprogesterone caproate and hydroxyprogesterone hexanoate. The orally active form of MPA was chosen rather than the depot form since the latter may occasionally maintain an elevated basal temperature and inhibit ovulation for several months after spontaneous abortion. Furthermore MPA is well absorbed orally and stable plasma concentrations around 27 nmol/litre are established on the regimens described (Yovich et al. 1985d). That study also examined the profile of steroid metabolites in maternal urine during the first trimester of pregnancy and showed no abnormal peaks on gas-liquid chromatography and mass spectrometry.

Genetic Abnormalities

These can be diagnosed by chorionic villus sampling for chromosome analysis and DNA probe analysis; amniocentesis for cytogenetic studies and alpha-fetoprotein (AFP) estimations; and midtrimester ultrasound scanning for anatomical abnormalities in high-risk patients. Several studies have shown the value of maternal serum estimations of AFP, unconjugated oestriol and beta-hCG to screen for Down's syndrome (see Chapter 11).

Ectopics

Only four of the 100 ectopic pregnancies presented in a ruptured state; two very early in the series and two others who were travelling and discontinued serial hormone monitoring. The benefits of the very early diagnosis of ectopic pregnancy are:

1. Avoidance of the life-threatening condition of rupture which is uncommon before the 7th week.
2. Early detection enables more conservative surgery to be considered (e.g. salpingotomy and microsurgical repair).
3. Unruptured ectopics may be treated without recourse to laparotomy.

Increasingly, unruptured ectopics are now treated by either laparoscopic aspiration (Pouly et al. 1986) or ultrasound-directed methods such as injection or the fetus of the gestational sac with methotrexate (Feichtinger and Kemeter 1987) or potassium chloride (Robertson et al. 1987); and needle aspiration (Davison and Leeton 1988).

Other Pregnancy Disorders

Serum hormones are generally in the normal range until the clinical event for those pregnancies which spontaneously miscarried. An ideal marker would discriminate between a normal and an abnormal fetus and thus allow rational hormone therapy. Similarly, the diagnosis of heterotopic pregnancy is difficult and may not be clear until tubal rupture. The diagnosis of non-heterotopic ectopics may be defined by the absence of PAPP-A in serum, but a positive marker is required for heterotopics because of the masking effect of the intrauterine pregnancy.

Late Pregnancy Treatments

During early pregnancy, the principles of management rest on the belief that most pregnancy losses are a consequence of embryo defects. Markers are sought to define the few cases of fetal loss which might be salvaged. However, in late pregnancy the principles of management assume that the fetus or fetuses are healthy and any treatment to restrict wastage is best directed towards assisting the maternal powers to carry the pregnancy to term. In this respect high-risk pregnancies such as high-order multiples are offered the following treatment at PIVET:

1. Maintain physical integrity of the cervix by the routine insertion of a cervical suture (Shirodkar type) as soon as a viable fetus is demonstrated (8th week).
2. Inhibit uterine contractility and irribility by MPA 20 mg q.i.d. orally throughout the pregnancy to 36 weeks if possible.
3. Reduce the risk of preterm labour by increasingly strict limitations of physical activity from 20 weeks gestation.

This regimen appears to be of benefit in reducing preterm delivery and perinatal mortality in triplet and higher order pregnancies (Yovich et al. 1989a). At PIVET it is now being applied routinely in the management of all multiples and other pregnancies categorized as high-risk for preterm labour.

Conclusions

Over the last two decades, major changes have occurred in the clinical management of early pregnancy complications. On the one hand the rapidly expanding use of assisted reproduction has been attended by an increased

prevalence of blighted ova, ectopic pregnancies and spontaneous miscarriages. On the other hand, rapidly advancing diagnostic techniques (particularly serum assays and ultrasound) have enabled earlier diagnoses and thus allowed a more rational, elective approach to treatment. For example, blighted ovum pregnancies can be evacuated without waiting for clinical signs of abortion and ectopic pregnancies are increasingly being treated by non-laparotomy methods such as injection of the sac/fetus, or laparoscopic aspiration. The life-threatening clinical picture of ruptured ectopic pregnancy can be avoided in high-risk patients (e.g. those conceiving by assisted reproduction procedures) by serial monitoring of serum hormones and early pelvic ultrasound, preferably transvaginal. This, of course, is an expensive and relatively intensive protocol which can only be justified in selected circumstances. However it is possible to envisage a single blood test performed between the 6th and 8th week of all pregnancies which might indicate the potential viability of that pregnancy (e.g. by quantitative beta-hCG and steroid levels) as well as the likelihood of tubal pregnancy (e.g. from PAPP-A levels) and even genetic defects in apparently normal pregnancies. It also remains a useful research pursuit to attempt to define those potentially viable pregnancies which might benefit from hormonal support. Hopefully, even the prediction of late pregnancy complications such as preterm delivery might be possible using an early pregnancy serum marker and this would have important therapeutic implications during the first trimester.

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