RACOG EDUCATION

Resource Unit 143

Progesterone Support for Early Pregnancy

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Historical Perspective

A consideration of the history of progesterone administration for the treatment of threatened or recurrent abortion is important because it may have influenced many contemporary obstetricians to eschew the practice. The concept of an essential hormone for the maintenance of pregnancy dates to the turn of the century and concluded in the 1950s with the isolation and identification of progesterone (1). Animal experiments, which involved removal of the corpus luteum with subsequent abortion, was at least partially duplicated in women by Csapo in 1973 who reported that seven of 11 patients who underwent luteectomy in the first trimester of pregnancy subsequently miscarried (2). In the preceding two decades progesterone was at first widely used for preventing pregnancy loss and then abandoned because controlled trials were unsuccessful in demonstrating benefit (3). In its enthusiasm to embrace evidence-based medicine, the obstetric discipline still refers to these appropriately conducted controlled trials as conclusive proof that it is misleading patients to prescribe progesterone for threatened or feared pregnancy loss. Yet these studies were mostly conducted in an era before ultrasound could evaluate the viability of an early pregnancy and before the epidemiology and common cause for most early pregnancy losses was appreciated. Studies of the natural history of recurrent abortion indicate that, even after three or more consecutive losses, the chance of a successful pregnancy is at worst 54%, and in practice, closer to 75% (4) ie not that much different to the overall rate of clinically successful pregnancies in the general population.

The epidemic of reproductive tract damage which arose from the use of stilboestrol in pregnancy, and the long term oncogenic potential for this practice was a further salutary lesson in obstetrics. For progesterone, its counterpart was demonstrated in instances of masculinization of the female fetus from the use of progestins during the period of fetal ontogenesis (5). Other studies had also suggested that orally administered progestins could be luteoloytic in pregnancy, ie to suppress the synthesis and release of ovarian progesterone, and this reinforced the caution already extant in the use of these agents for the treatment of recurrent abortion. Seemingly conclusive proof for a non-essential role for 'normal or ovulatory' concentrations of progesterone in early pregnancy was provided in 1993 with the publication of a study of 118 women whose serum concentrations were followed from the time of assisted conception (IVF or GIFT). Eight patients had serum progesterone values at four weeks gestation which were below the 5th percentile, one as low as 1.9 nmol/L, but each one subsequently delivered a term infant (6). A similar patient was described by Sultan et al (7).

However, two other developments in human reproductive endocrinology has again focussed attention on the importance of progesterone in early pregnancy support. The first is the high efficacy of the progesterone antagonist Mefepristone in medical termination of pregnancy (8) and the second is reports of successful pregnancy in oophorectomized women whose endometrium is primed with sequential oestrogen and progesterone and who are then the recipients of transferred embryos after in vitro fertilisation of donor oocytes (9). For these women progesterone (and oestrogen) administration is usually continued into the second trimester of pregnancy when the placental production of these hormones is sufficient to sustain the pregnancy.

In a meta-analysis of randomised control trials of progestational agents in pregnancy, Goldstein et al concluded in 1989 (3) that the rate of term livebirth in a subgroup of women who had two or more miscarriages suggested no benefit for this therapeutic intervention (7 studies, odds ratio 1.02, and 95% confidence intervals 0.70 to 1.50). In a contrary view, published within the same issue of the British Journal of Obstetrics and Gynaecology, Daya (10) concluded from a meta-analysis of three trials in women with recurrent abortion that progesterone was effective in the maintenance of pregnancy to 20 weeks gestation (odds ratio 3.09 and 95% confidence intervals 1.28 to 7.42). Both investigators concluded that the question required further study.

Progesterone Concentrations in Early Pregnancy

Most studies of serum concentrations of progesterone in the first trimester of successful pregnancies have concluded that the lower limit of normal (5th centile) is in the vicinity of 30-40 nmol/L (6,11). This is, coincidently, similar to the lower limit of normal for the midluteal peak in an ovulatory cycle with a normal luteal phase (12). However, studies have also demonstrated a dip in serum concentrations between weeks 6 and 8 of gestation in individual patients (13). This is supportive evidence for the luteo-placental shift in steroidogenesis but sometimes misinterpreted by patients and their carers as a sign of imminent pregnancy loss. This misapprehension may arise from a simultaneous study of beta HCG concentrations in which falling levels are strongly predictive of pregnancy demise (14). Sometimes there is enormous pressure from patients and their significant others to provide progesterone support in such situations particularly if the pregnancy has arisen from a highly contrived cycle of assisted conception or if the woman is the distressed victim of recurrent abortion.

However, the interpretation of serum levels of progesterone needs to be tempered by two further observations. Firstly, progesterone secretion from the corpus luteum, at least in the secretory phase of a menstrual cycle, is a pulsatile one and serial sampling may reveal fluctuations of between two and threefold in the space of hours (15) and similar fluctuations occur throughout pregnancy (16). Secondly, there is evidence from the administration of progesterone to the vagina that progesterone may act in the pelvis, not as a circulating hormone, but as a local trophic factor for the endometrium (17). Blood concentrations therefore may not accurately reflect uterine concentrations of progesterone.

Progestational Agents and Routes of Administration

Many of the classic studies of progesterone support in both early and late pregnancy have used synthetic progestins which have the advantage of either oral administration or a depot effective after intramuscular use. However, each of these have several disadvantages for use during pregnancy and particularly during the first trimester. First, there is the concern about their potential teratogenic effects although this relates more to the androgenic derivatives of nor-testosterone. Secondly, there is the possibility that these agents may actually suppress progesterone secretion from the corpus luteum or the placenta (18). One could hypothesise that this could occur with any progestational agent, including progesterone itself if administered in sufficient quantities, and if indeed a feedback inhibition to synthesis does exist. The final problem is that these agents cannot be monitored in the same way that natural progesterone can with readily available and accurate assays of serum progesterone.

Until recently the only form of progesterone which was readily available required intramuscular administration (Proluton available as 25mg in oil from Schering P/L) and it is expensive. The manufacturer does not support its use in pregnancy. Daily or twice daily injection of between one and four ampoules is required to maintain serum concentrations in some pregnant women within the normal range and, over the course of the first trimester, this can cost several hundred dollars. Pessaries of progesterone in 100mg and 200mg doses are now becoming available and have the advantage of simpler administration although the cost is similar to that of the intramuscular preparation. This route however, carries the disadvantage that measurements of serum levels may not accurately reflect concentrations reaching the endometrium and there is evidence for highly variable absorption even within the same individual using the same vaginal dose (19, 20). Not all pessaries are equally as efficacious and the base in which the progesterone is mixed is an important variable (21). Elsewhere, oral micronised progesterone, transdermal and even nasal administration of progesterone has been used with effect in functionally agonadal women (22).

A Practice of Progesterone Support

It should be acknowledged that several well-conducted studies have shown that close psychological support has a positive benefit for patients with recurrent abortion (23) and it is possible that frequent and supportive contact with the physician or a clinic is as important to patients as the progesterone itself.

In the author's practice, over the past 15 years, progesterone support is considered for three categories of patient:

1. Those with a history of recurrent abortion (two or more spontaneous first trimester losses) and **for whom there is documented deficiency of serum progesterone** at the time of confirmation of their pregnancy (random morning assay PROG<35 nmol/L). Included in this category are patients who may have been demonstrated to have had a luteal phase deficiency in non-pregnant cycles (midluteal PROG<30nmol/L) and patients with proven or suspected immunological causes for recurrent abortion ie antiphospholipid syndromes or even just a significantly positive ANA (titre >1:40).

2. Those who are anovulatory or functionally agonadal and receiving hormone replacement therapy with frozen and thawed embryo transfer.

3. After a cycle of assisted reproduction in which a GnRH agonist was used to down regulate the pituitary prior to ovarian stimulation with FSH. In this situation HCG is administered prior to egg collection but, if ovarian hyperstimulation is suspected, progesterone rather than HCG may be used in luteal support in order to reduce the risk of (22) ovarian hyperstimulation syndrome (OHSS).

Of these three, the last is the most unlikely to require progesterone support for very long because ovarian function is intact and trophoblastic HCG is likely to promote development of functioning corpora lutea from the multiple residual follicles. In contrast, patients who are receiving donor eggs because of ovarian failure are those who are most dependant on their exogenously supplied hormones, and generous progesterone support throughout the first trimester of pregnancy is required until there is clear evidence that the trophoblast is self sustaining. These patients require both oestrogen and progesterone support and fertility clinics who manage such patients will each have their preferred protocols.

Prior to the commencement of progesterone support (and preferably prior to the commencement of pregnancy in patients with a history of recurrent abortion) the woman and her partner are counselled about the role of progesterone in pregnancy and some of the controversies which have been addressed above. It is explained that there is no conclusive evidence that certain blood levels of progesterone are essential for the maintenance of pregnancy. Some patients then elect to not receive treatment (often with successful outcome). Some other patients benefit from the reassurance of twice weekly measurement of serum progesterone which remains >35 nmol/L without therapy. The safety of natural progesterone use in pregnancy is addressed and all of the points reinforced by a handout for the couple to take away and study (this is available from this author at the listed address).

Progesterone in oil (Proluton 25 mg/ml) by intramuscular injection is favoured because of its known effects and ease of monitoring. Doses of two ampoules daily are commenced and the serum progesterone measured 24 - 48 hours after the first dose. If the serum concentration remains less than 35 nmol/L, then the dose is increased and rechecked after 24 hours. Serum the level monitoring is thereafter continued on a twice weekly basis. If the serum concentration exceeds 70 nmol/L one week after commencement of therapy then the dose of progesterone is reduced at weekly inervals with continued monitoring.

With each blood sample quantitative beta HCG is measured and plotted on a nomogram of normal values until a viable pregnancy is confirmed by vaginal ultrasound at 6.5 weeks gestation (4.5 weeks post-conception). Beta HCG monitoring is then suspended so as to avoid confusion and alarm for the patient and her carers when the physiological fall in this hormone occurs at 8 - 9 weeks gestation. While the demonstration of fetal heart motion at 6.5 weeks gestation is a reasonable assurance of a good prognosis, it needs to be remembered for all patients that 5 - 8% can still experience pregnancy loss and a repeat ultrasound is recommended at 8 - 9 weeks gestation.

The dose of progesterone is adjusted according to serum concentrations and it is usually possible to suspend therapy before the end of the first trimester. If there is threatened abortion at any time, ie vaginal bleeding, then the pregnancy is rechecked by ultrasound and progesterone resumed if embryonic development is normal. In order to reassure all involved that the progesterone therapy is not supporting an abnormal conception prenatal diagnosis for chromosomes by chorionic villus sampling or amniocentesis is offered to all patients, but is rarely taken up.

Alternatives to the use of intramuscular progesterone include vaginal progesterone pessaries 200 - 400mg twice daily or oral Provera 40mg daily in divided doses. The latter is used for patients who are unable to afford progesterone by injection or pessary. However, in both of these situations (and particularly with Provera use), blood testing of progesterone is not used other than for the initial test to decide whether therapy is warranted. The dose of Provera or progesterone by pessary is simply reduced and ceased by about 12 weeks gestation. However, it should be acknowledged from both of the meta-analysis studies conducted by Goldstein et al (3) and Daya (10) that a case could be made for long-term progesterone support in pregnancies at risk of preterm delivery or pregnancy loss after 20 weeks gestation.

Conclusion

It could be reasonably argued that few pregnancies are lost because of an obstetrician's failure to provide exogenous progesterone support, and there is no justification for the indiscriminant use of progestational agents in the first trimester of pregnancy, even for the majority of women who have experienced previous pregnancy losses. However, there are grounds for believing that some women, and certainly those who have undergone certain programs of assisted conception, may benefit from administered progesterone. There is a great deal of data on the physiology and pharmacology of progesterone in early pregnancy which can provide a scientific basis to therapy and one such approach is described in this Resource Unit.

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