

Chapter 1

Induction of Ovulation: Solutions and Problems

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Over the last couple of decades there have been remarkable advances in the treatment of infertility. In the case of anovular infertility particularly, we now expect to achieve pregnancy rates that are no different from those in normal women of the same age (Hull *et al.*, 1979). What we do find however is that these superb results are often compromised by multiple pregnancy rates that are much higher than occur in normal women. While the increase is mostly attributable to twins, sadly higher order multiple pregnancy remains a frequent complication of infertility treatment. I discuss below in some detail why this is so serious a problem. Here I wish to emphasise that the health of children born as a result of multiple pregnancy and the welfare of their families may be so impaired that the target of our efforts should now be shifting from efficacy (the clinic's pregnancy rate) to the quality and safety of outcome (as indexed by the *singleton* birth rate, together with the rates of perinatal mortality and morbidity). Fertility clinicians sometimes do not fully consider the devastation that can be wrought on a whole family with the arrival of multiple sibs, each with special and sometimes overwhelming health problems. Moreover, the damage inflicted may last for more than one generation. We always need to ask ourselves whether, in our efforts to help couples with infertility problems, we are also attending to the welfare of the unborn child and to the needs of other children in the family.

It is instructive to start with the context in which ovulation induction takes place. The importance of accurate diagnosis and

assessment is set out in Chapter 3, in which the role of adequate nutrition is rightly stressed. This includes attention to vitamin and mineral intake but in my opinion the relevance of adequate overall nutrition cannot be overemphasised. As described in Chapter 6, a number of women with anorexia nervosa present to infertility clinics with anovulatory infertility. In my experience, it is more common for women referred with the latter diagnosis to be discovered to be underweight (BMI less than 19 kg/m^2), with the characteristic endocrine profile of low serum LH and oestradiol concentrations. On ultrasonography they are found to have multifollicular ovaries and a small uterus with little endometrial thickening (Adams *et al.*, 1985). Bone densitometry usually reveals skeletal decalcification. In clinics drawing referrals from universities such patients may represent as many as 20% of those referred with amenorrhoea (Balen and Jacobs, 1997).

In considering the optimum method for underweight women with amenorrhoea to recover their fertility, two important issues should be considered. The first relates to the experience of such patients as mothers, the second to more medical concerns, such as the immediate outcome of pregnancy. As mentioned in Chapter 6, the obstetric outcome of underweight women who conceive without treatment is often impaired – they have, for example, twice the rate of small-for-dates babies as do women of normal weight. When underweight women with amenorrhoea conceive as a result of induction of ovulation, the proportion of small-for-dates infants rises to 50% and there is a significant increase in the rate of obstetric interventions needed to protect the baby (van der Spuy *et al.*, 1988).

When these observations are coupled with the problems in parenting that may be experienced by women with anorexia nervosa (Russell *et al.*, 1998) and the adverse effects of impaired nutrition during pregnancy on patterns of childhood and adult health (Barker, 1997), I find the arguments against induction of ovulation in underweight women most compelling. In my opinion, appropriate management is by weight increase, often coupled with psychiatric

support. Women with weight-loss related amenorrhoea can expect to resume ovulation when their body mass index reaches 19–19.5 kg/m² (Knuth *et al.*, 1977). A point to remember, however, is that some 20% of women have ultrasound detected polycystic ovaries (Polson *et al.*, 1988), including those with amenorrhoea caused by loss of weight. It has been known for some years that a similar proportion of women recovering from anorexia nervosa do not resume menstrual cycles when they reach their target weight (Crisp and Stonehill, 1971). It is appropriate therefore to monitor recovery with serial ultrasonography (Treasure *et al.*, 1988) and offer induction of ovulation to those who achieve their target weight but do not resume regular and predictable ovulation cycles.

Turning now to medical treatment, the immediate risks are ovarian hyperstimulation syndrome (OHSS) and multiple pregnancy. How might one reduce them? Practical clinical advice is given in Chapters 7 & 10 where the importance of using low doses of gonadotrophins is rightly emphasised. As indicated in these chapters, OHSS only occurs after therapeutic ovarian stimulation, most particularly after administration of human chorionic gonadotrophin (hCG) and it nearly always occurs in women with polycystic ovary syndrome (MacDougall *et al.*, 1993). McLure and colleagues first demonstrated an increase in vascular endothelial growth factor (VEGF) in the ascitic fluid of patients with OHSS (McClure *et al.*, 1994). Their results, obtained with a laborious bioassay, have since been confirmed using technically much less demanding immunological methods of measurement (Agrawal *et al.*, 1997).

VEGF is an endothelial cell mitogen which also increases capillary permeability. It is involved in neovascularisation and movement of fluid from within blood vessels into the extra capillary space. VEGF concentrations rise after ovulation because of the need to generate new blood vessels in the ovary to convert the avascular preovulatory follicle into a corpus luteum with its characteristically extensive blood supply. The rise is greater in women who develop ovarian hyperstimulation than in women who do not. The highest levels are

found in women with polycystic ovaries, in whom concentrations are in fact raised *before* treatment (Agrawal *et al.*, 1998), results which reflect the immunochemical demonstration of extensive VEGF staining in the hypercellular theca of the polycystic ovary (Kamat *et al.*, 1995).

There is a striking enhancement of the ovarian response to gonadotrophic stimulation of women with amenorrhoea and normal ovaries, compared with women with polycystic ovaries, whether symptomatic or asymptomatic (Shoham *et al.* 1992). This finding exemplifies the notion that the essential feature of the response of the polycystic ovary to gonadotrophic stimulation is loss of the normal intra ovarian autoregulatory process that underlies emergence of a single dominant follicle, with suppression of cohort follicles. Part of the explanation is that the normal diversion of blood flow towards the dominant follicle and away from the cohort follicles is lost in the polycystic ovary because of the wide distribution of VEGF throughout the ovary. If the excessive amounts of VEGF leak from the ovary into the general circulation the patient is placed at risk of OHSS.

The practical consequence of these observations is that in the patient with polycystic ovaries, both symptomatic and asymptomatic, particular care is required in monitoring the response to gonadotrophin treatment. It is essential therefore that careful ultrasonography is undertaken before ovulation induction begins, otherwise patients and their clinicians will continue to be surprised by the outcome. The points to note are the presence of the characteristic morphology of the polycystic ovary (Figure 1). Development of multiple small and intermediate sized follicles as ovarian stimulation proceeds indicates a risk of OHSS; development of several large follicles (over 15 mm in diameter) indicates a risk of multiple ovulation and therefore multiple pregnancy.

Turning now to the problem of multiple pregnancy, we have to accept that it is not only doctors who may not appreciate how serious the matter is. It is indeed easy to understand how a couple engaged in the seemingly endless struggle with infertility might actually welcome the birth of twins. Such a couple will inevitably be

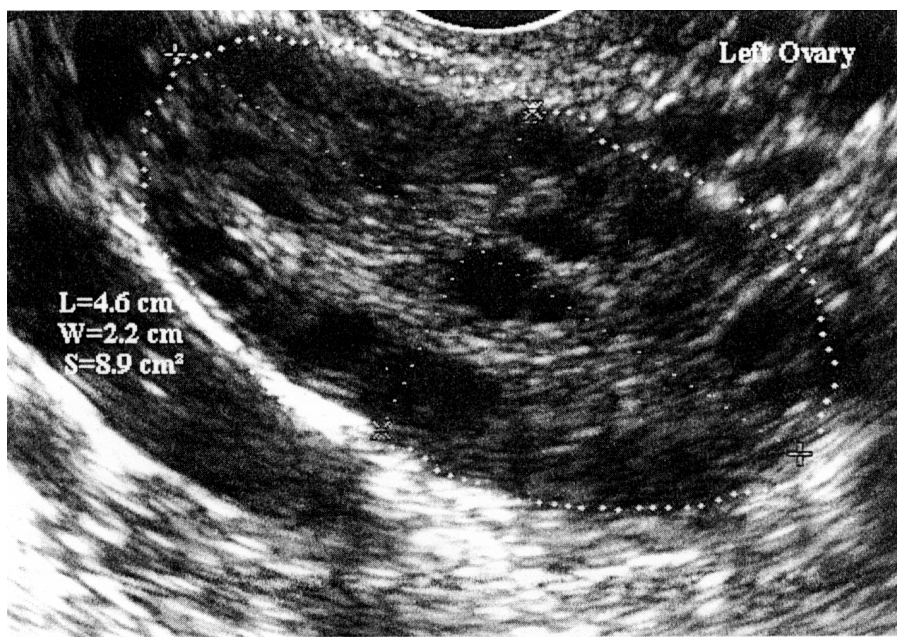


Fig. 1. Ultrasound image of polycystic ovary. The ovarian length (4.6 cm) and width (2.2 cm) are increased as well as the ovarian area (8.9 cm²). The follicle number, with a diameter between 2 and 5 mm, is more than ten. The distribution within the ovary is mainly peripheral, but some follicles can be seen in the central part of the ovary. From Robert *et al.*, 2000.

devastated when told that after all the treatment they have gone through, the injection of hCG is to be withheld and the cycle to be abandoned. I do hope it is accepted that as part of pre-treatment counselling couples have explained the reasons for avoiding multiple pregnancy and the means that have to be employed.

The starkest account of the risks to the progeny of multiple pregnancy is shown in Table 1 which reproduces the 1991 vital statistics for England and Wales in relation to multiple pregnancy (Doyle, 1996). Over the last few years in the field of IVF there has been a commendable and steady movement towards replacing fewer

Table 1. Mortality and multiplicity of birth in England and Wales in 1991

Mortality	Singleton babies	Twin babies	Triplet and higher order babies
Stillbirth rate (late fetal deaths per 1000 total births)	4.4	14.2	19.3
Early neonatal mortality rate (deaths in first 6 days per 1000 live births)	2.9	22.8	75.6
Late neonatal mortality rate (deaths at ages 7–27 completed days per 1000 live births)	0.8	3.9	10.6
Postnatal mortality rate (deaths at ages ≥ 28 days but < 1 year per 1000 live births)	2.4	6.3	15.1
Infant mortality rate (deaths at age < 1 year per 1000 live births)	6.1	33.0	101.4

Reproduced from Doyle 1996, with permission.

embryos, so the major cause of higher order multiples is now ovulation induction. I think that Table 1 reproduced here should be displayed in each fertility unit and be a focus for discussion so staff and patients are aware of the risks and appreciate the need for vigilant monitoring. Compared with singletons, in 1991 the neonatal mortality was seven times higher in twins, 15 times higher in triplets and 50 times higher in higher order births. Survivors suffered higher rates of cerebral palsy and other neurological impairments.

The finding of an infant mortality rate that rises from 6.1 to 101.4 per 1000 live births is tragic. It is a humbling statistic when one remembers that these births are the result of medical treatment and nothing else. Fortunately not all multiple births end in so terrible a way but that means we must also consider what happens to the survivors and their families over the ensuing years. I have found the papers of Garel and Blondel (Garel and Blondel, 1992; Garel *et al.* 1997) particularly illuminating. In their study of families with surviving triplets they observed maternal bonding to be impaired,

the mothers were physically exhausted and at four months the parents were socially isolated, suffering marital disharmony and experiencing domestic overload. Some of the mothers avoided emotional involvement with their children because of the fear of competition between siblings. The parents complained of exasperation and hostility because of their continual exhaustion. Little expert advice was available and home help faded after six months. Three of the 12 mothers required treatment for major depressive illness, six had serious psychological problems and three had problems that were less intense. Four years after delivery the mothers of triplets still reported fatigue, emotional stress and difficult relationships with their children. Note that these families were of high socio-economic status and these particular children did not suffer from the sequela of prematurity – this then is the best case scenario.

To conclude, as this book describes, modern treatment of anovulatory infertility is highly successful. The risks however impose a burden of responsibility on clinicians and potential parents alike. I do not think clinics should undertake induction of ovulation unless they have adequate ultrasound equipment and skilled personnel to offer high quality surveillance of the ovarian response to gonadotrophic stimulation. I advise couples not to seek such treatment if they are not in a position to commit themselves to the required level of monitoring. I think patients and their medical advisors need a clear idea of the limitations of treatments, that is to say, of the risks of adverse outcomes as well as the effectiveness of treatment.

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