As the treatment was too short to affect the spermatogenesis. spermatozoa/ml. There was a considerable improvement. FSH concentrations, sperm counts increased to 37 × 10^6 spermatozoa/ml and normal FSH concentrations, 30% of them had a history of azoospermia with high FSH concentrations. As shown by testicular biopsy a normal spermatogenesis is found (Silber and Rodriguez-Rigau, 1981). The delicate structure of the epididymis can be damaged by infections which can cause complete or incomplete obstruction resulting in azoospermia or oligozoospermia. Partial obstruction of the epididymis could be responsible for 10–20% of the cases of severe oligozoospermia (<5 × 10^6 spermatozoa/ml) according to Schoysman (1980) and Silber and Rodriguez-Rigau (1981). In an epidemiological study of 350 patients consulting for infertility, the aetiology was idiopathic in 19% of the cases. Among the 30 idiopathic patients with <5 × 10^6 spermatozoa/ml and normal FSH concentrations, 30% of them had a history of urethritis with possible epididymitis suggesting a partial obstruction (R.Martin-Du Pan, unpublished observation).

Since partial obstruction is essentially due to an inflammatory process following infection we wondered whether it would be possible to diagnose a partial or a reversible obstruction of the epididymis by using an anti-inflammatory drug. We treated a total of 20 patients; 10 presenting with severe oligozoospermia (<1 × 10^6 spermatozoa/ml) and 10 having azoospermia, with 100 mg of diclofenac, for 3 weeks. After diclofenac treatment the sperm count had improved in 13/20 cases including six azoospermic patients. In four of the latter, one with high FSH concentrations, sperm counts increased to >15 × 10^6 spermatozoa/ml. There was a considerable improvement (>70 × 10^6 spermatozoa/ml) in two oligozoospermic patients. As the treatment was too short to affect the spermatogenesis we postulate that the beneficial effect observed is due to the anti-inflammatory action of diclofenac which transiently relieves an incomplete obstruction of the epididymis. As this (unpublished) study was uncontrolled we cannot exclude a spontaneous improvement of the spermatozoa. In one case however, azoospermia returned after the cessation of the treatment.

Impaired sperm transport through the genital tract can lead to oligozoospermia, asthenozoospermia and even in certain cases to necrozoospermia (Wilton et al., 1988). Whereas in normozoospermic men, sperm counts decrease with sequential ejaculation, an improvement in sperm cell motility and in the total motile sperm count has been observed in patients with oligoasthenozoospermia when a second ejaculate was collected 2–4 h after a first one (Tur-Kaspa, 1994; Barash et al., 1995). In cases of oligozoospermia, the time taken for spermatozoa to be transported through the epididymis could be three times longer than in normozoospermic patients (Johnson et al. 1988). Partial obstruction could be responsible for this slow transit and sequential ejaculation could improve it (Tur-Kaspa et al., 1994). However, in contrast to diclofenac treatment, sequential ejaculation did not improve sperm count. Hence, oligozoospermic patients improving their sperm motility after sequential ejaculation could be selected for a trial with diclofenac. In our hands, this anti-inflammatory treatment has proven to be efficient in some azoospermic patients and even in one case of azoospermia with high FSH concentrations. As shown by Hauser et al. (1995b), a high FSH concentration does not rule out the possibility of obstruction and the capacity for fertility after bypass microsurgery. The appearance of some spermatozoa after diclofenac in azoospermic patients could allow intracytoplasmic sperm injection (ICSI) to be carried out, thus avoiding invasive procedures such as testicular biopsy with sperm extraction (TESE) under general anaesthesia. We believe, therefore, that a 3 week trial with an anti-inflammatory treatment seems useful before performing TESE in all azoospermic patients.

References


The reproductive performance of habitual aborters in in-vitro fertilization (IVF)/embryo transfer is still unknown; therefore any contribution to the data on this subject, such as the paper of Balasch et al. (1996) is of great importance. However, our results concerning pregnancy outcome in habitual aborters after IVF with embryo transfer are different (Raziel et al., 1996a).

Since maternal recognition of pregnancy seems beneficial for the survival of the embryo, replacing several embryos into the uterus of habitual aborters instead of ‘old treatments’ such as paternal lymphocyte immunization (Recurrent Miscarriage Immunotherapy Trialists Group, 1994) or i.v. immunoglobulins (Raziel et al., 1996b) is a new approach for treatment.

Balasch et al. (1996) had excellent results when using IVF and embryo transfer in habitual aborters: eight out of 12 women conceived (75%) and all pregnancies concluded in delivery of healthy neonates. We performed IVF/embryo transfer in habitual aborters (median 3, range 3–20 abortions) suffering from concurrent secondary infertility and compared their reproductive performance with matched controls (median 0, range 0–2 abortions), based on the same age and IVF/embryo transfer indications. Pregnancy rates were similar in both groups (32 and 29% per cycle). However, pregnancy outcome remained as unsuccessful as that before treatment: 50% abortions (seven out of 14) compared with an 8% abortion rate (one out of 12) in the control group.

The process of IVF/embryo transfer can be divided into early stages which include ovarian stimulation, oocyte retrieval, fertilization and cleavage while the later stages include implantation, pregnancy and embryonic development. Based on our results, it appears that the early stages of IVF/embryo transfer are similar, if not better, in habitual aborters compared with the controls. However, despite similar pregnancy rates, pregnancy outcome of habitual aborters in IVF/embryo transfer is as unsuccessful as before the treatment. Unfortunately, the data on these early and late stages in the paper of Balasch et al. (1996) is incomplete.

Based on our preliminary results, IVF/embryo transfer is not an efficient therapeutic approach for repeated miscarriages, and so we come to a conclusion opposite to that of Balasch et al. (1996). No doubt further studies in this field are warranted to throw light on the unresolved question of the aetiology of habitual abortions, namely, whether the fetus (or the prior gamete), maternal systemic pathology, and/or local uterine factors are responsible for repeated abortions.

References


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Dear Sir,

Weinberg et al. (1995) reported a significant association between follicular phase length in human conception cycles and the sex of the resulting offspring. Short follicular phases were associated with subsequent births of boys, and long ones with girls. In commenting on this finding, I noted that there is a good deal of direct and indirect data suggesting that the sex of zygotes is dependent on the timing of the insemination (or formation of the zygote) vis-à-vis ovulation (James, 1995). These seem probably (though not necessarily) competing hypotheses. So I suggested that if Weinberg et al. (1995) were correct, then (since the variance of the follicular phase greatly exceeds that of the luteal phase) the sex of offspring should correlate with a woman’s mean cycle length; women with short cycles producing an excess of sons.

I have since located some data on this point (Nakamura et al., 1987). Since they were published in a relatively inaccessible journal, they are reproduced here in Table I. The mean cycle length of women who produced boys was 30.2 days and that of women who produced girls was also 30.2 days. Thus there is no evidence in this sample that the sex of offspring is associated with the mean cycle length of their mothers. I would infer provisionally that a sampling error may have occurred in the data of Weinberg et al. (1995); however, both studies need replication before the point is settled.

A curious feature may be noted in the data of Table I. They may be dichotomized between mean cycle lengths of 29 and 30 days, or between 31 and 32 days. However, it may be confirmed that the results of such arbitrary dichotomies are opposite. In the first case one would infer an association between long cycle lengths and male offspring; in the second, between short cycle lengths and male offspring. Nakamura et al. (1987) followed the latter procedure and invalidly concluded that short cycle lengths are associated with male births in their data.

However, these authors report further data which, if confirmed, would have implications for the present discussion: (i) they report a significant association between the sex of offspring and the month of the mother’s birth. Mothers born in the first half of the year reportedly bear more sons than daughters, while mothers born in the second half of the year reportedly bear more daughters than sons; (ii) they report that mothers born in the first half of the year have shorter menstrual cycles, on the average than those born in the second half of the year; (iii) they report higher gonadotrophin and lower oestrogen concentrations in women with long menstrual cycles.

It will be noted that firstly, if findings (i) and (ii) were confirmed, then one would expect (contrary to the direct data reproduced here) at least some slight association between mean menstrual cycle length and offspring sex ratio. Secondly, if findings (i) and (iii) were confirmed, then they would provide confirmation for my hypothesis that offspring sex ratios (proportions male) correlate positively with the oestrogen and negatively with the gonadotrophin concentrations of the parents around the time of conception (James, 1996). These studies all urgently require replication.

References


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Dear Sir,

We thank Dr James (1997) for drawing our attention to the work of Nakamura et al. (1987), recognizing its connection with our findings (Weinberg et al., 1995). We appreciate the opportunity to respond, though a fuller treatment must await completion of analyses now in progress.

In our report, based on healthy couples conceiving with no medical interventions, we had found that conception cycles with short follicular phases produced more boys, while conception cycles with long follicular phases produced more girls. The timing of intercourse relative to ovulation was unrelated to the sex of the baby, both by the relatively crude method reported in Table I of Weinberg et al. (1995), and by a more sophisticated analysis carried out separately by the competing risks method of Weinberg et al. (1994) but not reported.

James suggested that the sex ratio may be negatively correlated with gonadotrophin concentrations around the time...
of conception. We have recently carried out assays of luteinizing hormone (LH), but not follicle stimulating hormone (FSH), concentrations adjusted for creatinine, for most of the cycles in our study and our analysis of sex ratio in relation to LH is underway.

While we agree with James that the data of Nakamura et al. (1987) regarding sex ratio in relation to the woman's mean cycle length do not strongly support a higher sex ratio (boys over girls) among women with short cycles, we regard this kind of data as yielding a weak and indirect test of our observations. Firstly, our findings were based on the length of the follicular phase in the conception cycle, not mean cycle length. There is considerable variability in follicular phase lengths from cycle to cycle within women, and because of this high intra-woman variability, a woman’s mean cycle length would be expected to be a poor predictor of the sex of her babies. If mean cycle length were a good predictor of sex ratio in general, the excess of sibships where one or the other sex predominates would be much larger than the slight excess discernible in population data. Because of these concerns, we would prefer to see evidence based on data that relate more directly to our actual observation.

References


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Why delay the obvious need for milder forms of ovarian stimulation?

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It is a compliment to be chided by a leading endocrinologist on the need for milder forms of ovarian stimulation (Fleming, 1996). His message would have been clearer had one or two references been included. This would have given us some firm targets to aim at rather than answering charges based on generalities.

Firstly, then, we will discuss some of the background facts that face us today in our practice of ovarian stimulation. We have no reservations whatsoever in condemning some routine treatments adopted by certain clinicians. Even since writing our original paper (Edwards et al., 1996), we have read some manuscripts and heard lecturers describing the routine use of 40, even 50 or more, ampoules of HMG in a single stimulation cycle for in-vitro fertilization (IVF) or intrauterine insemination (IUI). This approach leads to various consequences. It under-values the need for proper patient care, i.e. to stimulate the fewest follicles necessary to achieve a particular aim. It involves the recovery of large amounts of oocytes from numerous follicles and risks hyperstimulation and multiple pregnancies. It leads some clinics to a most unethical step as they are forced to use fetal reduction on the majority of their pregnant patients, to produce a pregnancy acceptable to the mother. If fetal reduction was planned as a consequence of heavy stimulation, then the ethical situation is even worse. No comment on correct clinical care is offered either in these manuscripts or lectures, nor is much time wasted on giving thought for the unfortunate patients who will spend some years regretting or grieving for their lost fetuses. These are the penalties for patients in the too easy acceptance by their doctors of massive amounts of hormones for ovarian stimulation, and this whole approach must surely be prohibited. Of course, it leads to high pregnancy rates, but it ignores good practice and places no value whatsoever on the resulting fetuses. We do not ascribe such treatments to our distinguished critic or to other responsible investigators; we are merely pointing out a widespread example of the dangers implicit in the uncritical use of large doses of hormones.

Turning to more routine forms of care, we still fail to understand why doses such as 20–30 ampoules are needed to routinely stimulate patients, except in certain situations. Follicles can be persuaded to grow with much less HMG than this, and perhaps with less than half of the total dosage. Are we really trying to obtain every possible oocyte that can be squeezed from an ovary? Since our patients are mostly cyclic women producing their own follicle stimulating hormone (FSH) and luteinizing hormone (LH) to assist in the stimulation of ovarian follicles, is there really a need to give daily doses of these hormones? The original use of exogenous gonadotrophins by Donini and Lunenfeld was for the treatment of agonadotrophic women with virtually no hormones of their own; the introduction of ovarian stimulation by Steptoe and Edwards was to support the natural menstrual cycle in women with adequate amounts of gonadotrophins to sustain their follicles. Would it not be wiser to start off the stimulation with low doses and then raise the amount later if necessary? Low dose protocols have proved their worth in several situations, and recently have even proved to be superior to high dose protocols for poor responders with high FSH levels on day 3. Modest doses of injected gonadotrophins shorten the stimulation period, result in more oocytes and high quality embryos, and of course reduce the cost (Feldberg et al., 1994; Olivennes et al., 1996). These protocols would probably be fully adequate for normogonadotrophic patients if given a try. But we encounter here one of our earlier criticisms, that too many doctors seem to place too high an emphasis on sheer numbers of eggs and embryos as a sign of a successful stimulation.

Moreover, some advantages claimed for longer term protocols seem to involve issues other than a better stimulation.
Some meta-analyses seem to claim all possible good for longer and longer protocols. Yet one study comparing short and ultrashort protocols found that follicular responses and pregnancy rates were virtually identical, but more ectopic pregnancies arose with ultra-short protocols (Marcus et al., 1992). This finding was interpreted by some investigators as showing that longer luteinizing hormone-releasing hormone (LHRH) protocols had a greater advantage in ovarian stimulation, when what it really did was to question the data base of the patients in each group. Even the correct use of clomiphene and HMG can lead to pregnancy rates equivalent to those gained using the agonists, but the problem here is that more monitoring is needed with the former treatment. The introduction of the LHRH antagonists will change this situation, as everyone agrees, yet it is essential to understand that some of the currently-used long LHRH protocols do not improve pregnancy rates but are more simple to use and permit clinics to time their oocyte collections.

By gaining every possible oocyte, we may be stimulating widely different cohorts of follicles and perhaps some follicles undergoing atresia. Where do these oocytes come from? Are 50 or more normal follicles available for stimulation by HMG during one cycle of treatment? Can successive cohorts be forced to grow by the massive amounts of injected HMG? The mean movement of follicles throughout the lifespan in female animals and women has been modelled, and such death/migration models show how fewer and fewer follicles migrate at successive stages of folliculogenesis (Faddy et al., 1976; Faddy and Gosden, 1995, 1996). Analyses on developmental variation among the large numbers of stimulated follicles are needed to assess their respective stages of maturation, e.g. by applying cluster analyses to levels of several distinct steroids in follicular fluid (Fowler et al., 1977). Such analyses revealed how several distinctly-different groups of follicles mature in response to low-level ovarian stimulation, as compared with two widely distinct groups (ovulatory and non-ovulatory) in natural cycles. Similar analyses should be applied to follicular fluids aspirated from patients with 50 or more follicles, to find out exactly what is happening in the ovary. An embryologist with 50 eggs in his dishes has very little idea of their respective value, so all of them are inseminated and those that are fertilized are then judged by the weak criteria of quality available today. Choosing the best oocytes out of a vast number to inject during intracytoplasmic sperm injection (ICSI) must give equally unsatisfactory results.

We question Richard Fleming’s statement that the application of more modest amounts of hormones would lead to a choice between fewer and more successful stimulations with higher dose of drugs versus more stimulations with lower dosages in order to reach the same number of pregnancies. We know of no actual data showing such a correlation. It is quite possible that the same proportion of patients given modest stimulation would produce as many high quality fertilizable oocytes as those patients given high order stimulation. Good quality growing follicles in the mid-follicular stage may be our best target, providing a pool which will respond to HCG or to maturation in vitro. In a recent report to the European Society for Human Reproduction and Embryology by Russell et al. (1996) and his colleagues, the extraction of several mature oocytes at this stage of the cycle of the natural cycle for in-vitro maturation resulted in good rates of fertilization and the establishment of several pregnancies. These oocytes would normally have been destined for atresia, and a simple form of maturation was sufficient to enable them to produce high-quality embryos. The contrast with the situation arising after ovulation stimulation, when 50 or more oocytes have been aspirated, could not be starker.

Richard Fleming also downgrades the dangers of excess amounts of steroids in the follicular phase during high-order ovarian stimulation by comparing them with the much higher amounts secreted during pregnancy (Fleming, 1996). This comparison is surely not strictly correct. The oestrogens are largely unopposed by progestrone during the follicular phase, in contrast with the situation arising during pregnancy. We have become familiar with the risks of unopposed oestrogens in studies on contraception. It is perhaps a little complacent to suggest that patients who have had 10 or 15 cycles of IVF are not exposed to the same dangers since many patients may undergo 10 or more IVF cycles. Since writing our earlier manuscript (Edwards et al., 1996), another possible concern has arisen in the large amounts of relaxin released from the numerous follicles in ovarian stimulation programmes (Kristiansson et al., 1996). It is of course possible that large temporary amounts of these hormones are well tolerated physiologically; of course, the opposite could be equally true and the hypersecretion of ovarian peptides may be more worrying than excess steroid secretion.

Richard Fleming raises the argument that the use of milder forms of stimulation may penalize clinics using them in the new race to become top-of-the-league in the new assessment protocols established by the UK Human Fertilisation and Embryology Authority, and perhaps by regulatory agencies in other countries. We fully accept that classifications published in these protocols can make or break a particular clinic, and that one overall consequence will be a search for the highest possible pregnancy rates. Perhaps we would agree with him that league ladders are totally unconstructive and misleading anyway, since complex regression analyses can never reflect all the complexities of patient care, and that league ladders should be banned from responsible analyses. Richard’s fears may be premature, since it may yet be shown that modest forms of stimulation give better results, so that clinics using them may end up at the top of the league.

In conclusion, we feel that a laissez-faire attitude to hormone stimulation today, with increasingly powerful agents becoming more freely available, encourages bad practice and short-cuts. This results in various risks to our patients, some known and doubtless others unknown. We stress again the need for greater care in deciding individual protocols for specific patients and for more research on new forms of treatment.

Erratum


Erratum

Prediction of ovarian hyperstimulation syndrome of baseline ovarian volume prior to stimulation
by B.Danninger, M.Brunner, A.Obruca and W.Feichtinger

Hum. Reprod., 11, 1597–1599

The title of this paper was printed incorrectly. The correct title is as follows:

Prediction of ovarian hyperstimulation syndrome by ultrasound volumetric assessment of baseline ovarian volume prior to stimulation