Letters to the Editor

Ultrasound guided embryo transfer does not prevent ectopic pregnancies after in-vitro fertilization

Dear Sir,

We would like to contribute to the ongoing discussion on the aetiology of ectopic pregnancies, giving our experience of 3543 ultrasound-guided embryo transfers as they relate to our ectopic pregnancy rates and recapitulate the historical background of our practice.

In 1961, Iffy published a paper arguing the point that the usual mechanism of tubal ectopic pregnancy is expulsion of the embryo from the uterine cavity into the salpinx at the time it is ready to implant. This was largely ignored until the era of in-vitro fertilization (IVF) and embryo transfer when Steptoe and Edwards (1976) and Tucker et al. (1981) each reported that their first embryo transfers after IVF had resulted in ectopic pregnancies. Initially, the high transfer volume used was thought to promote embryos being flushed into the Fallopian tubes at the time of embryo transfer. The volume was gradually reduced especially as Knutzen et al. (1989) demonstrated that as little as 50 µl radio opaque dye injected into the uterine cavity could later be found in the Fallopian tubes in 44% of their patients.

As indications for IVF broadened, it became more noticeable that tubal factor infertility was a risk factor (Verhulst et al., 1993). This further supported the ‘reflux’ theory: Embryos placed in the uterine cavity and subsequently reaching the Fallopian tubes would implant there if they, by some pathological process, were prevented from returning to the uterus. However, the question is whether the position of the catheter tip, the transfer volume used, or number of embryos replaced, would promote embryos being washed into the tubes at the time of transfer or whether an altered hormonal environment changes the uterine and tubal contractility and thus favours ‘migration’ of correctly placed embryos into the tubes (Fernandez et al., 1991).

The discussion of how the embryos reached their ectopic sites has been hampered by the fact that no data are available in the literature. Embryo transfer is a ‘blind’ procedure in most major centres, where the operator guesses by the feel of the catheter tip where to place the embryos. Until recently, the only controlled trial of ultrasound-guided embryo transfer involving a total of 94 patients was carried out by Hurley et al. (1991). They did not find that ultrasound guidance improved the implantation rate and the ectopic pregnancy rate was 11% in both groups. Recently, Woolcott and Stanger (1997) addressed the blind approach to embryo transfer and found that in 17.4% of cases their embryo transfer catheter unintentionally abutted the fundal endometrium and that in 7.4% of cases the guiding catheter was adjacent to the internal orifice of the Fallopian tube. They did not comment on ectopic pregnancy rates.

All of our 3543 embryo transfers have routinely been done under ultrasound guidance since the opening of our IVF Unit in 1986. Following the report of Yovich et al. (1985) of increased numbers of ectopic pregnancies with placement of embryos high in the uterine cavity, it has been our routine to place the tip of the transfer catheter in the low mid-cavity. A maximum of four embryos were replaced on the second or third post-ovum retrieval day. The embryos were suspended in a total of 25 µl of transfer medium in a Wallace® catheter (Semcare Ltd, West Sussex, UK). Under the guidance of abdominal ultrasound, the tip of the catheter was introduced into the lower mid-cavity of the uterus and the transfer column slowly released here. The luteal phase was supported by progesterone. Clinical pregnancies were confirmed by demonstrating an intrauterine gestational sac or adnexal mass by ultrasound.

The procedure resulted in 328 clinical pregnancies of which 11 (3.3%) were ectopic pregnancies. The overall indications for IVF were tubal factor infertility in 49% of our patients. All but one of the ectopic pregnancies (91%) had tubal pathology as indication for their inclusion in the IVF programme; the remaining pregnancy was a cervical pregnancy. The rate of ectopic pregnancies in the tubal group was 6.3% per embryo transfer. In all cases, the embryos had been placed correctly. The two air bubbles in the transfer column were often seen to make their way slowly up to the fundus of the uterus after a short phase of ‘resting’. This was also seen to occur when the uterus was retroverted with the fundus below the level of the internal os indicating some active form of transport mechanism. Only on rare occasions did we see air bubbles remaining at the deposition spot or moving towards the cervix.

Based on these observations, and knowing well that we lack a suitable control group, we too find tubal pathology to be a risk factor for ectopic pregnancies in IVF. Our ectopic pregnancy rate of 6.3% per embryo transfer in the tubal group is comparable with the average 5% found in earlier studies where most IVF attempts were carried out in women with tubal pathology.

A recent debate about the increasing rates of ectopic pregnancy has, amongst others, focused on the women who have had ectopic pregnancies in the absence of any risk factor, particularly where no known pelvic disease was diagnosed prior to the occurrence of the ectopic pregnancy (Ankum, 1996; Fernandez et al., 1996; James, 1996; Job-Spira et al., 1996; Parazzini, 1996). In this context it should be noted that in some cases the diagnosis of tubal disease was made only on the pathology specimen following removal of the pregnancy and the surrounding Fallopian tube. It would appear, therefore, that not only overt but also occult pre-existing tubal disease (possibly with a background of endometriosis) may be a risk factor (Speirs, 1996) and that sequelae from subclinical endosalpingitis might be underestimated.

Various authors have incriminated different stimulation protocols. Abnormal uterine contractility and altered tubal motility and cilia movements could be the result of very high oestrogen concentrations and/or the anti-oestrogenic effect of clomiphene citrate. However, clomiphene citrate has been considered a risk factor in some units only as its use by them was associated with increased numbers of ectopic pregnancies. It is interesting to note that one of these units has a particular low overall rate of 6.3% per embryo transfer. In all cases, the embryos had been placed correctly. The two air bubbles in the transfer column were often seen to make their way slowly up to the fundus of the uterus after a short phase of ‘resting’. This was also seen to occur when the uterus was retroverted with the fundus below the level of the internal os indicating some active form of transport mechanism. Only on rare occasions did we see air bubbles remaining at the deposition spot or moving towards the cervix.

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decoptic pregnancy rate (2.24%) (Verhulst et al., 1993), in spite of ~38% of their pregnant patients receiving clomiphene citrate in the stimulation protocol (247 out of 646). None of our protocols included the use of clomiphene citrate.

A retrospective observational analysis with no suitable control group cannot answer the question of whether ultrasound guidance is helpful in reducing the numbers of ectopic pregnancies in IVF programmes. We doubt it, as our figure of 6.3% ectopic pregnancies in the risk group compares well with the overall 5.2–5.8% reported in earlier studies. It is of course impossible to say whether this figure would have been higher had we not used ultrasound-guided embryo transfer or whether the actual or relative oestrus concentrations contribute to a possible migration into the Fallopian tubes.

References


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Chronic genital inflammation in the male—an easily missed diagnosis

Dear Sir,

We read with great interest the letter to the editor by Martin-Du Pan et al. (1997) and would like to add some comments.

Chronic genital inflammation is a frequent cause or at least a concomitant factor of male fertility disturbances. Hence, anti-inflammatory therapy represents one of the few causal treatment modalities in andrology. Like Martin-Du Pan et al. we also perform anti-inflammatory treatment with diclofenac and yield similar good results. However, in our opinion it is not necessary to apply this treatment routinely to all patients with highly impaired sperm parameters or azoospermia. We do not believe that the reason for decreased sperm count and motility in cases of chronic epididymal inflammation is a partial obstruction of the epididymal duct; a condition that is difficult to imagine. We assume a functional disturbance of sperm transport caused by mediators of inflammation to reduce sperm parameters. For example, autoimmune orchitis may lead to azoospermia despite only slightly affected spermato genesis.

Complete restoration of normal semen parameters after anti-inflammatory/immunosuppressive treatment was observed (Hendry et al., 1990), which indicates a disturbance of sperm outlet rather than an obstruction.

Although diagnosis of inflammatory changes is difficult, it is still possible. As the epididymis contributes only 10% to the seminal fluid one may easily overlook signs of inflammation, particularly in cases of chronic epididymal inflammation where only few leukocytes are present. In this context we have pointed out earlier that macrophages (and in non-azoospermic cases) typically stained sperm tails are signs of chronic epididymal inflammation and dysfunction (Haidl, 1990). Moreover, determination of granulocyte elastase is helpful in detecting inflammatory processes (Wolff et al., 1992).

Nevertheless, the contribution by Martin-Du Pan et al. (1997) is important and can help to refer several patients to intracytoplasmic sperm injection by ejaculated spermatozoa instead of testicular sperm extraction. In addition, it may give rise to intensive discussions.

References


Coital rates and sex ratios

Dear Sir,

Martin (1997) presented an ingenious model which implies that human parental coital rate and sex ratio (proportion male of the resulting offspring) are powerfully and positively associated. Here, direct numerical data are given (apparently for the first time) on the relationship between human parental coital rates and offspring sex ratios. The relationship is positive and, though significant, is very weak, implying that some feature of Martin’s model is in error.

Renkonen (1970) reported that in Australia 1908–1967, the sex ratio (proportion male) of legitimate live births was highest in those conceived in the first month of marriage, and steadily declined with the duration of the interval between marriage and conception. There is evidence that, in Western societies at any rate, coital rates roughly halve (or used to halve) across the first year of marriage (James, 1981, 1983), so I postulated that the decline in sex ratio with duration of marriage was due to this decline in coital rate (James, 1971). I suggested that the association between sex ratio and coital rate was secondary to associations of both with timing of insemination within the cycle.

More recently, my hypothesis has been invoked [invalidly, I suggested (James 1994)] by a number of anthropologists to sustain inferences about coital rates from data on sex ratios in relatively small societies (Brewis, 1993; Underwood, 1993; Whiting, 1993; Martin, 1994). My grounds for supposing these inferences to be invalid was that Renkonen’s data could be construed to support only a very weak association between coital rate and sex ratio. Martin (1995) responded with the suggestion that this claim ‘is guaranteed by aggregating subpopulations which differ in their reproductive behaviours, so that their differences cancel each other’. Martin gave no empirical evidence for this supposed heterogeneity, so it is reasonable to suspect his argument of circularity. As far as I know, no data have hitherto been published which directly relate human coital rates to the sex ratios of the resulting births. The point of this letter is to report such data.

During this century, the USA white live birth sex ratio has oscillated with maxima every 20–30 years (James, 1995). It seems that this sex ratio is under some form of homeostatic stabilizing mechanism, and I suggested that the coital rate may play some part in this. The sex ratio rose from around 1965 to around 1975 and declined thereafter. The evidence that there was a corresponding variation in coital rate is set out below.

Trussell and Westoff (1980) showed that age-standardized reported marital coital rates of USA white women increased by 22% during 1965–1975. J.C.Abma (personal communication), citing from Cycle IV of the US National Survey of Family Growth, noted that in contrast with the 1975 data, the mean marital age-standardized coital rate of white, once-married, currently-married women aged 15–44 years had declined by 27% by 1988.

About 25% of conceptions in year i correspond to births in year i. The other 75% of the conceptions in year i correspond to births in year (i + 1). The volumes of the US Vital Statistics give the numbers of white male and female live births each year. From them I have estimated the sex ratios of white US live births corresponding to conceptions in 1965, 1975 and 1988. They are 0.51314, 0.51405 and 0.51296 respectively. It may be confirmed that though the difference (between the value for 1975 and the other two) are tiny, they are statistically significant (there being 2.5–3×10⁻⁶ white births in the US in those years).

However, these data suggest that a change of ~25% in coital rate corresponds to a change of only ~0.2% in sex ratio. If these estimates are correct and may be applied to other societies, then the inferences of the anthropologists cited above are invalid. I have cited evidence that there is a positive (and in some cases apparently substantial) correlation between coital rate and sex ratio in some other mammalian species (James, 1996), but in man this correlation seems to be tiny. If, as suggested above, the correlation between human coital rate and sex ratio is secondary to correlations of both with timing of insemination within the cycle, then the correlation would be expected to be very small. Rough calculation suggests that this cannot be the sole cause of the correlation between coital rate and offspring sex ratio (James, in press) and I suggest there that this correlation is also mediated by paternal hormone concentrations. This hypothesized further increment is apparently also small because there have been direct reports on relatively small samples (Guerrero, 1968; Singh and Zambrano, 1997) of failures to detect any significant correlation between coital rate and sex ratio (as would be expected if the true correlation has the order of magnitude suggested here).

It may be acknowledged that among the US population, those who conceive in a given year are a small and non-random sample of the total; for example, they would be expected to have a rather higher mean coital rate than the US average. But I cannot see how the fact of this non-randomness can be deployed to support Martin’s thesis. If Martin were correct (that there is a substantial correlation between human coital rates and offspring sex ratios) then it should be possible to demonstrate on a relatively small sample. Instead, Wadley and Martin (1997) write that ‘... data on societies other than the Havasupai exist which suggest that coital rate may powerfully affect secondary sex ratios’. Yet none of the studies with which they substantiate this sentence gives numerical data on coital rates, neither does Martin’s own study on the Havasupai. In the absence of such evidence, caution would dictate a suspension of belief in this feature of Martin’s model.

Acknowledgement
I am grateful to Dr Joyce C.Abma (Family Growth Survey Branch, Division of Vital Statistics, US National Center for Health Statistics, Hyattsville, Maryland, USA) for the data on US coital rates, 1988.

References
Dear Sir,

To argue that in large, behaviourally heterogeneous populations changes in mean coital rates are not associated with proportionally equivalent changes in the secondary sex ratio misses the point. What is relevant for the sex of offspring is the history of Havasupai fertility and its implications for human sex ratio variation. Curv. Anthropol., 35, 255-266.


Martin, J.F. (1997) Length of the follicular phase, time of insemination and low in these cases as it was in the study of France et al. The births attributed to inseminations on ovulation day or the day before probably resulted from early ovulation and couples reigniting sexual relations too soon after a period of abstinence. We may presume that the frequency of coitus in the fertile period was low in these cases as it was in the study of France et al. (1984) in which couples engaged in intercourse but once in the fertile period. The sex ratio among the 339 births attributed to insemination on days –1 and 0 in these three studies is 45.1% male.

In contrast, in the Weinberg (1995) study couples were trying to conceive and engaged in coitus on average 2.5 times in the days –5 through ovulation day. The sex ratio among the 101 births attributed to inseminations on days –1 and 0 is 50.5% male. The couples in Harlap’s data (1979) claimed to have abstained through menstruation and for 7 days (or more) thereafter, reigniting relations no sooner than day 11 or 12 of the cycle. If their abstinence was followed by acts on successive days, as Harlap suggests, then they too engaged in coitus a number of times in the days just before ovulation when endogenous mucus penetrability is good. The sex ratio among the 1527 births attributed to inseminations on days –1 and 0 in the Harlap data is 51.6% males. Pooling the Harlap and Weinberg data yields 1628 births for these days of which 50.5% male. The couples in Harlap’s data (1979) claimed to have abstained through menstruation and for 7 days (or more) thereafter, reigniting relations no sooner than day 11 or 12 of the cycle. If their abstinence was followed by acts on successive days, as Harlap suggests, then they too engaged in coitus a number of times in the days just before ovulation when endogenous mucus penetrability is good. The sex ratio among the 1527 births attributed to inseminations on days –1 and 0 in the Harlap data is 51.6% males. Pooling the Harlap and Weinberg data yields 1628 births for these days of which 51.5% are male. This is 14.2% higher than the 45.1% male produced by late inseminations in conception cycles in which coitus was less frequent.

We should expect the effects of coital rate to be diminished when conception is due to an insemination earlier in the fertile period. We should expect this because before the fertile period and very early in the fertile period poor endogenous mucus penetrability should reduce sperm penetration and the resultant debris left in the cervix. The limited data available are consistent with that expectation. When rhythm failure produces conceptions due to inseminations well before the time of ovulation, the failures are likely the result of miscounting or early ovulation. In these cases couples continue sexual activity into the early fertile period. When this occurs, the sexual acts in the fertile period follow previous acts which should lower the already poor mucus penetrability. The sex ratio among the 430 births attributed to inseminations ≥2 days before ovulation in the Guerrero (1974) and Perez (1982) data is 57.9% male. If the Weinberg (1995) data in which couples were trying to conceive are added, the sex ratio among the 456 births attributed to early inseminations in cycles with coital acts immediately preceding the responsible acts is 57.9% males. In the Harlap data, in which women abstained through menstruation and for 7 days thereafter, it is unlikely that intercourse

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was often resumed much earlier than days –2 or –3. Those data, like those of France et al. (1984) in which intercourse occurred but once in each conception cycle, should reflect early endogenous mucus penetrability relatively unaffected by debris from previous coital acts. The sex ratio among the 5170 births attributed to insemination on days –2 and earlier in these data is 53.1% male. While this is significantly ($\chi^2 = 3.84, P = 0.05$) lower than the sex ratio among conceptions where the probability of coital acts is greater, the effects of those earlier acts are not as great (a 9 versus a 14% increase) as they are when endogenous mucus penetrability is better.

References

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