Letters to the Editor

Modified natural cycle IVF for poor responders

Sir,

The article by Kolibianakis et al. (2004) has concluded that the retrieval of an oocyte(s) in women with high day 3 FSH and poor ovarian reserve using a modified natural cycle protocol is not an effective treatment. They state that ‘patients should be counselled appropriately and either proceed to oocyte donation or abandon infertility treatment’. I write this letter to vehemently disagree with this last statement (Kolibianakis et al., 2004).

Their manuscript was submitted March 15, 2004 and resubmitted May 11, 2004, so unfortunately they did not have access to an article we recently published concerning 259 retrieval cycles and 72 transfers in poor responders using minimal or no gonadotrophin stimulation without agonists or antagonists (Check et al., 2004). These patients were divided into four age groups (≥35, 36–39, 40–42 and ≥43 years) and their mean serum day 3 FSH levels were 19.7, 20.6, 18.8 and 21.9 mIU/ml. If one eliminates the oldest group, the delivered pregnancy rate for 47 embryo transfers in women up to 42 years of age was 12/47 (25.5%). Approximately 50% of retrievals resulted in an embryo (about half were transferred fresh and half frozen). The median number of embryos transferred was one. The implantation rate was 21.6% (13/60) for the three groups and was 33.3% for patients aged ≤35 years and 28.6% for women aged 36–39 years (Check et al., 2004). We have in fact published a case report of a 42 year old woman with tubal factor in imminent menopause who did not progress past the early antral stage either naturally or with gonadotrophins who responded to restoration of down-regulated FSH receptors by lowering the elevated serum FSH with ethinyl estradiol alone without gonadotropins and was able to form a mature follicle and delivered a live baby following transfer of a single embryo (Check et al., 2002). Another woman in imminent menopause who failed to attain a mature follicle on her own or with gonadotrophins alone was able to respond to gonadotrophins once her FSH was suppressed by ethinyl estradiol and she successfully delivered following transfer of two embryos (Check et al., 2000).

I tried to see if there are differences in methodology. We waited for the follicle to attain an 18 mm average diameter instead of 16 mm as performed by Kolibianakis et al. and we retrieved the oocyte at 34–36 h from hCG injection rather than 32 h. Admittedly we missed the oocyte about half the time (though retrieval was avoided). Also our protocol usually, but not always, lowered the serum FSH with ethinyl estradiol.

The authors do state that ‘the possibility cannot be excluded that modifications of the protocol applied in the current study could be associated with an improved outcome’. Despite this caveat, however, the authors concluded with the extremely strong negative statement previously quoted, suggesting donor oocytes or abandoning infertility treatment.

For many couples the use of donor oocytes is precluded for religious, personal, legal, or financial reasons. The majority of the patients that we treated were told that IVF could not work for them and that their only choice was donor oocyte or adoption. Though our data are published and available to physicians to read, Human Reproduction is one of the two frequently read infertility journals and the data by Kolibianakis et al. are likely to profoundly influence treating physicians. Even more worrisome, based on the gruesome statistics that they present, is that many insurance companies paying for IVF may use these data as reasons to exclude patients from this benefit when they have decreased oocyte reserve. I thank Human Reproduction for the opportunity to present to the readership somewhat more encouraging data and would welcome the opinions of Kolibianakis et al. about my concerns.

References


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Reply: Modified natural cycle IVF for poor responders

Sir,

We would like to thank Dr Check for his interest regarding the study published by our group in Human Reproduction (Kolibianakis et al., 2004).
Although it is quite clear that Dr Check strongly disagrees with the conclusion reached by our study, we could not identify in his letter arguments against the interpretation of the data presented. Apparently, Dr Check bases his strong disagreement on his own data (Check et al., 2004).

Several differences exist between the above two studies, some of them already mentioned by Dr Check in his letter. More importantly, however, the study by Kolibianakis et al. (2004) is a prospective evaluation of the modified natural cycle (MNC) for IVF in 32 poor responders with high FSH levels and previous unsuccessful IVF attempts. These patients, who were offered but did not accept oocyte donation, performed 78 MNC for IVF using recombinant FSH and GnRH antagonists. The study by Check et al. (2004) is a retrospective report of unstimulated or minimally stimulated cycles without the use of GnRH analogues. It is not clear from the study by Check et al. (2004) (or the letter of Dr Check) how many patients were treated in their study or how many previous IVF attempts the patients analysed had performed.

What is clear, however, from the study by Check et al. (2004), but not from Dr Check’s letter, is that 12 deliveries were achieved after 259 IVF cycles. Thus the delivery rate per cycle is 4.6% (12/259), 95% CI 2.4–7.9. In the study by Check et al. (2004) is a retrospective report of unstimulated or minimally stimulated cycles without the use of GnRH analogues. It is not clear from the study by Check et al. (2004) (or the letter of Dr Check) how many patients were treated in their study or how many previous IVF attempts the patients analysed had performed.

I agree with the author that the theoretical coefficient between X and Y chromosomes in the ejaculates is 1:1 and that it has been experimentally demonstrated in mammals that during meiosis equal numbers of X and Y sperm are produced. However, there are differences between X- and Y-bearing sperm that have been used to separate these populations. For example, the X chromosome is larger than the Y chromosome and therefore contains more DNA. It may be expected that differences in DNA mass between X and Y chromosome-bearing sperm would influence swimming speed. Among those methods devised to separate X- and Y-bearing sperm by apparent physical characteristics, the albumin gradient method described by Ericsson et al. (1973) is based on the faster swimming speed of the smaller Y-bearing sperm, which enables those sperm to reach the bottom of the gradient before the X-bearing sperm. This method has been offered to clinicians for many years as an effective method for sex preselection. Also, several reports indicate a sex-related differential characteristic in human sperm allowing separation of X- and Y-bearing sperm using swim-up (Han et al., 1993) and producing a high percentage of male births after insemination with sperm isolated by a modified swim-up procedure (Check et al., 1994).

We have previously reported that there is an association between maturation stage of bovine oocytes at the time of IVF and sex ratio of in vitro-derived embryos (Gutierrez-Adan et al., 1999). We hypothesized that the differential ability of X- or Y-bearing sperm to fertilize oocytes is due to differences in the physiological activity (motility/viability or capacitation/acrosome reaction) of X- or Y-bearing sperm before fertilization. Even though during meiosis in mammals equal numbers of X- and Y-bearing sperm are created, this might not reflect the proportion of the sperm population that reaches oocytes in the oviduct. There is also some evidence confirming the existence of differences between X- and Y-bearing sperm; it has been reported that in a simple salt solution, Y-bearing bull sperm do not swim faster than X-bearing sperm but may be distinguished from X-bearing sperm on computer-assisted sperm analysis (CASA) on the basis of linearity (LIN) and straightness of path (STR) (Penfold et al., 1998); also we have reported that using a double swim-up sperm preparation method we can obtain differences in the percentages Y-chromosome DNA-bearing sperm in some of the sperm fractions, suggesting that there are intrinsic differences in capacitation of X- and Y-bearing sperm that might be used to produce embryos of the desired sex with IVF (Madrid-Bury et al., 2003).

The primary sex ratio (male:female ratio at the time of fertilization) in humans differs remarkably from the theoretically expected ratio of 1:1, and may be as high as