based on the acceptance of the patients’ preference for genetically related children. ICSI was developed because men find the use of donor sperm unacceptable for psychological, ethical and religious reasons. It seems that the clinicians are already taking into account the values and beliefs of patients. However, Thomas goes one step further: he wants the infertility protocol to be tailored-made for religious groups. As Thomas rightly points out, this demonstrates a patient-friendly attitude (Pennings and Ombelet, 2007). One example is given by Yairi-Oron et al. (2006): in Israel, it is currently common practice to delay ovulation in orthodox women by the administration of estrogen. Orthodox Jewish women with a prolonged menstrual flow or short follicular phase may be unable to attend the ritual bath early enough in their cycle to engage in sexual intercourse and thus for conception to take place. Yairi-Oron et al. call this religious infertility. Hirsh (1996) argued already more than a decade ago that post-coital sperm retrieval could bypass the prohibition in many religions to masturbate. Nevertheless, the patients’ religious convictions do not oblige the physician to act against his or her own view of appropriate treatment and good clinical practice. The patient-friendly approach makes the wishes of the patient one of the criteria, not the supreme or absolute criterion. Let me give a few examples. Suppose a man belongs to a church that categorically forbids any form of masturbation and that he requests a testicular biopsy. Although testicular biopsies are performed for specific forms of male infertility, doctors may refuse to perform this procedure because they, for instance, do not want to take a non-medically justified risk or do not want to cause unnecessary harm to patients. Thomas mentions the case of the transfer of oocytes to the lower tubes combined with intercourse. Even if this method would be acceptable for Catholics, it would be unacceptable for clinicians to offer this method when it turns out (these are hypothetical examples) that it has a success rate of 1% or leads to an ectopic pregnancy in 25% of the cases. Criteria like cost-effectiveness, equal access and not harming should also be taken into account.

The first task of a researcher is to find a treatment or method that fulfills the standards of high-quality care. These standards guarantee in principle that all patients, regardless of their religious or cultural beliefs, can avail themselves of the best solution. Religious beliefs should not determine this research, neither by closing certain paths of investigation nor by directing the research efforts in certain ways. If the best method is unacceptable for certain groups, other methods can be looked at. If the method can be adapted to fit certain religious beliefs, the altered version can be offered to believers. It would be possible when infertile religious people can also realize their child wish. However, there is no positive duty on the part of the researchers to look for such methods. Take another example within the field of reproduction: contraception. People want to control their reproduction. The first task of the medical community is to look for a safe and efficient method of contraception. When researchers have found such method, they have no obligation to look for other methods just because one religion believes that a person cannot take artificial measures to separate sexuality from reproduction. Obviously, Catholic researchers and institutes should be free to develop natural family planning methods but there is no duty for non-Catholic researchers to do so. The lack of effort by fertility specialists to look for ‘religious’ treatments does not lead to unjustified discrimination of these groups. In practice, it would also be very difficult for researchers given the multitude of religions and the multitude of opinions within one religion. Moreover, many believers do not strictly abide by the rules of their religion. Finally, religious beliefs do not have a special status. Religious convictions have the same worth and weight as other people’s beliefs about for instance the sacredness of nature. Some people reject all kinds of high-tech medical intervention. Does this mean that out of respect for these convictions, the medical community should invest in the natural ‘solutions’ these groups usually prefer?

It will be interesting to see whether the practitioners, who wish for special steps to be taken when religious infertility is concerned, will require the same equitable approach to other types of social infertility (like lesbians, post-menopausal women and similar categories) where there is no medical reason for the treatment.

References


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Androgen priming before ovarian stimulation for IVF

Sir,

We would like to congratulate Lossl and associates on an in principle very well-designed prospectively randomized study (Lossl et al., 2008), but would at the same time like to point
out some potentially important facts, which may somewhat modify the conclusions reached by the authors.

Considering the quality of their study design, there is little argument with the authors’ principal conclusion that the short-term administration of aromatase inhibitors (AI) before controlled ovarian hyperstimulation (COH) failed to improve ‘in their study’ the number of top-quality embryos. Their data, however, raise a number of significant questions, among them whether their finding may not actually reflect their stimulation protocol, and why AI would even be expected to show an effect on ovarian function in women with normal ovarian reserve.

Without wishing to enter the controversies surrounding use of antagonist versus agonist protocols and their respective impacts on COH (Al-Inany et al., 2006; Huirne et al., 2007), it would seem reasonable to assume that in average patient populations, pre-stimulation antral follicle counts, stimulated follicle counts, peak estradiol (E2) levels and E2 levels per follicle should correlate with number of ultimately retrieved oocytes. Expectations also are that the number of retrieved oocytes statistically correlates with oocyte quality and, therefore baring differences in semen parameters and timing of ovulation induction, should reflect fertilization potential of oocytes and, ultimately, pregnancy outcomes (Roest et al., 1996). This study, however, paradoxically deviated from these expectations in all of these parameters. Although the AI-treated group demonstrated significantly more pre-ovulatory follicles ($P = 0.014$), peak E2 ($P < 0.001$) and E2 per follicle ($P = 0.005$), oocyte number were not higher and the fertilization rate was, indeed, significantly lower ($P = 0.007$). Moreover, ongoing pregnancies, though statistically similar, demonstrated a trend against the utilization of AI.

It, of course, is possible that different pharmaceutical agents, leading to increases in intraovarian androgen levels, may affect outcomes differently. Such a conclusion seems, however, unlikely under the proposed assumption that intraovarian androgen levels, indeed, can affect ovarian function. Why, as quoted by the authors, Casson et al. (2000) and we (Barad and Gleicher, 2005, 2006; Barad et al., 2007), after androgenization with dehydroepiandrosterone (DHEA), would see the expected correlation between pre-oocyte retrieval COH parameters and subsequent oocyte numbers, but Lossl et al. did not, is, therefore, difficult to understand and possibly suggests that their observation may be the consequence of ovarian stimulation, rather than evidence of absence of effects of AI on ovarian function. Adverse effects on oocyte numbers in antagonist cycles in comparison to short agonist cycle have, of course, been reported (Franco et al., 2006).

Our biggest concern about this study arises, however, from patient selection. As the authors note in Materials and Methods, prior poor ovarian response to COH was an exclusion criteria. In practical terms, this means that women with diminished ovarian reserve were excluded from their study. The quoted claims of prior reported efficacy of ovarian androgenization by Casson et al. (2000) and our group (Barad and Gleicher, 2005, 2006; Barad et al., 2007) relate, however, exclusively to women with severely diminished ovarian reserve. In humans, there really, therefore, is no prior reported support for beneficial effects of androgenization in women with normally functioning ovaries.

Indeed, our concern would be that, assuming a normal intraovarian milieu with normal intraovarian androgen levels, added additional androgenization could result in excessive levels and well recognized adverse effects of excessive androgenization, widely reported in the literature (Taniguchi et al., 2007). We, therefore, caution from interpreting the data of Lossl et al. as relevant to women with diminished ovarian reserve and object to any comparison of their study outcome to outcomes reported by Casson et al. (2000) and our group (Barad and Gleicher, 2005, 2006; Barad et al., 2007).

Paradoxically, in this case, the authors’ ability to conduct such a well-designed prospectively randomized study offers further evidence of normal ovarian function in their patient cohort. In attempts to prospectively randomize women with severely diminished ovarian reserve between DHEA and placebo, we have twice failed in recruiting adequate patient numbers, willing to undergo potential randomization to placebo. A first attempt had to be abandoned in New York City in 2006 and a second trial, started in January of 2007 in collaboration with European investigators in a number of European countries, had later that same year to be stopped for the same reasons. In view of their severely limited reproductive life span, women with significantly diminished ovarian reserve, on both sides of the Atlantic, apparently are not willing to risk lengthy randomization to placebo.

This raises our final criticism of the paper by Lossle et al.: the efficacy of androgenization, at least as it relates to DHEA supplementation, appears directly associated with length of use. Our data strongly suggest that beneficial effects of DHEA on ovarian function only peak after 4–5 months of supplementation, though significance is already reached at ~2 months (Barad et al., 2007). This observation also correspond with much milder effects observed by Casson et al. (2000) after only short-term DHEA supplementation in comparison with our much longer supplementation (Barad and Gleicher, 2005, 2006; Barad et al., 2007).

Lossl et al. used only short-term androgen priming and still, as earlier noted, observed a number of significant ovarian function improvements, such as larger follicle numbers, higher peak E2 levels and higher E2 levels per follicle. In addition, they confirmed the expected increases in intrafollicular E2 ($P = 0.007$) and androgen levels ($P = 0.014$). It, therefore, is entirely possible that not only their stimulation protocol may have prevented them from achieving significant results, but also an insufficiently short time of treatment with AI.

The one conclusion their study, therefore, in our opinion allows is that it may, after all, also be worthwhile to investigate longer-term androgenization, even in women with apparently normal ovarian function. This is a conclusion we recently also reached after recognizing in a collaborative study with Canadian colleagues that DHEA supplementation apparently decreases miscarriage rates in women age of >35 years with diminished ovarian reserve by up to 50–80% (Gleicher et al., 2008).
Letters to the Editor

References


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Reply: Androgen priming before ovarian stimulation for IVF

SIR,

We thank N. Gleicher and D.H. Barad for their interest in our newly published study (Lossl et al., 2008). We both share the same interest in exploring elevated androgen levels as a mean to improve the outcome of infertility treatment. The concept is that androgens may augment FSH-receptor expression and stimulate granulosa cell proliferation. This could potentially increase oocyte yield, by increasing the number of follicles responding to exogenous FSH administration and by improving the quality and pregnancy potential of the retrieved oocytes.

Whereas Gleicher and Barad have mainly focused on administering androgens systemically, through the use of the relative week androgen DHEA, we have focused on increasing the ‘local’ intraovarian androgen levels, without affecting circulating levels, by giving an aromatase inhibitor (AI) to prevent conversion of androgens into estrogens, and hCG to stimulate local androgen synthesis within the theca cells (Lossl et al., 2006, 2008; Yding Andersen and Lossl, 2008). The other main differences between the studies performed by the two groups are the patient selection and the duration of treatment. Gleicher and Barad treated poor responder patients with long-term (months) administration of DHEA (Barad and Gleicher, 2005, 2006), whereas we used short-term (days) androgen priming in patients with a presumably normal ovarian reserve.

First of all, we do agree that the use of androgens for priming purposes remains an attractive possibility to improve the ovarian response, probably both in low and normal responders. In our point of view, the overall goal is to create a ‘temporary reversible PCO-like condition’ with an enhanced follicular response to gonadotrophins. The protocol, as used in our recent prospective randomized study, does, however, need adjustments (Lossl et al., 2008), but with the many drugs presently available including GnRH analogues, androgens, AI, recombinant LH/hCG and FSH preparations, although being a challenge, it may be possible.

Although we failed to find an increased number of embryos in the androgen primed group, it is correctly stated by Gleicher and Barad that we observed a higher peak estradiol level and a higher estradiol level per follicle, and that this usually correlates with oocyte quality and ultimately pregnancy potential. This was, however, accompanied by a lower fertilization rate in the androgen primed group when compared with the control group. We believe that this is due to a dual action of androgens during the follicular development (Yding Andersen and Lossl, 2008). We think that we actually did obtain an increased responsiveness of the follicles by the androgen priming of the small antral follicles, but that a prolonged exposure to high androgen levels in the late follicular phase created unfavourable intrafollicular conditions, which reduced the fertilization potential of the retrieved oocytes from the large pre-ovulatory follicles. This was substantiated by the significantly increased levels of androgens found in the pre-ovulatory follicular fluid at oocyte retrieval, which was an unexpected finding, since AI administration was withdrawn almost 12 days earlier.

In contrast, we did not find differences in the systemic levels of androgen during the period of androgen priming and ovarian stimulation. This is probably one of the main differences between the ‘systemic’ approach by Gleicher and Barad and our ‘local’ approach. To create increased intrafollicular levels of androgens capable of stimulating the androgen receptor to a degree that results in an increased FSH-expression may require high amounts of biological active substances like testosterone or prolonged systemic administration of weaker androgens like DHEA.

We used a modified antagonist protocol, and combined the ‘priming’ with the use of high-dose antagonist in order to prevent follicular growth during the ‘priming’. Indeed, early follicular-phase antagonist administration is not an established option. However, as an extension of our first pilot study (Lossl et al., 2006), we also pilot-tested the priming concept in a