LH/FSH ratio as a predictor of ovarian hyperstimulation syndrome

Dear Sir,

We have read with great interest the important article by Danninger et al. (1996) in which they demonstrated that volume of the ovaries could help to detect patients at risk and prevent the occurrence of ovarian hyperstimulation syndrome (OHSS). The method is a very simple procedure and is recommended for all infertility departments. Here we describe our preliminary observations associated with OHSS to confirm the main idea of the publication by Danninger et al. (1996); that of methods and procedures which can predict the risk of OHSS.

OHSS is a well recognized iatrogenic complication of gonadotrophin therapy. In its severe form, OHSS is characterized by marked ovarian enlargement, ascites, pleural effusion, sodium retention and oliguria. This iatrogenic condition is a potentially lethal disease, the pathophysiological hallmark of which is massive extravascular exudate accumulation combined with profound intravascular volume depletion and haemoconcentration. Monitoring by oestriadiol measurement (Haning et al., 1988) or ultrasonic studies (Blankstein, 1987) has been accepted with an attempt to predict incidence of hyperstimulation, but results were not always satisfactory. Gustafson et al. (1992) suggested that women with an increased ovarian contribution to circulating androstenedione not related to polycystic ovarian disease (PCOD) also constitute a group at risk for OHSS. Elevated androstenedione concentrations in the OHSS group prior to down-regulation was a major finding in this study.

It is well established that OHSS is more frequent in patients with PCOD (Kemman et al., 1981). PCOD patients are mainly characterized by hyperandrogenism and an inverse luteinizing hormone/follicle stimulating hormone (LH/FSH) ratio (>2.0) which may be associated with disturbed ovarian steroidogenesis. In a recent study, the clinical and hormonal data of 12 patients with OHSS were analysed retrospectively particularly with regard to the LH/FSH ratio and compared with patients (n = 12, selected by age, body weight, parity) without OHSS. Serum concentrations of androstenedione, dehydroepiandrosteronesulphate (DHEAS), sex hormone-binding globulin (SHBG), testosterone, FSH, LH, prolactin and oestradiol were routinely measured in 24 ovulatory women prior to ovarian stimulation in an in-vitro fertilization and embryo transfer programme at the Women’s Hospital, University of Tübingen, Germany. In all cases, ovarian stimulation was performed using combined suppression/stimulation therapy. The gonadotrophin-releasing hormone agonist triptorelin (Decapeptyl; Ferring, Kiel, Germany) was used in a long protocol. The stimulation was performed with individual dosages of human menopausal gonadotrophin (Humegon; Organon, Oberschleissheim, Germany), varying from two to six ampoules depending on the follicular maturation. Ovulation was induced by injection of 10,000 IU human chorionic gonadotrophin (HCG, Predalon; Organon), and aspiration of follicular fluid was performed 36 h later by ultrasound-guided vaginal puncture. All women received between one and three cleaved oocytes at embryo transfer 2 days later. Hormonal support with 2 × 5000 IU HCG was given to all women if no signs of OHSS were present.

The important clinical and laboratory data are summarized in Table I. There were significant differences between two groups in LH/FSH ratio and in plasma androstenedione concentrations. Further clinical and laboratory data were very similar and without significant differences in the two groups.

Significantly higher frequency of inverse LH/FSH ratio in the OHSS group was the major finding in the present retrospective study. Our results suggest that an elevated LH concentration may indicate the increased chance of OHSS development. Furthermore, they confirm the observation of Gustafson et al. (1992) with elevated androstenedione concentrations in OHSS group.

The steroidogenic cells of the follicle are under primary control of pituitary gonadotrophic hormones, FSH and LH. Androgen production appears to be a principal steroidogenic function of the theca cells, because that is the rate limiting factor in oestrogen synthesis. LH is required for significant

<table>
<thead>
<tr>
<th></th>
<th>OHSS group</th>
<th>Control group</th>
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<tbody>
<tr>
<td>Number of patients</td>
<td>12</td>
<td>12</td>
</tr>
<tr>
<td>Age (years)</td>
<td>31 (25–42)</td>
<td>32 (26–42)</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>151 (158–173)</td>
<td>150 (157–173)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>55 (49–76)</td>
<td>54 (49–76)</td>
</tr>
<tr>
<td>Cycle length (days)</td>
<td>28 (24–34)</td>
<td>28 (24–34)</td>
</tr>
<tr>
<td>HMG (days)</td>
<td>10 (8–14)</td>
<td>10 (8–13)</td>
</tr>
<tr>
<td>HMG (ampoules)</td>
<td>28 (17–46)</td>
<td>27 (17–44)</td>
</tr>
<tr>
<td>Recovered oocytes</td>
<td>8 (3–17)</td>
<td>8 (2–14)</td>
</tr>
<tr>
<td>Cleaved oocytes</td>
<td>4 (2–8)</td>
<td>4 (1–9)</td>
</tr>
<tr>
<td>Embryos transferred</td>
<td>3 (2–3)</td>
<td>3 (1–3)</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Testosterone ng/ml</td>
<td>0.5 ± 0.1</td>
<td>0.5 ± 0.2</td>
</tr>
<tr>
<td>Free testosterone pg/ml</td>
<td>2.5 ± 0.9</td>
<td>2.4 ± 0.8</td>
</tr>
<tr>
<td>Androstenedione mg/ml</td>
<td>2.3 ± 0.7</td>
<td>1.7 ± 0.8*</td>
</tr>
<tr>
<td>DHEAS mg/ml</td>
<td>2.7 ± 1.1</td>
<td>2.9 ± 1.4</td>
</tr>
<tr>
<td>SHBG mM/l</td>
<td>77 ± 24</td>
<td>82 ± 28</td>
</tr>
<tr>
<td>LH/FSH &gt;1</td>
<td>9</td>
<td>1**</td>
</tr>
<tr>
<td>LH/FSH = 1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>LH/FSH &lt;1</td>
<td>2</td>
<td>10**</td>
</tr>
</tbody>
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*p <0.01; **p <0.001.

HMG = human menopausal gonadotrophin; DHEAS = dehydroepiandrosteronesulphate; SHBG = sex hormone-binding globulin; LH = luteinizing hormone; FSH = follicle stimulating hormone.
rates of androgen production by theca cells (Gore-Langton and Armstrong, 1988). The observed LH dominance (in front of FSH) in this study and in PCOD patients may explain the higher rate of androgen production. We may suggest that this LH dominance leads to the disturbed androgen–oestrogen conversion and to higher ability of OHSS.

In conclusion, on the basis of our results we would like to propose that great attention should be paid to performing ovulation induction in patients with an inverse LH/FSH ratio prior to therapy. We suggest that our observations can improve the sensitivity of ovarian volumetry suggested by Danninger et al. (1996); however, the results need to be confirmed by a prospective study.

References

Dear Sir,

We would like to thank Bódis et al. (1997) very much for their appreciation.

First of all we wish to take the opportunity to correct the title of our paper which was misprinted; the correct title is ‘Prediction of OHSS by ultrasound volumetric assessment of baseline ovarian volume prior to stimulation’.

We have read the article with great interest. It is a very important supplement, that not to mention the oestradiol measurements like Haning et al. (1988) did, there are some other hormones which can help to detect high risk patients.

The most important data are the differences between the two groups (ovarian hyperstimulation syndrome and the control group) with regard to the luteinizing hormone/follicle stimulating hormone ratio and plasma androstendione concentrations. However, this method requires infertility clinics with laboratories on site, whereby ultrasound is available everywhere. Ultrasound volumetric assessment is an easy way to detect high risk patients; every infertility clinic has conventional transvaginal two-dimensional ultrasound which can be used as well as three-dimensional ultrasound. In conclusion we agree that both methods are complementary.

References

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Preimplantation diagnosis in older patients

Dear Sir,

The debate by Munne and Cohen (1997) on preimplantation genetic diagnosis (PGD) in older women could be amusing, were it not for the fact that patients are involved, and this makes it tragic.

Regarding the basic issue, Munne and Cohen go to a length to convince the reader, sparing all proof, that it is ‘not a matter of debate, but an arithmetic fact’ that implantation increases after PGD; unfortunately, shortly after, they have to prepare the reader (‘pregnancy rates should increase’) for the final blow (‘results after more than one hundred embryo biopsies...have not shown this expected increase’).

All other statements in their text are also based on faith alone. Munne and Cohen hope (and so do I) that improved techniques may, in the future, allow a better implantation rate, a decrease in spontaneous abortion and a reduction in the number of multiple gestations, but none of these benefits has already been attained.

To promote research on preimplantation diagnosis, there is no need to mislead the public or to use misquotation unfairly. Earlier in the debate, I (Egozcue, 1996) opposed ‘the systematic biopsy of human embryos...to discard aneuploidy’ because so far the results do not justify this practice, but in no case did I oppose research; in fact, Munne and Cohen (1997) acknowledge that I ‘rightly stated that other aneuploidy result in greater embryo wastage’, and suggested changing some of the probes used.

Finally, I never argued that the non-transfer of an 8-cell embryo is tantamount to termination of pregnancy. What I said—and this is an objective fact—is that a good number of couples hold this belief (and to me their opinion is worthy of respect).

In summary, and for the sake of good medical practice, I would like to see a lot more research on this subject, as well
as facts harder than faith alone, before PGD (and this was the main subject of the debate) is systematically applied to older patients.

References


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Dear Sir,

We read with interest the last part of the debate by Munné and Cohen (1997), and it is a great honour for us to be able to comment on the remarks made by these pioneers in the field of preimplantation genetic diagnosis (PGD).

Like Munné and Cohen we believe that PGD of aneuploidy in older in-vitro fertilization (IVF) patients is an evolving and promising clinical tool for the reduction of aneuploidy in this age group. This approach may serve as an alternative to invasive prenatal screening and therapeutic abortions, and may also increase the chances of an implanted embryo to arrive to term. However, we find that it is still uncertain whether this approach will significantly improve pregnancy rates.

Indeed, the data supporting the correlation between maternal age and the rate of chromosomal imbalance in oocytes and embryos is quite convincing (Angell et al., 1993; Munné et al., 1995; Dailey et al., 1996), and it is undeniable that the increase in aneuploidy with age is inversely correlated with assisted reproductive techniques (ART) success rates. Yet, do these facts guarantee that routine PGD in all women of advanced age will significantly improve pregnancy rates per cycle? Will it prove cost effective? It is our view that several issues have still to be investigated before the answer ‘Of course’ can be given. Some of these issues are as follows.

Firstly, at present there is no proof in humans that embryo biopsy does not reduce implantation rate. It is possible that such an adverse effect of embryo biopsy will counteract the benefits in terms of pregnancy rates which are expected following PGD.

Secondly, poor oocyte quality has a prominent role in the age related fertility decline. There is accumulating evidence that the decline in oocyte quality with age is a result of the degeneration and malfunction of multiple cellular components (Tarín, 1996). If these degenerative processes are not closely linked to chromosomal imbalance, the selection of the euploid embryos for transfer might have only a marginal effect on implantation rates, as failure of implantation could still result from other age related sequelae.

Thirdly, the decline in ART success rates is most pronounced in women aged >40 years. These women usually have a small cohort of embryos (Plachot et al., 1988), and even if four or more embryos are produced, in many units, all embryos will be transferred. Under such circumstances, the chromosomally balanced embryos of the cohort are transferred in any case, and it seems unlikely that their selection by PGD would increase pregnancy rates. The implementation of PGD could be more relevant in the age range of 35–40 years, where production of a large cohort of embryos is common. Yet, both the increase in aneuploidy and the decline in pregnancy rates are less pronounced in these women. Therefore, it is doubtful whether PGD would significantly increase pregnancy rates in this age group.

Fourthly, chromosomal mosaicism, a frequent phenomenon among IVF embryos, raises an additional uncertainty. The current approach is to discard mosaic embryos. However, the biological significance of mosaicism is uncertain. It was recently suggested that abnormal cells in the early mosaic embryo are subsequently eliminated or diverted to the trophoderm and thus do not impair normal development (James and West, 1994). Therefore, discarding mosaic embryos may lead to the loss of potentially normal embryos and hence hamper the expected beneficial effect of PGD on pregnancy rates.

Fifthly, false FISH results may also lead to an erroneous unwanted loss of normal embryos (although to a lesser extent).

Finally, the issue of cost effectiveness is not yet clear. Although PGD of aneuploidy is expected to reduce the abortion rate, it does not necessarily imply an improved delivery rate per cycle. It will be possible to calculate the cost effectiveness of this process only when the extent to which PGD will improve the delivery rate per cycle is determined.

In conclusion, PGD of aneuploidy is undoubtedly an important step towards accurate assessment of embryo quality. This approach may prevent aneuploidy at birth while avoiding the moral and religious impediments of pregnancy termination. It may also reduce the rate of abortions which are highly related to chromosomal imbalance. Still, it is unclear whether routine implementation of PGD in patients aged >35 years will improve pregnancy rates per cycle and will prove to be financially effective. Hence, the question: ‘to biopsy or not to biopsy?’ all embryos of older IVF patients needs further study.

References


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