Reply: Variability of ovarian reserve tests

Sir,

We thank Dr Elter et al. for their comments concerning our paper on intercyclical variability of ovarian reserve tests.

The authors raise the issue of possible differences between day 2 and day 3 FSH values which in our study may have contributed to the observed variation of FSH between cycles. In the first place, only in ~10% of the participants was FSH not measured on all three days of the cycle. The cited small subanalysis in 20 patients by Brown et al. (1995), indicated a possible within-cycle coefficient of variation for FSH of 14.8%. It should be realized that such a variation also included the assay variation (4.8% intra-assay variation and 6.2% inter-assay variation) and that value indicates that the within (intra)-cycle variation of FSH measurement is probably only limited. And indeed Hansen et al. (1996), in the study that we cited, measured FSH on cycle days 2–5 in order to investigate the intra- and intercycle variability in a healthy population of 44 women with regular menstrual intervals in a total of 66 cycles on cycle days 2, 3, 4 and 5, and FSH concentrations were not different between the various cycle days.

The second point raised was about the possible carry-over effect of clomiphene from one cycle to the other. Indeed, it has been reported that significant plasma concentrations of clomiphene citrate could be detected up to 1 month after treatment with a single dose of 50 mg (Mikkelson et al., 1986). But this is predominantly the so-called isomeric Zu variant of clomiphene. Glasier et al. (1989) investigated the effects on follicular development of clomiphene citrate and its two isomers En clomiphene and Zu clomiphene. It was concluded that the En isomer, which has largely the antiestrogenic properties, is the isomer active in inducing follicular development. The biologically active En clomiphene is eliminated much more quickly than the biologically inactive Zu clomiphene. Moreover, Opsahl et al. (1996) showed that patterns of gonadotrophin response, follicular development, and endometrial growth and maturation remain consistent across consecutive cycles of clomiphene citrate treatment. This is why we believe that there is no carry-over effect of clomiphene citrate. Taking this altogether, we assumed that a biological carry-over effect of clomiphene in our study could be negligible.

The third point raised was whether the bias of pregnant subjects may have biased the results in the study. Indeed we do have a potential bias here in that women who became pregnant during the three test cycles did not reach the IVF cycle in which the ovarian reserve was evaluated. We admit the possibility of this bias but we could not think of a way to avoid it in an ethically acceptable manner. It turned out that the number of pregnant subjects was (relatively) small. Therefore this bias, if present, has only contributed to a limited extent.

Finally, it was suggested that we should have calculated the variance per subject, i.e. variance within-subject over cycles. This is in fact exactly what we have done: SD = square root of variance measured within each female patient.

References


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J.Kwee, R.Schats, J.McDonnell, C.B.Lambalk and J.Schoemaker

Division of Reproductive Endocrinology and Fertility and the IVF Centre, Department of Obstetrics and Gynaecology, Vrije Universiteit Medical Centre, Amsterdam, The Netherlands

E-mail: j.kwee@vumc.nl

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Reciprocal translocation carriers in recurrent miscarriage parents may yield an unbalanced fetal chromosome pattern

Sir,

We read with interest the study by Goddijn et al. (2004) on clinical relevance of structural chromosome abnormalities in couples with repeated miscarriage. The authors concluded that karyotyping of 1324 couples ascertained for repeated miscarriage did not yield an unbalanced fetal chromosome pattern after the ascertainment of parental carrier status. We disagree with the conclusion because reciprocal translocation cases do exist for recurrent miscarriages who give birth to offspring with unbalanced fetal chromosomes.

Our recent analysis showed that one of 34 offspring of successful pregnancies of reciprocal translocation carriers examined for recurrent miscarriage had an unbalanced translocation (Sugiura-Ogasawara et al., 2004). This 2.9% is not negligible and is equivalent to the frequency at which 43 year old women have a fetus with an abnormal chromosome karyotype ascertained by amniocentesis.

We have another patient with 46,XX, t(4;15)(q33; q26) who was found to be a carrier after examination for recurrent miscarriage in another hospital and who gave birth to two malformed children with 46,XX, t(4;15)(q33; q26)-mat and 46,XX, der(4)t(4;15)(q33;q26)mat after three miscarriages. Our previous study did not include this case because the patient came to our hospital for preimplantation genetic diagnosis.

Midro et al. (1991) also reported 10 families with reciprocal translocations and one woman with 46,XX, t(6;13)(q27;q12) who had two malformed children with three spontaneous...
abortions. De Braekeleer and Dao, (1990) compared the distribution of the chromosomes involved in reciprocal translocations in couples experiencing recurrent miscarriages after birth of malformed children and put forward differences in the translocation breakpoints as an explanation for the outcomes.

In conclusion, the frequency with which reciprocal translocation carriers with a history of recurrent miscarriage give birth to a child with an unbalanced translocation is 2.9%, and couples with reciprocal translocations are at risk of an unbalanced fetal chromosome pattern. Thus, we should inform our patients of this risk and offer amniocentesis as a diagnostic aid.

References


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Mayumi Sugiura-Ogasawara
Department of Obstetrics and Gynecology, Nagoya City University Medical School, Mizuho-ku, Nagoya 467, Japan

E-mail: og.mym@med.nagoya-cu.ac.jp

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Reply to ‘Reciprocal translocation carriers ascertained for recurrent miscarriage have a possibility to yield an unbalanced fetal chromosome pattern’

Sir,

We thank Mayumi Sugiura-Ogasawara et al. for their comments on our paper (Goddijn et al., 2004). In this paper, we concluded that karyotyping of 1324 couples ascertained for repeated miscarriage did not yield an unbalanced fetal chromosome pattern after the ascertainment of parental carrier status.

Sugiura-Ogasawara et al., on the other hand, showed that in their Japanese cohort one out of 34 successful pregnancies (2.9%) in carrier couples had an unbalanced translocation (Sugiura-Ogasawara et al., 2004).

If we combine the evidence from the Japanese cohort (1284 couples) with the equal-sized Dutch cohort (1324 couples), regardless of possible differences in cohort composition, only one unbalanced translocation was observed in the live offspring of 2608 couples with repeated miscarriage. In our view, this risk is a very low risk which cannot be compared with the risk of having a chromosomally abnormal fetus in a 43-year-old woman at amniocentesis.

The low risk emphasizes even more the need to find a subgroup with an apparently low frequency of carrier status. We now await the results of a large Dutch multi-centre study to confirm or refute our previous results.

References


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Mariëtte Goddijn, Hannie Joosten, Lia Knekt, Fulco van der Veen, Maureen Franssen, Gouke Bonsel and Nico Leschot
Center for Reproductive Medicine, Department of Obstetrics and Gynecology, H4-205, Academic Medical Center, Meibergdreef 9, 1105 AZ Amsterdam, The Netherlands

E-mail: M.Goddijn@amc.uva.nl

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