Reply: Pregnancy is predictable: a large-scale prospective external validation of the prediction of spontaneous pregnancy in subfertile couples

Sir,

We thank Drs Smeenk and colleagues for their interest in our work. The authors address several issues. First, they state that a prognostic model is only useful if it changes the prior probability for pregnancy in an accurate way, and suggest that the Hunault model does not change the prior probability of 32% that most couples would have for spontaneous conception within 12 months. We disagree with the interpretation of Smeenk et al. Figure 3 of our article shows clearly that the 10% of the couples with the best prognosis have a mean predicted probability of over 50%, and indeed 50% of these couples conceive. Even so, of the 20% of couples that have a predicted probability of around 20%, only <20% conceive. We feel that such information is relevant for clinical practice.

Secondly, Smeenk et al. remark that in 1104 couples (36%) the probability of a spontaneous pregnancy was over 40%, whereas only two deciles corresponding with 611 couples with a probability of over 40% were described in the calibration plot. The authors are correct to point this out, which provides us with the opportunity to clarify this apparent discrepancy. The number of 1104 couples was based on predictions with a model with the Post Coital Test (PCT), whereas the 611 couples were based on the model without the PCT.

Finally, the authors claim that our work was threatened by bias because the evaluated model was also used to decide which couple would be treated and which couple not. This criticism would be true if we had not considered the time that each couple was trying to conceive without medical assistance. However, as we used time to spontaneous conception as outcome measure, we took into account that some couples were treated soon, whereas others waited longer before treatment was started.

Smeenk et al. then assess the prediction model with the c-index and go on to state that pregnancy cannot be predicted in a reliable way with a poor discriminative capacity. They state that a model in order to be useful has a virtually perfect discriminative capacity (c-index or area under the curve, AUC of 1.0). Prognostic tests differ from diagnostic tests concerning their discriminative capacity. Diagnostic tests, for example a laparoscopy for the diagnosis of two-sided tubal pathology, often show a good discriminative capacity with a high AUC. Prognostic tests have an inherent level of difficulty that differs from problem to problem. In reproductive medicine, prognostic models show AUCs around 0.6, when validated in an external population. In reproductive medicine the consequence of a false-negative prediction, i.e. the prediction that pregnancy will occur whereas it turns out that the couples does not conceive, only implicates a delay of treatment of 6 or 12 months. Especially for this good prognosis group, treatment will offer no benefit over an expectant management and as such the model helps us to offer tailored management without claiming to become fortune-tellers. As a consequence, the discriminative capacity (c-index) is often misinterpreted in reproductive medicine, as has been addressed in the longer and the recent past (Diamond, 1992; Mol et al., 2005). More important is the aim to create a model with a good calibration, in which we have succeeded. We have shown that prediction models can be used to classify subfertile couples accordingly, and we have shown that such an approach can prevent overtreatment (Steures et al., 2006) (http://www.freya.nl/probability.php).

In summary, we are not dreaming of crystal balls to make predictions in individual couples. We do feel however that it is important to identify subfertile couples who have a good or a poor prognosis for spontaneous pregnancy. We also feel that we have shown in our research that this validated model, albeit not a perfect model, goes a long way in this direction.

References


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Spontaneous pregnancy and normal delivery after repeated autologous bone marrow transplantation and GnRH agonist treatment

Sir,

A 14.5-year-old female received chemotherapy and concomitantly monthly GnRH agonist injections (Decapeptyl CR 3.75 mg/month) and ’miniMantle’ irradiation (2500 cGy) in 1995 due to stage IV ALK positive anaplastic large cell lymphoma (Blumenfeld and Eckman, 2005). Several months later, she underwent autologous stem cell transplantation (SCT) with BEAC (carmustine, etoposide, cytarabine and cyclophosphamide) protocol, due to persistent disease. The GnRH agonist injections were also administered before bone marrow transplantation (BMT). Later she was found to have chronic active hepatitis secondary to hepatitis C infection and was treated with α interferon with no response. At the age of 24, she married and spontaneously conceived, but pregnancy ended in an early spontaneous abortion. A month later, she conceived again, and this pregnancy developed normally until 24 weeks of gestation when recurrence of anaplastic large cell lymphoma was diagnosed. DVIP chemotherapy (dexamethasone, etoposide, ifosfamide and cisplatin) was administered and subsequently intrauterine growth retardation was diagnosed, followed by intrauterine demise. After pregnancy termination (780 g male fetus without malformations), the patient received monthly injections of GnRH agonist in parallel to DVIP chemotherapy and subsequently underwent a second autologous BMT following conditioning with BEAC protocol. Before the GnRH agonist, the FSH was 12.1 and LH = 1.17 U/l and follicles were sonographically detected in both ovaries. The option of IVF and ovarian cryopreservation were denied by another center. Three months later, she had a spontaneous menstrual bleeding, but 5 days afterwards, the FSH = 69.8 U/l, LH = 44.3 U/l and estradiol = 125 pmol/l. The abdominal and chest CT was normal. Three months later, the FSH = 4.1 U/l, LH = 4.7 U/l and estradiol = 1034 pmol/l and she continued experiencing regular menstruation. An attempt for IVF was stopped due to poor response, but 3 months later, she spontaneously conceived and after a normal gestation, she delivered on 30 August 2006 a normal, term, female neonate, 3450 g, with normal Apgar scores.

Bone marrow transplantation almost invariably induces ovarian failure, irrespective of patient age or treatment protocol (Meirov, 2000; Blumenfeld and Eckman, 2005; Lobo, 2005; Donnez et al., 2006). A large survey of fertility after SCT involving 37 362 patients found that only 0.6% of patients conceived after one autologous or allogenic SCT. The estimated odds for spontaneous conception after two BMTs are negligible (Meirov, 2000; Salooja et al., 2001; Donnez et al., 2006). The administration of GnRH agonist before and in parallel to chemotherapy suggests it might have minimized the gonadotoxic effect of chemotherapy and increased the chance of spontaneous ovulation and successful conception and delivery (Blumenfeld and Eckman, 2005). Since most of the methods involving ovarian or oocyte cryopreservation are not yet clinically established and highly successful, one should provide these young patients with all the information concerning the various attempts to minimize gonadal damage and preserve ovarian activity and fertility (Blumenfeld and Eckman, 2005; Lobo, 2005).

References


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doi:10.1093/humrep/dem066
Advance Access publication on April 23, 2007

Independent counselling on embryo donation for infertility patients

Sir,

A key issue of contention in reproductive ethics is the perspective that human life begins at the onset of fertilization (Young, 1994; Sullivan, 2003), so that the disposal of surplus frozen embryos, not otherwise donated to other infertile couples,