Reply: The danger of ignoring pregnancy and delivery rates in ART

Sir,

We were surprised to read the Letter to the Editor “The danger of ignoring pregnancy and delivery rates in ART” by Gleicher and colleagues as a reaction to our paper (De Neubourg et al., 2013). We are not ignoring pregnancy and delivery rates but we want to stress the danger of ignoring the risks of twin and multiple delivery rates in assisted reproductive technology (ART).

We still wonder why Gleicher and colleagues ignore the risks of twin and multiple pregnancies while there is compelling evidence that the risks of multiple pregnancies on physical, psychological, perinatal, economical, social and financial aspects are substantial to the couple, the child(ren) and society (Scholz et al., 1999; Glazebrook et al., 2004). We cannot understand why the authors refute the existing evidence that perinatal morbidity and mortality are much higher for twin and higher order multiple pregnancies than for singleton pregnancies (Bergh et al., 1999) and that by decreasing the numbers of embryos for transfer, we hold the possibility to reduce this detrimental side effect of ART. According to a recent meta-analysis comparing perinatal morbidity and mortality for elective single embryo transfer (SET) relative to double embryo transfer (DET), elective SET-conceived singletons were less likely to be born either preterm (relative risk 0.37) or with low birthweight (relative risk 0.25) than DET conceived infants (Grady et al., 2012). In a recent analysis of >50,000 children born after ART in Australia and New Zealand perinatal mortality rates were 58% higher for children born after DET relative to children born after SET (Sullivan et al., 2012). Therefore, SET should be advocated as the first-line management in ART as it is the single most effective public health intervention for preventing excess perinatal mortality among ART pregnancies.

In Europe, awareness of the importance of SET led, as early as 2003, to a consensus document published by the European Society for Human Reproduction and Embryology (ESHRE) stating that the essential aim of ART is the birth of one single healthy child, with a twin pregnancy being regarded as a complication (Land and Evers, 2003). In the USA, the American Society for Reproductive Medicine (ASRM) and the Society for Assisted Reproductive Technology (SART) published practice guidelines recommending the maximum number of embryos for transfer in 2013 (ASRM/SART, 2013). Recently, a misguided campaign launched in the USA against the goal of SET and singleton birth in ART (Gleicher and Barad, 2006) was brilliantly refuted on a solid scientific basis by another American group (Stillman et al., 2013). They refute what proponents of twins argue, namely that patients prefer twins, that multiple embryo transfer maximizes success rates, that the costs per infant are lower with twins and that one twin pregnancy and birth is associated with no higher risk than two consecutive singleton pregnancies and births.

In Europe, we also do care about the cumulative live birth rates per patient, and not only about the pregnancy rate per cycle. In Belgium, legislation was introduced in 2003 to reduce the number of embryos allowed for transfer, coupled to laboratory reimbursement of six ART cycles in women up till the age of 43. A retrospective cohort study was performed in one fertility center with a study group of patients undergoing ART after implementation of the new ART legislation (July 2003 to June 2006) and a control group of patients who received ART treatment before implementation of legislation (July 1999 to June 2002). The study showed that there was no negative impact on the cumulative delivery rate per patient based on realistic estimates within six fresh cycles or 36 months after start of ART treatment (Peeraer et al., 2014).

We are worried about the changing attitude of the Human Fertilisation and Embryology Authority (HFEA) toward the implementation of a restriction in the number of embryos for transfer in ART in the prevention of multiple pregnancies and are concerned about what ending targets on numbers of multiple births for fertility clinics will mean to patients and the National Health Service in the United Kingdom (Arie, 2014). One has to ask who should pay for the medical cost and societal burden of multiple pregnancies after ART treatment; government or specialists in reproductive medicine? The Belgian model which consists of a combination of restriction of the numbers of embryos for transfer in ART coupled to reimbursement of the greater part of ART related costs, proves that with judicious application of SET, the multiple pregnancy rate can be reduced to 11% with cumulative delivery rates remaining constant per ART cycle and per patient. We want to point out that this model is offering a public health model for regulation and reimbursement of ART practice worldwide (De Neubourg et al., 2014).

We feel it is a danger to the patients who need ART treatment if one is focused and blinded by pregnancy rates only and ignores the important risks and costs of multiple pregnancies for mother and child as well as for society.

References

De Neubourg D, Bogaerts K, Wyns C, Albert A, Camus M, Candeur M, Degueldre D, Delbaere A, Deligne A, Delhove J, et al. Deliveries and Embryology Authority (HFEA) toward the implementation of a restriction in the number of embryos for transfer in ART in the prevention of multiple pregnancies and are concerned about what ending targets on numbers of multiple births for fertility clinics will mean to patients and the National Health Service in the United Kingdom (Arie, 2014). One has to ask who should pay for the medical cost and societal burden of multiple pregnancies after ART treatment; government or specialists in reproductive medicine? The Belgian model which consists of a combination of restriction of the numbers of embryos for transfer in ART coupled to reimbursement of the greater part of ART related costs, proves that with judicious application of SET, the multiple pregnancy rate can be reduced to 11% with cumulative delivery rates remaining constant per ART cycle and per patient. We want to point out that this model is offering a public health model for regulation and reimbursement of ART practice worldwide (De Neubourg et al., 2014).

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Ovarian suspension for longer than 36 h is necessary for temporary ovarian suspension to fulfil its remit

Sir,

We read with great interest the recent study published in Human Reproduction which assessed the effectiveness of temporary ovarian suspension after endometriosis surgery (Hoo et al., 2014). The study failed to find a statistically significant reduction in adhesion formation associated with ovarian suspension; this finding is unsurprising and could have easily been predicted from the outset.

The aim of temporary ovarian suspension is to suspend the ovaries whilst the regions of excised peritoneum heal in order to prevent contact between the ovaries and the regions of excised peritoneum. Following healing of the peritoneum in these regions, the sutures suspending the ovaries are cut; as the peritoneum will now have mostly healed, in theory, ovarian adhesions are now less likely to form (Trehan, 2002).

It has been known for decades that peritoneal healing takes 5–8 days to occur (Ellis et al., 1965; Eskeland, 1966; Glucksman, 1966; Hubbard et al., 1967; Raferty, 1976), and further, blood in the pelvic cavity may be involved in adhesion pathogenesis (Ryan et al., 1971), which has been shown to take up to 8 days for absorption from the pelvic cavity (Jackson, 1958). In light of this, is 36 h really long enough to allow for peritoneal healing before cutting the ovarian sutures? Hoo et al. state that they chose their suspension time of 36 h based on a single rodent study in which a laparotomy was made and a region of anterior abdominal wall parietal peritoneum and a layer of underlying muscle was excised; the caecum was then elevated to be in close proximity to the anterior abdominal wall, and the anterior abdominal wall and caecum were then abraded with a scalpel, left exposed to air for 10 min, and a silastic sheet placed between the two surfaces, and the laparotomy then closed (Harris et al., 1995). The silastic sheet was then removed at various time intervals, and the incidence of adhesions was noted after 7 days. The study found that adhesions between the abdominal wall and the caecum only formed if the silastic sheet was removed prior to 36 h. Whilst an interesting study, it would be dangerous to assume that based on these findings in a single artificial animal model, no ovarian adhesions form in women >36 h after surgery for deep endometriosis, and that therefore suspension for longer than 36 h would not be beneficial.

Hoo et al. also note that they chose this short length of ovarian suspension partially based on an apparent risk of small bowel strangulation and wishing not to discharge patients with suspended ovaries. None of the published studies on temporary ovarian suspension with longer suspension times have ever noted this complication (Abuzeid et al., 2002; Trehan, 2002; Ouahba et al., 2004; Poncelet et al., 2012), and so we question whether this purely theoretical concern is borne out in clinical practice. Hoo et al. also note the cost of suture removal at a later date as a further disincentive for longer periods of suspension; yet keeping patients, who could be discharged after an overnight hospital stay, in hospital for two nights for not wishing to discharge patients with the ovarian sutures in situ, in fact represents a much larger cost than having sutures removed in the community at a later date. In our current practice, the ovarian suspension sutures are removed in the community by 7–9 days post-operatively, usually at their general practice surgery by a practice nurse.

There is also the obvious limitation associated with assessing adhesion formation via ultrasound rather than second-look laparoscopy; clearly ultrasound is cheaper and less time consuming; however, recent studies assessing the impact of certain interventions on adhesion formation in other contexts have used repeat laparoscopy (Trew et al., 2011).

Temporary ovarian suspension is a theoretically compelling means of reducing ovarian adhesions; we hope that readers of Human Reproduction will not be deterred from performing temporary ovarian suspension on the basis of a study in which the ovaries were not suspended for an appropriate length of time. In order to gain a definitive answer on the effectiveness of temporary ovarian suspension, future studies should assess the impact of ovarian suspension for at least 5 days (perhaps even for a minimum of 7 days in order to ensure complete healing before the ovarian sutures are cut), use larger patient numbers and utilize second-look laparoscopy in order to assess adhesion formation.

References