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.

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