

Implication of the liberal use of ART in Nordic countries: should stricter guidelines be created to prevent unnecessary stillbirth and preterm delivery?

Sir,

With interest we read the article of Henningsen *et al.*, who compared pregnancy outcomes in singleton pregnancies after ART to singleton pregnancies that were conceived naturally. The authors report a significantly increased risk of stillbirth after ART before a gestational age of 28 weeks. They conclude that in view of the fact that the increased stillbirth risk was observed before 28 weeks only, prevention of stillbirth in the third trimester might be sufficient.

We have two comments. First, the authors have acknowledged that a proportion of the cohort of women with ART singleton pregnancies (estimating background rate 1 in 10 (Henningsen *et al.*, 2014)) initially might have had a vanishing twin. They have also acknowledged the subsequent possible implications for early stillbirths in this group. It would be crucial to know what proportion of the singletons after ART would be the result from single embryo transfer (SET) or from double embryo transfer (DET). This information is not provided, but may be available to the authors. Moreover, as SET in Scandinavia was introduced well before the end of the study period, the authors might be able to look at trends over this time.

Secondly, when the increased perinatal mortality rate before 28 weeks indeed can be linked to the use of ART, we would like to challenge the opinion of the authors on the liberal use of ART in Nordic countries, where >3% of the babies are conceived after ART, with Denmark leading the way with 4.5% of infants born through ART (Ferraretti *et al.*, 2013). Considering the fact that many couples would conceive naturally when allowed a longer expectant management period we could imagine stricter guidelines around use of ART in Scandinavia to prevent unnecessary stillbirth and preterm delivery.

References

- Ferraretti AP, Goossens V, Kupka M, Bhattacharya S, de Mouzon J, Castilla JA, Erb K, Korsak V, Nyboe Andersen A. Assisted reproductive technology in Europe, 2009: results generated from European registers by ESHRE. *Hum Reprod* 2013;**28**:2318–2331.
- Henningsen AA, Wennerholm UB, Gissler M, Romundstad LB, Nygren KG, Tiitinen A, Skjaerven R, Nyboe Andersen A, Lidegaard O, Forman JL *et al.* Risk of stillbirth and infant deaths after assisted reproductive technology: a Nordic study from the CoNARTaS group. *Hum Reprod* 2014;**29**:1090–1096.

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Reply: Implication of the liberal use of ART in Nordic countries: should stricter guidelines be created to prevent unnecessary stillbirth and preterm delivery?

Sir,

We thank Dr Hughes and colleagues for their valuable comment on our findings on the risk of stillbirth and perinatal death among ART children.

Single embryo transfer (SET) was only introduced in Nordic countries towards the end of our study period, with a delay in some countries; therefore, the majority of ART singletons in our cohort were born after double embryo transfer (DET). A follow-up study investigating trends in birth outcomes over time has recently been completed. However, we only have a few years of data with SET; unfortunately we are unable to show an impact of vanishing twins on a rare outcome such as stillbirth. Not all Nordic ART registries gathered data on the number of embryos transferred during this study period. Therefore, we are not able to estimate the proportion of children born after SET versus DET in the Nordic population. We agree that vanishing twins is an important aspect and, based on national Danish data, it has previously been shown that one in ten ART singletons is born after, what started as, a twin gestation and therefore may be effected negatively by the vanish of their co-twin (Pinborg *et al.*, 2005).

Access to ART is high in Nordic countries and the proportion of ART children in national birth cohorts is markedly higher compared with other countries. Still it has been demonstrated that the mean length of infertility at referral to a tertiary fertility centre for couples in Denmark is 4.1 (\pm 2.3 SD) years and that less than one fifth of couples referred to a public infertility programme eventually conceive spontaneously (Pinborg *et al.*, 2009). The risk of stillbirth in ART singletons has been compared with spontaneously conceived siblings in the same mother. This comparison suggests that the underlying infertility is associated with the increased risk of stillbirth and not the technology *per se* (Romundstad *et al.*, 2008). Additionally, it has been shown that the risk for adverse perinatal outcomes after spontaneous conception

increases by increasing time to pregnancy. In summary, there is strong evidence that factors associated with infertility influence the perinatal outcomes of children regardless of ART treatment or not (Pinborg *et al.*, 2013).

On a European level, the major reproductive challenge is the delay in childbearing. Hence we do not believe that expectant management of couples seeking fertility treatment with a mean female age of 34 years is the best way forward.

References

- Pinborg A, Loft A, Schmidt L, Andersen AN. Morbidity in a Danish national cohort of 472 IVF/ICSI twins, 1132 non-IVF/ICSI twins and 634 IVF/ICSI singletons: health-related and social implications for the children and their families. *Hum Reprod* 2005;**20**:2821–2829.
- Pinborg A, Hougaard CO, Nyboe Andersen A, Molbo D, Schmidt L. Prospective longitudinal cohort study on cumulative 5-year delivery and adoption rates among 1338 couples initiating infertility treatment. *Hum Reprod* 2009;**24**:991–999.
- Pinborg A, Wennerholm UB, Romundstad LB, Loft A, Aittomaki K, Söderström-Anttila V, Nygren KG, Hazekamp J, Bergh C. Why do singletons conceived after assisted reproduction technology have adverse perinatal outcome? Systematic review and meta-analysis. *Hum Reprod Update* 2013;**19**:87–104.
- Romundstad LB, Romundstad PR, Sunde A, von Düring V, Skjaerven R, Gunnell D, Vatten LJ. Effects of technology or maternal factors on perinatal outcome after assisted fertilisation: a population-based cohort study. *Lancet* 2008;**373**:744–749.
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