



## Editorial

## Assisted reproductive technology and adverse pregnancy outcome- focus on maternal death



Trends in women's older age at the first attempt to get pregnancy with an increased availability of diagnostic treatment modalities are associated with needs of infertility treatment, which is common mediated by assisted reproductive technology (ART) to achieve parenthood in couples in modern society.<sup>1–3</sup> However, with an aid of ART, there are many issues worthy of our attention, because there is much concern about the increased risk of morbidity and/or mortality during and after treatment, influencing not only fetus but also mother, and of most importance, the risk might be continuous for many years.<sup>4–7</sup> We are glad to learn that Dr. Engin Üstün's study published in this issue of the *Journal of the Chinese Medical Association* attempted to use the national database in Turkey to investigate one of the above-mentioned issues—the maternal death rate in Turkish women giving birth after ART.<sup>8</sup>

The authors retrospectively reviewed 10,369,064 live births and 1788 maternal deaths between 2007 and 2014 and found that 28 maternal death cases following ART.<sup>8</sup> Among these 28 patients, two-fifths of women were over 35 years of age.<sup>8</sup> Hypertensive disorders, pulmonary embolism, and cardiovascular disease were the most common causes for maternal death.<sup>8</sup> It is a valuable article worthy of a further discussion.

To claim the increased risk of maternal mortality after ART should be based on the background data from the same country. As shown by authors, the maternal mortality ratio (MMR) of Turkey in the 2007–2009 and 2014 periods was 19.7 and 15.2 per 100,000 live births, respectively, compared with 20.6 per 100,000 live births after ART in the 2007–2014 period, suggesting that the pregnant women after ART might be really risky for increasing maternal death, although the authors found that there was no statistically significant difference between ART pregnancies and overall pregnancies in terms of MMRs.<sup>8</sup> This finding did not support the concepts that women after ART have a high risk of both maternal and perinatal morbidity and possible mortality from the recent publications addressing the same topic.<sup>9,10</sup> There are many background data which might bias the finding.

It is well-known that multi-pregnancy often occurs after ART, and multi-pregnancy is correlated with increased adverse pregnancy outcomes, regardless of subfertile women

conceived with and without *in vitro* fertilization (IVF).<sup>9</sup> In fact, 1.7% of all live births in the United States are the result of ART, contributing to the distribution of 1% of singletons, 19% of twins, and 25% of triplet or higher multiples after IVF, and 4%, 21%, and 52%, respectively after non-IVF ART.<sup>10</sup> There are at least six adverse pregnancy outcomes specific to multi-pregnancy, including gestational diabetes, pregnancy hypertension, uterine bleeding, placental complications [placenta abruption, placenta previa, and vasa previa], prenatal hospitalizations and primary cesarean section.<sup>9</sup> A recent report showed that the risk for those 6 adverse pregnancy outcomes were significantly increased for the subfertile and IVF groups, with highest risks for uterine bleeding (adjusted relative risk ratios [arRR], 1.92, and 2.58, respectively) and placental complications (arRR, 2.07 and 1.83, respectively),<sup>9</sup> and all of which might increase the MMR in ART twins. In addition, the increased risk of maternal adverse outcomes is also noted in ART singletons, because IVF mothers have a significantly higher risk of severe maternal morbidity compared with fertile mothers, regardless of the use of donor oocytes or the use of thawed embryos.<sup>10</sup> For example, pregnancy-induced hypertension (PIH) was significantly higher in the ART groups than that in the spontaneous conception with adjusted odds ratio (aOR) of 1.43, 95% confidence interval (CI) 1.14–1.78 (donor oocytes group) and 1.30, 95% CI 1.08–1.57 (thawed embryos group), respectively.<sup>10</sup> PIH and its severe form-preeclampsia and eclampsia is still main cause of both maternal and fetal morbidity and mortality.<sup>11–13</sup> Cromi and colleagues retrospectively assessed the difference of severe maternal morbidity between women treated with ART and with a spontaneous conception, and data showed that the odds of a maternal near-miss at delivery were increased for ART-conceived pregnancies compared with non-ART-conceived pregnancies (aOR 3.61, 95% CI 1.61–8.09, for ART-conceived pregnancies with autologous oocytes; aOR 13.57, 95% CI 5.45–33.77, for ART pregnancies conceived with donor oocytes).<sup>7</sup> Dr. Engin Üstün's study also showed the main cause of maternal death in ART group was due to hypertensive disorders (followed by pulmonary embolism and cardiovascular diseases).<sup>8</sup> All supported the findings that the adverse pregnancy outcomes are really present in pregnancies

conceived via ART, especially those conceived with donor oocytes.

However, should ART procedures be criticized? A recent study from Denmark showed that women undergoing ART might have lower mortality than age-matched with untreated women from the background population.<sup>6</sup> The results showed that the risk of death was lower among ART-treated women during the first 2 years after ART treatment (hazard ratio [HR], 0.68, 95% CI 0.63–0.74); in addition, having children prior to ART treatment was associated with markedly reduced mortality (HR 0.45, 95% CI 0.38–0.53).<sup>6</sup>

Although subfertility, with or without IVF ART treatment to achieve a pregnancy, is associated with increased risk of adverse of maternal and perinatal outcomes, this risk should not be totally declared to the ART itself. The major risk from IVF treatments for multiple births has been reduced over time, with single and better-quality embryo being transfer. In addition, much more cautious use of ovulation induction to avoid over-stimulation of ovary should be further emphasized. Finally, compared with fertile women, these subfertile women who need IVF ART and non-IVF ART tend to be older, might have more preexisting chronic condition and all contribute to increasing risk of adverse pregnancy outcomes. Every obstetrician should always keep in mind to consider all ART pregnant women as high-risk population, which needs special care.

### Conflicts of interest

The authors declare that they have no conflicts of interest related to the subject matter or materials discussed in this article.

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