Preeclampsia: more than just a maternal disease

The concept of a "dangerous father" is not new in the context of the risk of maternal preeclampsia in relation to the identity of the male partner. Previous studies have suggested that the underlying cause is due to paternal human leukocyte antigen characteristics or even seminal fluid cytokines creating an abnormal maternal immune response that, in turn, leads to an abnormal development of the vessels at the maternal fetal interface (1). It is these initial abnormalities of placentation that are potentially responsible for the changes in the maternal cardiovascular system that eventually lead to a diagnosis of preeclampsia and why delivery of the placenta seems to be the cure. Although we are still far from understanding the true underlying pathophysiology, the work by Stenqvist et al. (2) may help identify those "dangerous fathers."

The current study is not the first to have investigated an association between high sperm DNA fragmentation index (DFI) levels and preeclampsia. The work by Hervás et al. (3) found an elevated, but nonstatistically significant, risk of preeclampsia when comparing a group with higher DFI, defined as >15%, with a group with lower levels. A key difference in the methodology was that the study by Hervás et al. (3) only included embryos created using intracytoplasmic sperm injection (ICSI), whereas the study by Stenqvist et al. (2) also included conventional fertilization. In addition to this difference, the study by Stenqvist et al. (2) included a much larger population, taking advantage of the Swedish birth registry. However, it should be noted that use of the Swedish birth registry does somewhat limit the generalizability given the restrictions placed on those allowed to pursue in vitro fertilization under the tax-funded Swedish health system. These limitations included a female age of <40 years, male age of <56 years, and body mass index of 18–30 kg/m^2 or a 10% weight loss if the body mass index was between 30 and 34 kg/m^2 (2).

Using the Swedish National Birth Registry, the investigators performed a prospective cohort study to evaluate the association between high sperm DFI and outcomes including preeclampsia, preterm birth, low birth weight, low Apgar scores, and being small for gestational age. These outcomes were tracked in couples diagnosed with infertility who underwent fresh or frozen embryo transfers with embryos created with autologous eggs and partner sperm. Most critically, the semen sample that was used for fertilization was the same sample that the sperm DNA fragmentation testing was performed on. Interestingly, the investigators found a difference in the rates of preeclampsia depending on the method of fertilization.

Specifically, the investigators found that when a DFI of <10% was used as the referent group, then the odds ratio of developing preeclampsia in the high DFI cohort increased in the combined conventional and ICSI fertilization groups and the conventional fertilization group alone but not in the ICSI group alone. Additionally, the association was seen in a dose-response effect. This finding would suggest that the use of ICSI is at least somewhat protective against the association seen between high DFI and preeclampsia. Until further studies are completed, we can only speculate what the underlying mechanism may be that is responsible for conferring or alleviating this risk. As the investigators suggest, it is not a stretch to think that it is a function of the oocytes' exposure to higher levels of reactive oxygen species that occurs with the coincubation of the oocyte with multiple spermatozoa during conventional fertilization but does not occur with ICSI.

Furthermore, consideration of this potential mechanism will be of particular interest to the ongoing debate regarding the use of ICSI or conventional fertilization. The recent study by Iwamoto et al. (4), comparing ICSI with conventional fertilization, concluded that the use of ICSI is difficult to justify. The findings by the investigators, if confirmed, may make the argument regarding noninferiority of conventional fertilization less clear. At the very least, the finding of Stenqvist et al. (2) will almost certainly prompt further studies on the strategies or treatments that can be implemented to address high DFI levels.

Such treatments for high DFI do already exist and have included everything from lifestyle changes, varicocele repair, obtaining testicular sperm, and, more recently, the use of microfluidic devices (5). Given that preeclampsia is responsible for 70,000 maternal deaths and 500,000 fetal deaths worldwide (according to the Centers for Disease Control and Prevention estimates, https://blogs.cdc.gov/genomics/2022/10/25/preeclampsia/), it will be of great interest to determine if any of these treatments can positively impact the percentage of those afflicted. To accomplish this goal, much work still needs to be performed to understand and identify the causative factors. It is especially exciting that the work by Stenqvist et al. (2) may help identify who is at risk before even conception and possibly even help mitigate that risk.

CRediT Authorship Contribution Statement

Robert T. Rydze: Writing – original draft. **Stephanie J. Gunderson:** Writing – review & editing. **Jay Sandlow:** Writing – review & editing.

Declaration of Interests

R.T.R. has nothing to disclose. S.J.G. has nothing to disclose. J.S. has nothing to disclose.

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