Frozen embryo transfers linked with high blood pressure risks in pregnancy

September 26 2022

Credit: American Heart Association

In vitro fertilization (IVF) using frozen embryos may be associated with a 74% higher risk of hypertensive disorders in pregnancy, according to new research published today in *Hypertension*. In comparison, the study

found that pregnancies from fresh embryo transfers—transferring the fertilized egg immediately after in vitro fertilization (IVF) instead of a frozen, fertilized egg—and pregnancy from natural conception shared a similar risk of developing a hypertensive disorder.

High blood pressure during pregnancy often signals preeclampsia, a pregnancy complication including persistent high blood pressure that can endanger the health and life of the mother and fetus. Approximately 1 out of every 25 pregnancies in the United States results in preeclampsia, according to the American Heart Association.

One IVF treatment process available utilizes frozen embryos: after an egg is fertilized by sperm in the lab, it is frozen using a cryopreservation process before being thawed and transferred to the uterus at a later date. The procedure is becoming more common because of the significantly improved freezing technology or cryopreservation methods that started in the late 2000s and because more patients are choosing to freeze embryos, according to the study authors. Yet, frozen embryo transfer is known to be associated with a higher risk of hypertensive disorders in pregnancy than both natural conception and fresh embryo transfer. However, prior to this study, it was unknown whether this was due to the freezing process or a risk factor from the parents.

"Frozen embryo transfers are now increasingly common all over the world, and in the last few years, some doctors have begun skipping fresh embryo transfer to routinely freeze all embryos in their clinical practice, the so-called 'freeze-all' approach," said Sindre H. Petersen, M.D., the study's lead author and a Ph.D. fellow at the Norwegian University of Science and Technology in Trondheim, Norway.

Researchers examined national data from medical birth registries from Denmark, Norway and Sweden of nearly 2.4 million women who were ages 20 to 44 years old who had single deliveries and gave birth during

the study period—from 1988 through 2015. These data were the basis of a population-based study that also included a comparison of women who had both an IVF pregnancy and a naturally conceived pregnancy, called sibling comparison. This approach was used to isolate if the potential reason for the hypertensive disorders was attributable to parental factors or to the IVF treatment.

The study included more than 4.5 million pregnancies, of which 4.4 million were naturally conceived; more than 78,000 pregnancies were fresh embryo transfers; and more than 18,000 pregnancies were frozen embryo transfers. Among all of the pregnancies, more than 33,000 were grouped for sibling comparison—mothers who conceived via more than one of these methods. The study is the largest to-date using sibling comparison. The odds of developing hypertensive disorders in pregnancy after fresh vs. frozen embryo transfers compared to natural conception were adjusted for variables such as birth year and the mother's age.

"In summary, although most IVF pregnancies are healthy and uncomplicated," Petersen said. "This analysis found that the risk of high blood pressure in pregnancy was substantially higher after frozen embryo transfer compared to pregnancies from fresh embryo transfer or natural conception."

Specifically, the study found:

- In the population analysis, women whose pregnancy was the result of a frozen embryo transfer were 74% more likely to develop hypertensive disorders in pregnancy compared to those who conceived naturally.
- Among women who had both a natural conception and an frozen embryo transfer IVF conception (the sibling comparison), the risk of hypertensive disorders in pregnancy after frozen embryo transfer was twice as high compared to pregnancies from natural

conception.
- Pregnancies from fresh embryo transfer did not have a higher risk of developing hypertensive disorders compared to natural conception, neither in population level analysis nor in sibling comparisons.

"Our sibling comparisons indicate that the higher risk is not caused by factors related to the parents, rather, however, that some IVF treatment factors may be involved," Petersen said. "Future research should investigate which parts of the frozen embryo transfer process may impact risk of hypertension during pregnancy."

Among other findings, women in the study who gave birth after IVF pregnancies were average age 34 years for frozen embryo transfer, 33 years for fresh embryo transfer and 29 years for those who conceived naturally. About 7% of babies conceived from frozen embryo transfer were born preterm (before 40 weeks gestation) and 8% of babies after fresh embryo transfer were born preterm, compared to 5% of babies after natural conception.

In addition to preeclampsia, the researchers defined hypertensive disorders in pregnancy as a combined outcome, including gestational hypertension, eclampsia (the onset of seizures in those with preeclampsia) and chronic hypertension with superimposed preeclampsia.

One limitation of the study was the lack of data on the kind of frozen embryo cycle, so they were not able to pinpoint what part of the frozen cycle or frozen transfer may contribute to the higher risk of hypertensive disorders. Another limitation is that data from Scandinavian countries may limit generalizing the findings to people in other countries.

"Our results highlight that careful consideration of all benefits and

potential risks is needed before freezing all embryos as a routine in clinical practice. A comprehensive, individualized conversation between physicians and patients about the benefits and risks of a fresh vs. frozen embryo transfer is key," said Petersen.

More information: Risk of hypertensive disorders in pregnancy after fresh and frozen embryo transfer in assisted reproduction: A population-based cohort study with within-sibship analysis, *Hypertension* (2022). DOI: 10.1161/HYPERTENSIONAHA.122.19689

Provided by American Heart Association