Primum non nocere: are we closer to saying that the trophectoderm biopsy does no harm?

Every year the Centers for Disease Control and Prevention (CDC) publishes its Assisted Reproductive Technology (ART) National Summary Report, and every year the total number of ART cycles have been steadily increasing. In 2016 the total number of cycles rose to over 263,000, which was almost double the number of cycles in 2007. The increase in cycle number has come with a broader social acceptance of the technologies involved, as well as increased access to these technologies. More recently, there has been a dramatic rise in the use of preimplantation genetic testing (PGT) (previously designated as preimplantation genetic diagnosis/preimplantation genetic screening). Between 2014 and 2015 the total number of cycles using genetic testing increased, and there was a relatively small increase in the percentage of total cycles using the technology rising from 4% to 5%. However, in 2016 there was a 360 % increase in the use of genetic testing as an adjunct to the ART cycle. Now, almost a quarter of all ART cycles involve the use of genetic testing (1).

Although the mechanics of the biopsy technique essentially remain the same, the timing of the biopsy and the type of subsequent genetic testing have changed in a very short amount of time. In fact, the technology for determining genetic anomalies has outpaced our clinical understanding of the long-term sequelae of the results. Originally, once the developing embryo reached cleavage-stage, biopsies were taken, and 1 or 2 cells were used for further testing. This technique has been shown to result in a direct insult to the developing embryo that is associated with a decreased implantation rate, ongoing pregnancy rate, and hence live birth rate (2). Like the cleavage-stage biopsy, blastocyst biopsy involves removal of cells from the developing embryo. Unlike cleavage-stage biopsy, the cells removed are not from the fetal cell lineages, but rather from the trophectoderm that later forms the placental tissue. So, although more cells are generally taken, these represent a significantly smaller proportional of the total cell mass of the embryo, and hence should be less likely to impact embryo viability.

Unfortunately, there have been very few studies that have looked at the obstetrical and neonatal outcomes of pregnancies derived from blastocysts that were biopsied for PGT. In this issue of *Fertility and Sterility*, He et al. (3) describe the results from the largest single center study to date looking at the neonatal outcomes of frozen embryo transfer after blastocyst biopsy when compared to frozen embryo transfer alone. This is a large cohort study with a very large sample size that was able to compare directly singleton births to singleton births and twin births to twin births. Previously demonstrated by Forman et al. (4) in their prospective randomized trial of single embryo transfer following blastocyst biopsy versus dual embryo transfer without biopsy, there were no untoward effects of the biopsy itself on the outcomes. The results of the BEST trial conclusively demonstrated the benefits of single embryo transfer following PGT in reducing neonatal complications, but the comparison of twin gestations to singleton gestations made the findings difficult to interpret in relation to the effects of the trophectoderm biopsy itself. In contrast, this study directly compared 888 neonates from the biopsy and PGT group to 833 neonates resulting from in vitro fertilization/intracytoplasmic sperm inject alone. Unlike the BEST trial where most of the pregnancies resulted from fresh transfers, all the pregnancies were the result of frozen embryo transfers. This is an important difference because the national trend in the U.S. has been steadily increasing numbers of freeze all embryo cycles, likely related to increased use of PGT (1).

For singleton pregnancies, consistent with numerous other reports, there was a gender bias for male versus female children in both groups. However, no effect of the trophectoderm biopsy was able to be demonstrated on any other variable in terms of neonatal outcomes or pregnancy complications. This is very reassuring that at least in this study, there are no harmful side effects in the short term that can be linked to trophectoderm biopsy. When comparing the twin pregnancies in each group to each other, very similar gender proportions were in the singleton groups. One significant finding, and the only one for this part of the study, was the increased risk for cesarean delivery (adjusted odds ratio 2.38 [1.08, 5.26]) in the PGT group, although all other neonatal and pregnancy parameters were essentially the same. The overall cesarean rates are extremely high in China, where the study took place, so this data may not be applicable to other populations outside of the study population and there was no identifiable physiological explanation for the difference seen between the groups.

A subgroup analysis was performed that also demonstrated strong evidence regarding the effects of biopsy size on neonatal outcomes. For the 150 singletons included in the subgroup analysis (where the total number of cells biopsied was known), almost no parameters were seen to be affected when less than 10 cells biopsied were compared to more than 10 cells biopsied. Previous studies from these investigators and others (5), have looked at the effects of trophectoderm biopsy size, along with embryo grade, and found that implantation potential is diminished for lower grade trophectoderms that have had a greater number of cells taken for analysis. However, there were no differences in the miscarriage rates. Now we can see that if the pregnancy implants, there is no harm to the growing fetus or increased risk during the pregnancy. Oddly, the one exception for increased risk was macrosomia in the poorer quality trophectoderm embryos that had the higher number of cells biopsied. Given the sample size, the significance of this finding is questionable, but may be worth investigating in future studies.

In summary, at this point the data is pointing towards the short-term safety of trophectoderm biopsies in terms of neonatal and pregnancy outcomes. However, there is a dearth of information regarding the long term sequalae and a large multinational/multicenter longitudinal study is warranted. With the rates of PGT rising almost exponentially, and the number of IVF cycles rising at a steadily increasing pace, it seems that this should be one of our priorities in this field.

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https://doi.org/10.1016/j.fertnstert.2019.04.009

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