Reassuring data concerning follow-up data of children born after preimplantation genetic diagnosis

Preimplantation genetic diagnosis (PGD) was initially developed to prevent the risk of transmitting genetic diseases to the offspring of the carrier or affected couples. Later, the same procedure was also applied as preimplantation genetic testing for aneuploidies (PGT-A), with the aim of avoiding the transfer of abnormal embryos. The subsequent spread of PGD/PGT-A technology in infertility centers worldwide generated an intense scientific debate about its safety. Children born after assisted reproductive technology (ART), in fact, have been reported to be at higher risk of adverse perinatal outcomes compared with those conceived naturally (1–3). It has been postulated that patient characteristics, such as subfertility and advanced maternal age, as well as clinical and biological procedures, especially hormonal administration, micromanipulation, and cryopreservation, could be responsible for such increased risk (1–3). A main concern involves the potential impact of embryo biopsy, an invasive procedure that can be performed on day 3 of culture at cleavage stage or on day 5, 6, or 7 of culture at blastocyst stage. In the first case only one, or rarely two, blastomeres are removed. In the blastocyst biopsy, few trophectoderm (TE) cells are extracted. It has been postulated that TE biopsy, removing a higher number of extra-embryonic cells, could allow a more accurate diagnosis with less impact on embryo development compared with blastomere biopsy. On the other hand, when performing cleavage-stage biopsy, there is enough time to obtain the genetic result, making a fresh transfer possible. When biopsy is carried out at the blastocyst stage cryopreservation becomes necessary, and ET has to be delayed until a subsequent cycle. However, extended culture per se has been associated with increased risk of adverse perinatal outcomes (4). Both strategies are largely applied worldwide, although the use of TE biopsy has recently been growing.

An important analysis performed on 88,010 singleton live births obtained after PGD or IVF/intracytoplasmic sperm injection (ICSI) cycles reported that there was no increased risk of preterm birth or low birth weight when PGD is performed, even after adjustment for confounding factors such as female age, period of treatment, infertility diagnosis, number of previous attempts, number of retrieved oocytes, insemination method, and day of ET, demonstrating the safety of embryo biopsy (1). This study, however, reports only data concerning fresh transfer cycles, without taking into account frozen embryo transfers. Moreover, information on the embryo's stage at biopsy is missing (1).

In this issue of *Fertility and Sterility*, Heijligers et al. (5) compared the health and the growth of 5-year-old children born after PGD with same-aged children born after ART (by means of IVF/ICSI) and after natural conception (NC) in families with a genetic disease. The authors measured the height, weight, body circumferences, body mass index, and blood pressure and performed dysmorphologic and neuronal examinations, focusing on the presence of major and minor congenital abnormalities in 103, 90, and 58 children in the PGD, IVF/ICSI, and NC groups, respectively. There were no differences in mean height, weight, and body mass index among the three groups. Analogously, the frequency of acute and chronic sickness was comparable in all groups. Similar major congenital abnormality rates were observed: 5.8% (six children), 4.4% (four children), and 8.6% (5 children) in the PGD, IVF/ICSI, and NC groups, respectively. No correlation between major and minor congenital abnormalities was reported. Finally, analyzing the motor abilities, only the mean sitting age was slightly anticipated in the IVF/ICSI group, whereas the mean walking and speaking ages were comparable among all groups. Summarizing, children born after PGD showed similar growth, health, and motor development compared with children born after IVF/ICSI and NC in families with genetic diseases, having no increased health risk, at least in their first 5 years of life.

Limitations of this work could be found in the population groups. First, the sample sizes are different, with the NC group showing the lowest number of children enrolled. This could have introduced a bias in the outcomes, as recognized by the authors themselves. In addition, a little heterogeneity in the baseline characteristics of the parents was found. The PGD group had the youngest parents and fathers with the highest body mass index, whereas in the IVF/ICSI had the highest number of smoking mothers. Finally, it is important to emphasize that the authors did not study the risk of cardiometabolic diseases that have been reported to be a risk factor in IVF offspring (2).

Longer-term development outcomes have been analyzed by Kuiper et al. (2) in a double-blind, randomized trial enrolling 99 9-year-old children born after IVF, with or without PGT-A. The authors found no differences in neurologic, cognitive, and behavioral development or in blood pressure or anthropometric measures when PGT-A was performed. However, the incidence of adverse neurologic outcomes in children born after ART was higher compared with the general population.

The strength of the study by Heijligers et al. (5) lies in the introduction of two control groups, which makes it possible to compare the hypothetical consequences of PGD not only with those related to the use of ART without embryo biopsy but also with those observed in families with genetic disorders.

Recently, a very innovative study (3) compared the birth outcomes of 2,776 children conceived thanks to infertility treatments with those born in the general population, finding lower birth weights and increased risk of preterm delivery in the former. Interestingly, when a deeper intrafamily analysis was performed, in which 1,245 ART children were compared with their naturally conceived siblings, the authors reported that the above-mentioned differences were weak, concluding

that the increased perinatal risks are due to intrinsic parental factors and the infertility condition rather than to the medical treatment itself (3).

A recent systematic review and meta-analysis aimed to compare the neonatal outcomes obtained with a blastocyst- vs. a cleavage-stage ET (4). In addition to the cumulative result, three subgroup analyses evaluating fresh only, frozen only, and combined fresh/frozen embryo transfer cycles were performed. The authors found a higher risk of preterm birth after fresh blastocyst-stage compared with fresh cleavage-stage transfers. However, in the frozen and fresh/frozen groups this difference disappeared. Conversely, less small-for-gestational-age and more large-for-gestational-age were found with blastocyst transfer only for fresh and frozen cycles, respectively. No differences were found for small-for-gestational-age and large-for-gestational-age among blastocyst- and cleavage-stage transfers in the other subgroups. Finally, no differences were found in perinatal mortality and incidence of congenital anomalies among groups, although very few studies enrolled in the meta-analysis analyzed these outcomes. The authors speculate that cryopreservation could somehow reduce the adverse effect of extended culture on neonatal outcomes, thanks to better embryo–endometrium synchronization and avoidance of supraphysiologic hormonal conditions. In any event, it is important to emphasize that in this review 14 heterogeneous studies, all retrospective, were included with a low level of evidence (4).

The article by Heijligers et al. (5) refers to blastomere biopsy carried out on day 3 with a fresh embryo transfer on day 4 of culture. Analogously, all biopsies in the study by Kuiper et al. (2) were performed at cleavage stage, although it is not specified whether fresh or cryopreserved embryo transfers were performed. In the work by Goisis et al. (3) data were obtained from Finnish registers, and the authors had no access to information concerning the specific procedures applied, making it impossible to further investigate the effect of embryo micromanipulations and the consequences of fresh or frozen embryo transfers.

In conclusion, the study by Heijligers et al. (5) provides reassuring data on the safety of PGD for two main reasons. First, a double control was introduced to compare the development and growth of children born after PGD in a population of ART patients and in one group of naturally conceiving fertile couples with a history of familiar genetic disorder. Second, data collection was extended for 5 years after the children were born, without limiting it to the perinatal period. In families at risk of transmitting a genetic disease to their offspring, PGD could be the only way to avoid the transfer of affected embryos. These findings, showing that PGD seems not to be associated with an increased risk of adverse outcome, can support both patients and professionals regarding the safety of PGD. The present study, however, refers to cleavage-stage biopsy with fresh embryo transfer. It should be advantageous to confirm these outcomes even when TE biopsy with delayed cryopreserved embryo replacement is carried out, because this is becoming the most applied method in PGD cycles. Finally, it should be very interesting to follow the children enrolled in the analysis further, ideally until they reach adulthood.

Ermanno Greco, M.D.
Alessia Greco, Ph.D.
Maria Giulia Minasi, M.Sc.
Centre for Reproductive Medicine, European Hospital, Rome, Italy

https://doi.org/10.1016/j.fertnstert.2019.02.017

REFERENCES

1. Sunkara SK, Antonisamy B, Selliah HY, Kamath MS. Pre-term birth and low birth weight following preimplantation genetic diagnosis: analysis of 88 010 singleton live births following PGD and IVF cycles. Hum Reprod 2017; 32:432–8.
2. Kuiper D, Bennema A, la Bastide-van Gemert S, Seggers J, Schendelaar P, Mastenbroek S, et al. Developmental outcome of 9-year-old children born after PGS: follow-up of a randomized trial. Hum Reprod 2018;33:147–55.
3. Goisis A, Remes H, Martikainen P, Klemetti R, Myrskylä M. Medically assisted reproduction and birth outcomes: a within-family analysis using Finnish population registers. Lancet. 2019;393:1225–32.
4. Alviggi C, Conforti A, Carbone IF, Borrelli R, de Placido G, Guerriero S. Influence of cryopreservation on perinatal outcome after blastocyst- vs cleavage-stage embryo transfer: systematic review and meta-analysis. Ultrasound Obstet Gynecol 2018;51:54–63.
5. Heijligers M, Peeters A, van Montfoort A, Nijsten J, Janssen E, Gunnewiek FK, et al. Growth, health and motor development of 5-year-old children born after preimplantation genetic diagnosis. Fertil Steril 2019;111:1151–8.