

# The health and development of children born after preimplantation genetic diagnosis

Citation for published version (APA):

Heijligers, M. (2021). *The health and development of children born after preimplantation genetic diagnosis*. [Doctoral Thesis, Maastricht University]. Maastricht University. <https://doi.org/10.26481/dis.20210421mh>

## Document status and date:

Published: 01/01/2021

## DOI:

[10.26481/dis.20210421mh](https://doi.org/10.26481/dis.20210421mh)

## Document Version:

Publisher's PDF, also known as Version of record

## Please check the document version of this publication:

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## Valorization

This thesis focuses on the safety of preimplantation genetic diagnosis (PGD), more precisely on the growth, health and development of children born after PGD. The societal value of the results of this thesis is described in this paragraph.

The World Health Organization defines 'patient safety' as *"The absence of preventable harm to a patient during the process of healthcare and reduction of risk of unnecessary harm associated with healthcare to an acceptable minimum. An acceptable minimum refers to the collective notions of given current knowledge, resource available and the context in which care was delivered weighed against the risk of non-treatment or other treatment"*.<sup>1</sup>

PGD is a complex and morally sensitive technology that involves biopsy, analysis and selection of human embryos, as well as the application of in-vitro fertilization (which is considered to be an invasive treatment) in fertile women with or without a genetic disorder themselves. It is therefore, that both government and society may have concerns about the safety of this procedure. The Dutch government is involved in the legislation of PGD and decided that only one Dutch center is licensed to coordinate the activities regarding PGD healthcare in the Netherlands, which is the Maastricht University Medical Center+ (MUMC+). Legal and ethical boundaries for performing PGD are formulated in the 'Embryowet' and PGD guidelines were published in 2009 in the Staatscourant.<sup>2</sup> Part of these guidelines is the obligation to provide annual reports on the PGD cycles performed in the Netherlands. Drawing up such annual report is also advised by the European Society of Human Reproduction and Embryology (ESHRE) PGD consortium.<sup>3</sup> Up until this thesis, the Dutch data regarding pregnancies and children born following PGD had not been evaluated thoroughly and/or compared to international data. In **chapter 2 and 3** of this thesis we aimed to evaluate these data and gathered additional data in order to assess the short term safety of PGD with regard to the risk of adverse obstetric and perinatal outcome. Additionally, the long term safety of PGD is discussed in **chapter 4 and 5** in which the growth, health and development of 5-year-old children born after PGD is evaluated. Thereby, the majority of the couples whom may consider PGD has no fertility problem and could conceive naturally. Especially for those, the knowledge about the safety of PGD for both mother and child may contribute to their reproductive choice. It is therefore that we

compared our data to data of pregnancies and children born after natural conception in families with a genetic disorder, since trying to conceive spontaneously might be a realistic alternative for the couples opting for PGD. Data on the health of children born after PGD are scarce and not easily accessible for couples who consider PGD. Earlier studies on the health of newborns and children born following PGD are mostly published in scientific journals and written in scientific language which may be difficult to read for non-medics. Thereby, most of these studies focus on preimplantation genetic screening which is offered to couples with subfertility instead of to couples with a high chance of conceiving a child with a genetic disorder.

In the last couple of years, the number of referrals for PGD has increased tremendously.<sup>4</sup> More couples apply for PGD. Also more hereditary disorders for which PGD can be offered can be diagnosed. The increasing number of diagnoses in patients in whom a genetic disorder is suspected is due to the improvement of genetic diagnostic techniques. This consequently leads to the ascertainment of more couples with an increased risk of conceiving a child with a genetic disorder. The introduction and growing application of preconception carrier tests is another way of identifying couples at risk for transmitting a genetic disorder to their offspring. A wider application of a delicate medical treatment such as PGD, that is administered with the involvement of the government, should be carefully evaluated. Not only the current study is part of this evaluation, but also other research projects on for instance the decision-making process regarding PGD and the implementation of the PGD National Indications Committee.

As with each medical treatment it is important that guidelines are followed. Additionally, the actual outcome should be in line with the expected outcome. In case of PGD, the expected outcome is the birth of a healthy child, more specifically of a child without the familial genetic disorder for which PGD was performed. The primary aim of PGD is to prevent the birth of a child without such genetic disorder and to soften personal harm for parents and families. As a side effect PGD may lead to a decline in healthcare costs since the diseases for which PGD is performed are, without exception, severe and sometimes even lethal at a young age. PGD, on itself, is however also a costly medical procedure. It is therefore important to evaluate whether the use of PGD introduces (new) health hazards in the forthcoming pregnancy and offspring. The evaluation of such adverse effects is also of economic

relevance since these could outweigh the saved costs on a child with a genetic disorder.

Besides economic relevance, there are also psychological aspects which are important to acknowledge when evaluating the application of PGD. PGD makes it possible to select embryos without a certain genetic disorder before an actual pregnancy is established. Only unaffected embryos will be transferred into the uterus. Invasive prenatal diagnosis is an alternative procedure to test whether a specific genetic disorder is transmitted to the offspring and to prevent the birth of affected children. Contrary to PGD, the latter is offered during pregnancy, mostly between a pregnancy duration of 10 and 15 weeks gestational age. If the fetus is affected with the familial genetic disorder, the couple can choose to terminate the pregnancy. Procedures for terminating a pregnancy are a medical abortion with use of medication and vacuum or suction aspiration. Such procedures can have large psychological impact on the couple, especially when performed in several consecutive pregnancies. The psychological impact of the PGD procedure, on the other hand, should also not be underestimated since it can take several years from the application for PGD to the birth of a live born child. Also the necessity of a medical treatment like IVF may have psychological impact.

The preference for either PGD or invasive prenatal testing is a very personal one which may change over time or may be influenced by certain (personal) events or religious background. For instance, as already mentioned, preconception carrier testing is increasingly applied. Such test is mostly offered to consanguineous couples because these have a higher risk for carrying the same autosomal recessive disorder than non-consanguineous couples. Consanguinity is more common in the Middle East, West Asia and North Africa. In some of these populations, a pregnancy termination is due to religious grounds not an option, whereas PGD, on the other hand, may be allowed.

The limited scientific information available on the safety of PGD also makes it difficult for healthcare providers and other professionals, for instance teachers, to judge whether the women pregnant following PGD and the children born following PGD need extra surveillance. The results in this thesis (**chapter 2 and 3**) may contribute to the formation of (inter)national guidelines regarding the surveillance of women who

are pregnant following Assisted Reproductive Technology (ART), in particular following PGD. Whereas the second part of this thesis (**chapter 4 and 5**) may be of importance in youth health care as well as for teachers of children born after PGD. The latter part focuses on the growth, health and development of 5-year-old children born following PGD. Evaluation of the growth and development of children is part of the national screening program. The executing youth health care physicians may not see many children born after PGD and thus lack knowledge about the safety of such procedure and possible effect on the growth and health of the children. Teachers may have never heard of PGD, and parents can be in doubt whether they want to inform the children's teachers about the PGD procedure. Plain and easily accessible information about PGD and the results of this thesis is thus desirable. We provided such information by means of a newsletter to all parents of the children who participated in the study with five-year-old children. Additionally, results of the study have been published in summary and plain language on the website of PGD the Netherlands. Stake holders and Dutch clinical geneticist whom counsel couples about PGD have been informed about the first results during a special organized stake holders day.

This thesis is the start of a broader follow-up program for children born after PGD. This program includes the study of 8-year-old children born after PGD, whom are compared to IVF/ICSI children and naturally conceived children of the same age. These 8-year-old children were the same children as included in the study of 5-year-olds. Examining the children at an older age contributes to the knowledge about long-term safety of PGD. Additionally, collection of complementary data on body composition, blood pressure and vascular dysfunction is part of the program in order to collect information about cardiometabolic outcome in the three groups of children. This information is of importance for the future health of the children since it gives information about cardiovascular morbidity and mortality risks later in life.

In summary, the evaluation of the safety of PGD is not only an important scientific and/or medical topic, but is also socially and economically relevant. Techniques and procedures necessary for PGD are, however, quickly developing over time, due to which the results of this thesis may become less valuable in the nearby future. The applied study methods and procedures can, though, be a blueprint for future follow-up studies on the safety of PGD.

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