Chapter 27
Preimplantation Genetic Screening for the Single Embryo: Aims and Responsibilities

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Introduction

Screening embryos to enhance the success rate of IVF is not new at all. Almost from the start, a check of the number of pronuclei in order to exclude haploid or triploid embryos was routine during IVF. Such embryos cannot result in a viable baby. Secondly, under the assumption that the morphologically best embryo has the best chance to survive and to yield a viable pregnancy, embryologists have always microscopically assessed embryos before transfer. However, some embryos which appear to demonstrate poor morphology under the microscope have been reported to develop into healthy children. On the other hand, the morphologically best embryo can still carry serious (and sometimes lethal) chromosomal abnormalities, meaning that there is still a level of uncertainty involved.

About 15 years ago, preimplantation genetic screening (PGS) for chromosomal aneuploidies was proposed as an add-on technology to IVF+ICSI, as almost all aneuploid embryos will give rise to implantation failure or pregnancy loss. PGS for

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aneuploidy can also be applied in the context of preimplantation genetic diagnosis (PGD), where patients are mostly fertile, but undergo IVF and PGD because they are at risk of transferring a severe genetic condition to their offspring. This approach also can be beneficial where patients carry a chromosomal translocation, which would make it hard for them to conceive or which would put them at risk of having severely handicapped offspring. Adding PGS to PGD entails combining the selection aimed at choosing an embryo without a specific condition for which PGD is performed, with the aim of selecting a single embryo that is most likely to develop into a successful pregnancy.

In this chapter, we will first briefly summarize the state of the debate about PGS for aneuploidies and highlight its ethical dimensions. Secondly, we will address the fact that PGS may serve different aims that require independent justification. As we will show, while these aims may overlap, they can also conflict, thus challenging the ethical basis for responsible embryo transfer decisions in IVF.

PGS for Aneuploidy

PGS and PGD make use of the same biopsy methods to obtain the cellular material for molecular analysis. At the time, when this screening was first proposed, this meant that one or two cells were taken from the 3-day-old embryo and analyzed using fluorescent in situ hybridization (FISH). Aneuploid embryos are neither transferred in utero nor cryopreserved, and they are also not donated to others for clinical use—they are discarded. A major challenge of PGS is that day 3 embryos are often mosaic and that cells taken from the embryo may not be representative of the entire embryo. An individual cell that is diagnosed as aneuploid may be the only abnormal constituent cell in the eight cell embryo, and the embryo may be able to overcome this abnormality and develop normally. There is also some evidence that IVF embryos are more prone to mosaicism [1–3]. Since FISH allows for the screening of a limited number of chromosomes, quite a few aneuploidies will slip through the net. A meta-analysis has shown that PGS using FISH to screen embryos biopsied at day 3 does not increase but actually *decreases* pregnancy rates [4]. This has led to position statements from international professional bodies stressing that PGS is experimental and should not be routinely offered to IVF patients [5]. Recently, it has been shown that biopsy at the cleavage stage might be responsible for this, since the process is invasive and appears to reduce implantation rate by about 4 % [6]. Therefore, alternative biopsy methods, such as polar body screening of the oocyte or screening of cells obtained from the trophectoderm (biopsy of the embryo at day 5), have since been developed [5, 7–11]. The drawback of polar body screening is that it only allows for the checking of *maternal* meiotic aneuploidies and will not identify paternal or postzygotic mitotic error. With the techniques of polar body and trophectoderm screening, some of the concerns regarding mosaicism may perhaps be lifted. For example, polar body biopsy occurs at a developmental stage when there is not yet any cell division, and the polar body is deemed to be representative of the maternal contribution to the future embryo. With trophectoderm PGS, more

cells are available for analysis, yielding a more representative sample. However, some embryos that may not make it to day 5 in vitro are viable when transferred at day 3, so potentially viable embryos are lost during the extended culture period required to obtain blastocysts. New freezing techniques such as vitrification may overcome the limited time frame for genetic testing.

A further development is that many new methods for analysis, such as Array-Comparative Genomic Hybridization (Array-CGH), genome-wide SNP analysis, qPCR-based detection, and next-generation sequencing (NGS), enable comprehensive screening of all chromosomes in a cell, hence giving a more complete picture of its status [12–18]. Although some believe that the introduction of these new biopsy and analysis methods in combination with vitrification will eventually be vindicated as a worthwhile addition to IVF and IVF/PGD, the technology is still highly contested [19, 20]. Taking into account the possibility to freeze all embryos for subsequent use, it has been pointed out that the benefit of PGS is to be sought in a shorter "time to pregnancy." Additional benefits are the reduced rate of failed implantation and spontaneous abortions, the psychological burden of which should not be underestimated [21]. Whether these benefits are important enough to make adding PGS for aneuploidy proportional depends on how much time pressure the patient is under, on the balance of the costs of PGS and related procedures on the one hand and the savings that may result from better "time to pregnancy" on the other. Moreover, in the context of IVF only, this gain would need to outweigh any possible adverse effects of the embryo biopsy and extended in vitro culture [22, 23]. If effective, it may be that PGS is proportionally beneficial only for certain subgroups such as patients with repeated implantation failure or for women of advanced maternal age. Furthermore, the screening of polar bodies or embryos might help to identify those patients who are likely to have abnormal embryos only [8]. Clearly, as long as it is not sufficiently established that PGS for aneuploidy does indeed work, the tendency to offer PGS as a routine component of fertility treatment defies the still valid position statements of ASRM and ESHRE is ethically problematic. Offering routine PGS may lead to disadvantaging patients undergoing fertility treatment by raising the cost of treatment for no good reason or even by effectively reducing their chances of having a child through IVF.

The Widening Aims of PGS

PGS traditionally refers to aneuploidy screening as a means to increase the chances of a successful pregnancy after IVF or IVF/PGD. As indicated, this should be qualified as improving the chances of having a successful pregnancy earlier rather than later. If done in the context of IVF, this aligns with the aim for which IVF is offered in the first place. If done in the context of IVF/PGD, things are more complex, at least when patients are fertile and opt for PGD not so much in order to have child but to have a child without the condition that they are at risk to transmit. However, if adding PGS means accelerating the time to a healthy (unaffected) pregnancy, then this can also be seen as serving the original aim of the treatment.

But already with PGS for aneuploidies, the aim may widen beyond the success of IVF or IVF/PGD treatment to also include avoiding the birth of a child with a chromosomal abnormality (unrelated to a possible PGD indication). Whereas most aneuploidies are lethal, some of them may lead to a viable pregnancy. Examples here are trisomy 13, trisomy 18, trisomy 21, and the sex chromosome aneuploidies. Although the chances that such embryos develop into a viable pregnancy vary from extremely low to decreased, there remains a possibility that transfer will result in a live birth. So when PGS leads to discarding embryos thought to be aneuploid, this may serve the overlapping aims of enhancing treatment success by improving time to pregnancy and avoiding the birth of a child with a handicap related to aneuploidy [24]. Of course, whether these objectives can be achieved depends on whether and to what extent PGS can overcome the problem of mosaicism, which is still a contested issue.

With the increasing resolution of microarray technology, the scope for testing embryos for conditions relevant to the health prospects of the future child will only enlarge. For instance, submicroscopic chromosomal abnormalities, including larger copy number variations (CNVs), are associated with an increased risk for conditions such as mental disabilities or autism, although as of yet, the relation between the abnormality and the condition seems one of susceptibility rather than causality. SNP arrays enable the detection of (a subset of) potentially disease-causing mutations at the DNA level, in addition to chromosome abnormalities.

With the advent of next-generation sequencing and single-cell whole genome sequencing, even more information about the genome of the embryo is expected to become available in the future. One might think here of PGS to test for a panel of genetic mutations that include the most common severe congenital disorders or for all genetic conditions that are accepted indications for PGD. Not transferring embryos carrying such mutations would help contribute to healthy offspring after IVF with PGD. Another idea is that health profiles of embryos could be established to determine transfer eligibility ranking. This would also include susceptibility genes or carrier status and may be appealing to clinicians and prospective parents alike. Whether this will indeed become feasible is still very much an open question. Recent research has suggested that these ideas about possible broad scope PGS may be naïve or at least premature. Indeed, some healthy adults have genetic mutations that are annotated as severe and disease causing and that if detected in an embryo would lead to negative transfer decisions. Several factors may explain this. Current tests may not be sufficiently sensitive, or the information in genetic databases may be incorrect. However, it may also be that our knowledge of epigenetics and protective genes remains rudimentary and that a simple extrapolation from genotype to phenotype is at least for the time being not fully feasible [25]. If this is the case, then the same goes for broad scope PGS to avoid health problems or select embryos with the best health profile.

Notwithstanding the feasibility of broad scope genomic embryo screening, it is important to note that PGS may serve two aims that are ethically quite different: treatment success and healthy children. Given the widely endorsed acceptability of IVF and IVF/PGD, and assuming for the sake of debate, cost-effectiveness of PGS for aneuploidies, the first aim (treatment success) is unproblematic from an ethical point

of view. However, things are less clear with regard to PGS to yield healthy offspring. Some would argue that also the justification of this second aim is already implied for that of IVF treatment, as all women or couples would rather have a healthy than an unhealthy child. This would even be more evidently the case in IVF/PGD treatment, which is already done to avoid the birth of a child with health problems. However, this is too simple, given that couples may prefer a child with certain health problems over having no (genetically own) child at all. The difficulty is that, when it comes to transfer decisions, the two aims of (a) successful treatment and (b) a healthy child do not always coincide and compromise may be necessary. This is clearly the case in the scenario of broad scope PGS, where testing would also include all kinds of genetic factors that are independent of the chances of a successful pregnancy.

Because only a limited number of embryos are typically available for transfer, testing for health may in fact lead to lowering the chances of a successful pregnancy. But the need for making trade-offs already emerges with the more limited scenario of PGS for aneuploidies only, given that some milder aneuploidies are only weakly related with lower chances of a successful pregnancy. From an ethical point of view, this is important because, given the different nature of the two aims, the question arises which trade-offs this should be and by whom.

Reproductive Autonomy and Professional Responsibility

In the context of prenatal screening and prenatal diagnosis, the overriding principle is that of reproductive autonomy of the pregnant woman. Because abortion decisions should remain personal, genetic counseling in this context should be nondirective. One might think that the same ethical framework with its emphasis on reproductive autonomy and nondirectiveness would then also apply to the context of assisted reproduction in general and "embryo selection" in particular. But things are more complex than that.

Of course, as long as PGS for aneuploidy is a costly accessory to IVF, couples should be free to make an informed decision not to have PGS. And clearly, as long as PGS for aneuploidy is experimental, no one should be offered this test without being made aware of its contested status. However, assuming that PGS for aneuploidy works and the couple has consented to this extra test, whenever this leads to transfer choices clearly relevant to improving treatment success, it can be argued that these are medical decisions that as such belong to the remit and responsibility of the IVF team. This would be very much the same as with regard to triploidy and morphology testing, which is also done in view of selecting out embryos that are nonviable or have lower chances of successful development. As there is no reason for discussing transfer policy based on the outcomes of those tests with the applicants, neither would there be a need to do so with outcomes of PGS aimed at improving treatment success.

There can be no debate about this when conditions are revealed that render the embryo nonviable or that would at best lead to a child facing early death from a

lethal condition like trisomy 13 or 18. In the latter cases, the two aims of PGS can be said to overlap and point in the same direction, given the low chances of a live birth and the severe health problems and short life span these children have. This means that if embryos with trisomies 13 or 18 are the only ones available, then transferring them would still be unacceptable. But what about an embryo with a sex chromosome aneuploidy? Embryos with 45,X are almost invariably lost during pregnancy. On the other hand, there does not appear to be selective loss of either 47,XYY and 47,XXX fetuses in spontaneous abortions, and about 50 % of all 47,XXY conceptions seem to be lost during early gestation. This is surprising in view of the usual lack of any severe anomalies among XXY live births [26, 27]. These Klinefelter males and their parents may be unaware of the extra chromosome until after puberty when infertility problems become manifest. The question is whether the existence of the extra X-chromosome is a sufficient reason to discard such an embryo, even when it is the only single embryo available for transfer and therefore may represent the couples' last chance of having a child that is genetically their own. Should priority be given to treatment success or to avoiding the birth of a child with (mild) health problems? And indeed whose decision should this be?

The second aim (healthy child) obtains a separate status when PGS is broadened to include conditions that may affect the future child's health, but are unrelated, or only weakly related, to treatment success. Here the question is, why to offer this wider testing in the first place? Is this to allow the intended parents to make autonomous reproductive decisions? Against the view that reproductive autonomy should be the guiding principle with regard to choosing between possible children [28], some have argued that, if doing so is reasonably possible in the circumstances, reproducers have a responsibility to choose the child whose life is expected to go best (reproductive beneficence) [29] or to make a decision that would not negatively affect others or society [30]. Following this line of reasoning, intended parents who make use of IVF/PGD may, under conditions of proportionality, have a responsibility to accept an offer of broad scope PGS and act upon its findings. Of course this would also depend on whether such testing leads to accurate predictions of the future child's phenotype, something that, as we have seen, is not always obvious.

But apart from whether reproducers do indeed have this responsibility to choose the best possible child or to make reproductive choices that avoid harm to others, the main reason why the idea of PGS to facilitate autonomous reproductive decisions cannot unconditionally be maintained is that it is at odds with acknowledging the co-responsibility that fertility professionals have for the welfare of the children in whose conception they are actively and causally involved. In comparison to the context of prenatal screening, this entails a shift of decision-making authority, requiring professionals to take their own responsibility rather than nondirectively accepting whatever decisions are made by prospective parents [31]. This is why fertility professionals may, for instance, refuse requests for assistance by applicants with a history of child abuse or otherwise lacking basic parental capacities. Debates about this issue have centered on the definition of the standard to be used for determining when professionals can be expected to refrain from collaborating with the reproductive project of the applicants [32]. The standard defended by the European

Society of Human Reproduction (ESHRE) is that professionals should refuse treatment if there is a high risk that the child will have a seriously diminished quality of life [33]. Clearly this is not a sufficient reason for making PGS a coercive offer for those wanting to have IVF or IVF/PGD. However, it does mean that if PGS outcomes allow transfer choices that are relevant for the health prospects of the future child, professionals should not go ahead with parental transfer requests that would entail "a high risk of serious harm." Of course, the application of this criterion to concrete cases may be a matter of debate, except for very serious or only mild conditions at both ends of the spectrum.

For example, on the basis of this criterion, it is obvious why transferring a trisomy 13 or 18 embryo should be out of the question even apart from considerations about treatment success, whereas on the other hand, there would not seem to be sufficient reason for rejecting a parental demand for transferring an embryo with a 47,XXY karyotype (Klinefelter syndrome) [31].

A more difficult case concerns trisomy 21 (Down's syndrome). Clearly, if PGS for aneuploidy works, there are good reasons based on the aim "treatment success" for preferentially not selecting any trisomy 21 embryos, because their viability is substantially restricted. But what if the only embryo left is a trisomy 21 embryo, and the intended parents ask for transfer of that single embryo, insisting that they would also be happy with a Down's syndrome child? Would proceeding with this request amount to a violation of the "high risk of serious harm" criterion? If so, then professionals should insist that no trisomy 21 embryos are to be transferred, even if they represent the couples' last chance of a (genetically related) child. For this position, one may refer to the often high comorbidity and related health needs of Down's syndrome children. Some would argue that also the high societal costs of caring for children with Down's syndrome should be considered in this context. Conversely, others may argue that Down's syndrome is a variable condition, that many persons with this condition live happy and rewarding lives, and that allowing societal costs to enter the equation is a first step on the path toward a morally problematic form of eugenics [24]. Following this line of reasoning, it may be argued that there is no "high risk of serious harm" and that professionals should leave the decision to the (well informed) parents. Professionals who would go ahead with a parental request to transfer a trisomy 21 embryo (if no other options are left) cannot be said, then, to act irresponsibly. Obviously, it is important that an institution's policy in these matters is clearly communicated to patients as part of the pretreatment informed consent.

Conclusion

The introduction of PGS in the context of IVF and single embryo transfer raises many difficult questions. First and foremost, it is still not clear whether the new biopsy and analysis approaches will make PGS for aneuploidy more successful in terms of improving treatment outcomes—and if it does, which specific subgroups of IVF patients will benefit? Given the possibility of freezing and subsequently

transferring single embryos obtained from a given follicular recruitment cycle, this improvement, if PGS works, would result in improving time to pregnancy by reducing the number of frozen embryo transfers needed and avoiding the related burden of implantation failures and spontaneous abortions. As long as the value of PGS for treatment success has not been proven, the screening should only be offered in the context of research.

Whereas improving treatment outcomes is a justified aim for adding PGS to IVF or IVF/PGD, the wider aim of routine testing for a healthy child requires separate justification. If this decision is conducted in the setting of single embryo transfer, then it becomes a particularly high-stakes choice. Where both aims overlap and point in the same direction, the second aim so to speak rides along with the first. But where wider testing leads to findings unrelated or only weakly related to treatment success, the question arises why such a test should even be added to IVF or IVF/PGD in the first place. This might be argued in terms of either the reproductive autonomy or the reproductive responsibility of the prospective parents. We have not discussed whether the latter line of argument is convincing, but stressed that the appeal to reproductive autonomy is at odds with acknowledging that, in the context of assisted reproduction, this principle is limited by professional co-responsibility for the welfare of the child. Fertility professionals may reject requests for transfer that, on the basis of PGS outcomes, they consider have a high risk of leading to a child with a seriously diminished quality of life, even if the embryo represents the couples' last chance of having a (genetically related) child. However, it does not follow that a coercive offer of broad scope PGS to all IVF or IVF/PGD patients can be justified by appeal to this professional responsibility for the welfare of the child. After all, there is no "high risk of serious harm" involved in transferring unscreened embryos—while (even voluntary) broad scope embryo screening would raise many issues that should be resolved first, related to both the suboptimal quality of current single-cell whole genome tests and to the adequate protection of the interests of all parties involved, including future children's right not to know [31, 34, 35].

Conflict of Interest The authors declare no conflict of interest.

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