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OPINION

Avoiding transgenerational risks of mitochondrial DNA disorders: a morally acceptable reason for sex selection?

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ABSTRACT: In this article, we discuss sex selection not intended to help a couple avoid having a child with a severe genetic disorder, but to avoid possible health risks further along the line of generations. Sex selection may be put to this use in the context of preventing mitochondrial DNA disorders by means of preimplantation genetic diagnosis (PGD) and possibly in the future also through nuclear transfer (NT; also known as mitochondrial gene replacement). A relevant analogy can be found in the context of PGD for X-linked diseases, where sex selection against healthy female carrier embryos would have the same 2-fold purpose of (i) avoiding difficult reproductive decisions for the future child and (ii) avoiding transmission of the mutation to a possible third generation. Because sex selection would still be done for reasons of health, this application should not give rise to the moral concerns associated with sex selection for non-medical reasons. However, the proportionality of adding the relevant procedures to PGD or NT is a relevant concern. We discuss post- and preconceptional sex selection strategies. We conclude that if PGD is already part of the procedure, either as the central technology or as a back-up test after NT, preferentially transferring male embryos could in principle be a morally acceptable way of reducing possible burdens and risks. To start an IVF/PGD-cycle especially for this purpose would be disproportional. The alternative approach of preconceptional sex selection may be morally justified as a means to increase the chances of obtaining male embryos.

Key words: sex selection / mitochondrial DNA disorders / transgenerational effects / ethical considerations

Introduction

Whereas sex selection for non-medical uses is highly controversial, it is generally accepted for medical reasons (Health Council, 1995; ASRM, 1999; Pennings, 2002). This is usually defined as sex selection to avoid the birth of a child with a severe genetic disorder. Actually, preimplantation genetic diagnosis (PGD) was first introduced to select female embryos in the case of X-linked disorders (Handyside *et al.*, 1990). In this article, we discuss sex selection not intended to help a couple avoid having a child with a genetic disorder, but to avoid possible health risks further along the line of generations.

The reason for bringing up this issue is that sex selection may be a helpful additional measure in the context of preventing the transmission of mitochondrial DNA (mtDNA) disorders (Box 1). As there is no curative treatment, helping carriers to have healthy children has been a central focus of attention. New techniques to achieve this are PGD and possibly in the future nuclear transfer (NT), also known as mitochondrial gene replacement. When applying PGD for mtDNA disorders, it is conceivable that only affected embryos are available for transfer. In that case, PGD would only be undertaken as a 'risk-reducing' strategy (Bredenoord *et al.*, 2008a). Provided, however, that only embryos with a mutant load (far) below the threshold for disease expression are transferred, is it very likely that the child will be free of the relevant disease (Bredenoord *et al.*, 2009).

In case of NT, a donated oocyte is enucleated and replaced with the nuclear DNA from a woman carrying an mtDNA mutation. To obtain these oocytes, both the oocyte donor and the recipient woman are required to undergo hormone stimulation and oocyte retrieval. The nuclear transplantation could be performed before or after fertilization. In the first case, the nucleus of an (immature or mature) oocyte of the prospective mother is inserted into the donated oocyte. This reconstructed oocyte is then fertilized with the prospective father's sperm. In the latter case, NT would be performed after fertilization, using either the pronuclei of the zygote or the nucleus

Mitochondrial DNA disorders

MtDNA disorders are a group of disorders relating to the mitochondria, which are the 'powerhouses' of the cell. Defects of mitochondrial function are increasingly recognized as important causes of disease. The clinical phenotype of mtDNA diseases is extremely variable, affecting patients at any age and in a wide variety of tissues.

Mitochondrial disorders can be caused by a mutation in the nuclear DNA, by a mutation in the mtDNA and by an unknown genetic defect. Diseases due to mtDNA defects show some specific characteristics, which make it very challenging to estimate recurrence risks correctly and to predict whether a future child will be clinically affected.

First, many mutations are heteroplasmic. This means that there is a mixture of normal and mutant mtDNA, the level of which can differ among tissues. If the mutant load, i.e. the ratio of mutant to normal mtDNA, exceeds a specific threshold, clinical features become manifest. However, the exact threshold to disease expression is often not known. This makes it complex to predict on grounds of a (prenatal/preimplantation) test result whether the child is likely to develop disease symptoms.

Secondly, the mtDNA is maternally inherited. Extreme shifts in mutant load can be observed between mother and child and also siblings can have variable levels of mutant load (Munnich *et al*., 1996; Thorburn and Dahl, 2001; Taylor and Turnbull, 2005).

of a blastomere of the embryo (Roberts, 1999; Brown *et al*., 2006; Bredenoord *et al*., 2008b). The resulting embryo is subsequently transferred to the prospective mother's womb. Theoretically, this procedure should lead to a child without mutant mtDNA. Whether this can be completely achieved in practice, however, is not yet clear. Preclinical experiments have suggested that it may be difficult to avoid small amounts of affected mitochondria coming along with the oocyte the pronuclei or the nucleus of the recipient woman (Sato *et al*., 2005; Nakada *et al*., 2008). However, the recently published data from the first application of NT for this purpose in non-human primates were reassuring in this respect (Tachibana *et al*., 2009). In this study, it was shown that the procedure can be accomplished without significant mtDNA carryover from the prospective mother's oocyte (Tachibana *et al*., 2009). However, it remains to be seen whether a clinical application of NT would indeed result in a child free of mutant mtDNA. As the authors observe, a mutant load of 3% would be undetectable, meaning that heteroplasmy may still be present.

Earlier we defended the view that medically assisted reproduction is acceptable as long as there is no high risk of serious harm for the resulting child (de Wert, 1998; Pennings, 1999; Bredenoord *et al*., 2008a). From this perspective, both PGD and NT for mtDNA disorders could be morally acceptable as long as only embryos with a mutant load below the threshold to disease expression are transferred (Bredenoord *et al*., 2009). The fact that even under this condition there may still be residual health risks is not a morally compelling reason to refrain from PGD or NT for mtDNA disorders. After all, it is unlikely that the resulting child will be exposed to a high risk of serious harm.

However, an important remaining concern is the possibility of recurrence of mtDNA disease in the child's offspring (Tachibana *et al*., 2009). Due to the existence of a genetic bottleneck (Poulton and Marchington, 2002; Cree *et al*., 2008; Marchington *et al*., 2009), a low-level mutant load in the second generation (the child to be conceived through PGD or NT), may rise to higher levels in the third generation (the couple's grandchildren). In the light of this concern, there is an important difference between further reproduction by either male or female offspring. As mitochondria are transferred maternally, male offspring will not pass on their mutant DNA to the next generation. This leads to the question of whether the avoidance of transgenerational health risks provides a morally acceptable reason for sex selection.

The case for sex selection

The fact that a low mutant load in their child may increase in their possible grandchildren may well be a cause of concern for the prospective parents. They may argue that both the possible burden of difficult reproductive decisions for the second generation and the health risks for a possible third generation are important enough to be prevented if reasonably possible. For most mtDNA diseases, sex selection will not reduce the health risks for the second generation (these risks are the same in both sexes). However, it will allow second generation males and their partners to reproduce with confidence. After all, they will not be confronted with the same difficult decisions their parents had to face. As males do not transmit the mtDNA mutation, a possible third generation will not carry the mtDNA mutation. For the couple to avoid transmission of an mtDNA disease, this may be a reason for preferring a son.

Clearly, the reproductive burdens and possible health effects that adding sex selection to PGD or NT would help to avoid, are uncertain. It is neither self-evident that second generation females want to have children (although most women do), nor certain that the mutant load will indeed increase in their offspring. It is also true that these women will themselves have the option of using PGD or NT (or even better strategies available at that time) to avoid having an affected child, or that a cure or procedure to prevent or ameliorate mtDNA disease may have become available.

A helpful analogy can be found in the context of PGD for X-linked diseases (de Wert, 2005). Whereas all daughters of a male patient affected by an X-linked disease, for example haemophilia, will be obligate (healthy) carriers, all his sons will be unaffected non-carriers. Sex selection against healthy female carrier embryos would in such cases have the same 2-fold purpose of (i) avoiding difficult reproductive decisions for the child and (ii) avoiding transmission of the mutation to the third generation. Notwithstanding the uncertainty of these effects, it has been argued that sex selection for this double purpose would be acceptable in principle in such cases (de Wert, 2005). Can we draw the same conclusion with regard to sex selection in the context of PGD or NT for mtDMA disease? It may be objected that the analogy is incomplete. The predictability and severity of the transgenerational health effects to be avoided through sex selection are considerably more certain in the case of X-linked disorders than in the case of mtDNA disorders. Of course, it is equally uncertain

whether any daughter of a man with haemophilia will reproduce. But if she does, 50% of her sons will be haemophilia patients like their grandfather. In contrast, it is far more difficult to predict whether and to what extent a possible grandchild of a couple that used PGD or NT for mtDNA disease may be affected by a transgenerational rise in mutant load. We agree that the case for additional sex selection is indeed less obvious here than where PGD for X-linked disease is concerned. But also in this context, adding this step is still defendable in principle. After all, chances that a possible daughter will want to reproduce are high and any remaining uncertainties about the possibility of her having a seriously affected child may well lead to difficult reproductive decision-making.

Sliding towards non-medical sex selection?

Sex selection is generally accepted as a way of avoiding the transmission of serious sex-linked diseases, but regarded as morally problematic if requested for non-medical reasons, e.g. because the parents want a male heir to carry the name of the family. Moral objections refer to gender discrimination and undesirable demographic and social effects of large scale application (Health Council, 1995; ASRM, 2001; Pennings, 2002). Sex selection for the purpose discussed in this article differs from the traditional understanding of sex selection for medical reasons (which we will refer to as 'the medical model'), in that it is not aimed at avoiding health risks in the child to be conceived in the current procedure. To the extent that it is aimed at avoiding health risks, these will only materialize (if at all) in a possible third generation, whereas with regard to the child to be conceived the aim is to avoid psychosocial burdens of reproductive decision-making, not health risks in the strict sense. Although sex selection for these purposes would not fall within the bounds of the medical model, neither does it seem correct to present it as an instance of sex selection for non-medical reasons. As in the above-mentioned analogy from the context of PGD for X-linked disease, we are dealing here with an intermediate form of sex selection: neither medical in the strict sense of the medical model, nor non-medical as referring to parental preferences that have nothing to do with health or disease (de Wert, 2005).

Although the concerns raised by those non-medical reasons do not apply to sex selection for the intermediate reasons discussed in this article, it can be objected that by accepting sex selection for other purposes than avoiding the birth of a child with a serious genetic disease, we are stepping on a slippery slope towards non-medical sex selection. Slippery slope arguments claim that we should refrain from acts or policies that, although morally acceptable in themselves, would take us down a slipway towards acts and policies that would be morally unacceptable. There are two versions of this type of argument, empirical and logical (Spielthenner, 2009). The empirical version claims that accepting Position A will, as a matter of fact, make us eventually accept Position B as well (now regarded as unacceptable). The logical version consists of the claim that by accepting Position A we are logically committed to also accept Position B. With regard to sex selection as a means to avoid reproductive burdens and transgenerational health risks, one could either argue that once we start loosening up the medical model, we will end up accepting clear cases of non-medical sex selection as well, or that we are logically committed to doing so once we accept sex selection for other reasons than avoiding serious disease in the child to be conceived.

As in all slippery slope arguments, the primary question is whether the imagined position at the bottom end of the slope is indeed morally objectionable. Although sex selection for non-medical reasons does indeed raise moral concerns, it is untenable to conclude that it would necessarily lead to unacceptable social consequences (Warren, 1985). Moreover, even if one would reject all instances of sex selection for non-medical reasons, the supposed inevitability of sliding down from accepting intermediate cases to accepting or having to accept non-medical sex selection is far from self-evident. It is important to note that sex selection as discussed in this article would still be for health-related reasons. Why would accepting these lead to also accepting the whole range of possible motives for non-medical sex selection? In its empirical version, the argument is highly speculative and therefore non-compelling. The logical version can simply be refuted by pointing to the compatibility of accepting sex selection for the intermediate purposes discussed in this article with rejecting sex selection for all kinds of non-health-related reasons. This leads us to conclude that the notion of a slippery slope towards non-medical sex selection is not a convincing argument against additional sex selection in the context of PGD or NT for mtDNA disease.

Proportionality

A further objection to be considered is that the (material and immaterial) costs of sex selection to avoid reproductive burdens and possible transgenerational health risks are not in proportion to the expected benefits. As the benefits are uncertain, the costs must indeed be low to justify sex selection. These costs depend on the chosen procedure. Below, we will discuss two strategies of sex selection and scrutinize whether it is morally acceptable to add (one of) these to PGD and/or NT for mtDNA disease, and if so which route is morally preferable.

Post-conceptional sex selection

Post-conceptional sex selection, i.e. sex selection of IVF-embryos, requires PGD followed by selective transfer of a male embryo. To assess the proportionality of adding sex selection at this stage, at least two (related) factors should be taken into consideration.

A first factor is whether and how large an extra step is needed for sex determination (ASRM, 1999). (1) No extra step would be needed if information about the sex of the fetus is available as a by-product of PGD already performed in the context of preventing the transmission of mtDNA disease. (2) Otherwise, sex determination may be added to PGD (i.e. included in the initial assay), supposing again that PGD would already be performed in the context of preventing the transmission of mtDNA disease. Whether this would involve no more than a small extra step also depends on whether this would require a further biopsy of an additional blastomere. (3) If PGD is not already performed (neither as the central approach nor as a back-up after NT), a complete IVF/PGD procedure would have to be done in order to be able to determine the sex of the embryos.

A second factor refers to how this information is subsequently used. One could aim to maximize the transgenerational benefits of adding

sex selection to PGD or NT for mtDNA disorders by discarding all female embryos, even if they are healthy and no suitable [healthy and (morphologically) good quality] male embryos are available for transfer. An alternative conditional approach would allow healthy and good quality female embryos to be transferred, but only if no suitable male embryos are available. This is similar to an earlier proposal for conditional sex selection in the context of PGD for X-linked disorders, according to which carriers are only to be transferred when non-carriers are not available (De Wert, 2005).

Should post-conceptional sex selection be added to PGD for mtDNA disorders?

If the woman undergoes IVF/PGD for mtDNA disorders anyway, information about sex may automatically become available (Situation 1, as described above) or be obtained without significant material or immaterial extra costs (Situation 2). Situation 3 is only relevant in the context of NT, where PGD is not necessarily part of the procedure (see below). With regard to situations in which PGD is the central technology, the necessary first step, sex determination, would not seem to be so costly as to render sex selection disproportional in advance. There is one qualification to this conclusion. Things may be more complicated if, in Situation 2, a further biopsy would be needed, involving a small extra risk of embryo loss and theoretical extra health risks for the child to be. Whether the limited benefits to be expected from sex selection would outweigh these extra risks is indeed debatable.

The next issue regards the proportionality of using this information in the context of selecting embryos for transfer. The maximizing approach to post-conceptional sex selection implies that, generally, 50% of the embryos (all female embryos) will be discarded. This is in addition to male or female embryos that are not suitable for transfer, either because of a mutant load above the threshold for disease expression, or because of low morphological quality (Bredenoord *et al.*, 2009). By adding embryonic sex as a further criterion of the same importance as mutant load and quality, the maximizing approach could make it almost impossible to find an embryo that would be eligible for transfer. This higher embryo loss can be regarded as problematic from two perspectives: the moral status of the human embryo and the general cost-effectiveness of PGD for mtDNA diseases. As we ascribe low independent moral value to preimplantation embryos, the former argument is not decisive. Other things being equal, the transgenerational benefits of sex selection may well outweigh the greater loss of (healthy) human embryos. However, this is to neglect the impact of embryo loss on cost-effectiveness, where costs refer to material costs as well as to the burdens and risks for the women involved. If female embryos are always to be discarded, this may either lead to transferring male embryos of lesser quality or to starting a new treatment cycle more often than would otherwise be the case. This would negatively affect the take-home-baby rate, expose women to greater burdens and risks and lead to a lower general cost-effectiveness. As the benefits of transgenerational sex selection are uncertain and probably small at best, maximizing those benefits at the cost of these effects would clearly be disproportional.

The alternative conditional approach also involves the introduction of embryonic sex as a third selection criterion, but without making this equivalent to mutant load and quality. In this approach the selection process is in two steps. The first step is to select male or female embryos that carry a mutant load below the threshold to disease expression and are of good morphological quality. If this does not lead to sufficient male embryos suitable for transfer, suitable female embryos may still be transferred. Only if suitable embryos of both sexes are available, male embryos are to be selected. This avoids the negative effects of the maximizing approach on the cost-effectiveness of PGD for mtDNA disease, but does so at the cost of losing some of the transgenerational benefits that sex selection may add. As this entails even smaller benefits, the proportionality of the conditional approach hinges on whether the remaining benefits are still important enough to justify any extra steps that may be needed for sex determination not necessarily followed by sex selection. As long as these steps are small and do not involve more than minimal extra costs and risks, we are inclined to a positive answer. Provided the couple gave consent, the preferential transfer of male embryos in a conditional two-step approach would in our view be a morally acceptable way of reducing (rather than avoiding) reproductive burdens and transgenerational risks in their offspring.

Should post-conceptional sex selection be added to NT for mtDNA disorders?

Again, the first relevant question is how embryonic sex is determined. Here also, this depends on whether PGD is done anyway. That might be the case if PGD is considered necessary as a confirmatory test after NT. This would be to ensure that the carryover (of affected mitochondria coming along with the oocyte, the pronuclei or the nucleus of the recipient woman) does not result in an unacceptable high mutant load and/or to ensure that all nuclear material has been removed from the cytoplasm of the enucleated donated oocyte (Poulton *et al.*, 2009). However, whether such a confirmatory PGD would be feasible and useful is debatable, as many questions are still unanswered. For example, if the carryover results in the presence of pathogenic mitochondria, will these segregate evenly over the blastomeres of the embryo?

Let us, for the sake of argument, first assume that PGD would indeed be useful as a back-up test after NT. In that case, the reasoning would be largely similar to that already provided above with regard to adding post-conceptional sex selection to PGD. The single difference is that with regard to NT, the disproportionality of restarting the whole procedure is enhanced by the necessary involvement of an oocyte donor, who would then also have to re-donate. This only strengthens our conclusion that a conditional 'two-step' procedure is the only morally acceptable approach to post-conceptional sex selection for the purposes discussed in this article. With regard to applying this after NT, an important caveat is that this approach would only be feasible if NT involves the reconstruction of several embryos at a time.

In the alternative scenario, PGD is considered unfeasible as a back-up test after NT. In that case, PGD would be added to NT solely for sex determination. Since this involves considerable additional costs, it is highly questionable whether these could be justified by the limited benefits that sex selection would add. Moreover, there is the further problem of whether a biopsy especially for this purpose can be justified, given additional risks of embryo loss (which may be larger after NT as the embryo is already manipulated) and also in light of possible health risks that this may theoretically entail for the

future child. Because of the theoretical nature of the latter risks, PGD is considered acceptable if the procedure can be expected to lead to important health benefits. But precisely that is less clear where PGD would only be needed to add sex selection to NT. Part of this equation should also be that in the proposed 'two-step' approach, sex determination is not necessarily followed by sex selection, thus further undermining the proportionality of adding PGD for this purpose. It is difficult to imagine that PGD, conducted solely for sex selection, could indeed be added to NT in a morally acceptable way.

Preconceptional sex selection

Alternatively, sex selection could be performed prior to fertilization. Preconceptional sex selection requires separation of X-bearing and Y-bearing spermatozoa, with subsequent selection for artificial insemination or IVF (ASRM, 1999). Several methods have been proposed, such as the use of albumin gradients. Although a recent case study reported the birth of a boy after sex selection by albumin gradients (Chen *et al*., 2008), the dominant view is that this method is not reliable for clinical use (Aleahmad *et al*., 2009).

The most promising preconceptional technique, already used in clinical practice, is sperm sorting by flow cytometry. Recent studies seem to indicate that this method may be conducted safely and relatively effectively (Schulman and Karabinus, 2005; Karabinus, 2009), but clinical follow-up is morally imperative to establish the long-term safety as well. In comparison with post-conceptional sex selection, preconceptional methods have the important benefit of not involving the discarding of embryos. In theory, preconceptional sex selection would allow maximizing the transgenerational benefits of producing boys without undermining the effectiveness of PGD or NT for mtDNA disease. In practice, it is important to note that even what is currently the most promising method for preconceptional sex selection is not fail-safe. Particularly with regard to the selection of Y-bearing sperm, the effectiveness of the procedure does not far exceed the range of 80% (Karabinus, 2009). This may be regarded as important enough, as it would at least considerably increase the chances of obtaining male embryos. And if an 80% result would not be seen as pre-empting the need for post-conceptional sex selection, it would certainly provide a much better starting position for attempts at selecting male embryos without compromising the effectiveness of PGD or NT for mtDNA disease.

Other benefits are that preconceptional sex selection is less intrusive and costly than IVF/PGD, assuming that the latter procedures would be specifically done for sex determination and selection. This, of course, will not be the case if PGD is already being done in the context of avoiding the transmission of mtDNA disease.

Should preconceptional sex selection be added to PGD for mtDNA disorders?

If the woman undergoes IVF/PGD for mtDNA disorders anyway, a simple and cheap method of sex determination is already available. But as the subsequent step of sex selection cannot be fully deployed without undermining the effectiveness of the procedures aimed at helping the couple have a healthy child, there might still be a case for preconceptional sex selection. At 80% selection of Y-bearing sperm, this may be regarded as an alternative approach that would be better able to achieve the transgenerational benefits that sex selection is expected to bring than the 'conditional' post-conceptional approach. Alternatively, it may be regarded as a preselection step in a combined pre- and post-conceptional approach which would come even closer to maximizing transgenerational benefits of sex selection. As neither of these options would negatively interfere with regular embryo selection, the proportionality of adding preconceptional sex selection (instead of or in combination with post-conceptional sex selection) would depend on the extra costs this would entail. As long as these are expected to be considerable, they may well outweigh the limited benefits that can at best be achieved by adding sex selection to PGD or NT for mtDNA disorders (Table I).

Table I Post-conceptional versus preconceptional sex selection: a comparison.

Post-conceptional sex selection	Preconceptional sex selection
Disproportional to start IVF/PGD solely to avoid transgenerational risk	In theory morally superior option: less intrusive, less costly, no embryo loss
Meaningful method if the couple needs PGD anyway	In practice: not fail-safe
'Two-step' approach	Particularly interesting if the couple does not need PGD

Should preconceptional sex selection be added to NT for mtDNA disorders?

In cases where after NT for mtDNA disorders, PGD would be performed as a confirmatory step, the arguments for and against adding preconceptional sex selection would be essentially the same as just given. Preconceptional sex selection may be particularly interesting in those cases where after NT, the patient is not already having PGD. In those cases, preconceptional sex selection prior to IVF/NT (or NT/IVF, depending on whether the transplantation occurs before or after fertilization) would be the least costly method, leading at least to considerably increasing the chances of being able to transfer a suitable male embryo. In theory, combining this with adding PGD solely for conditional post-conceptional sex selection after NT would allow improving on this. Apart from the disproportionally high extra costs that this would entail, it is questionable whether performing a biopsy especially for this purpose could be justified by the small extra benefits this might yield.

Conclusion

Even if the use of PGD or NT to prevent the vertical transmission of mtDNA disorders leads to a healthy child, there is the possibility that a latent mutant load will rise again above the level of disease expression in a third generation. Given the maternal inheritance of mtDNA disease, this also depends on whether the child to be conceived is a girl and whether she will decide to have children herself. Since most women want to reproduce, helping the present couple to have a boy could be a meaningful way to avoid the transgenerational health

risks and related reproductive burdens that might otherwise result from a clinical application of PGD or NT for mtDNA disorders. We have argued that adding sex selection for this purpose is morally acceptable in principle. Even though the health of the child to be conceived is not at stake (as required in the traditional justification of sex selection for medical reasons), the reason for choosing or preferring a boy is still health-related. The moral concerns associated with sex selection for non-medical reasons do therefore not apply.

Sex selection can either be done post- or preconceptionally. We have considered the proportionality of adding these different methods to PGD or NT for mtDNA disorders. With regard to post-conceptional sex selection, we have concluded that the only approach that may be acceptable is one in which sex selection only comes in after suitable embryos for transfer are already selected on the basis of health and morphological quality. A further requirement is that the steps needed for the preceding sex determination are small and do not involve more than minimal extra costs and risks. This would only leave room for post-conceptional sex selection in cases where the women is already having PGD, and do so at the price of giving up on part of the possible benefits of adding sex selection. Saying this, we are aware that the pressure already exerted on the embryo-selection process by conventional criteria (health, quality) is high, and that the notion of there being much of a choice left at the second stage of the conditional approach may well be quite theoretical. And the more it is theoretical, the further this undermines the proportionality of any extra steps needed for sex determination.

None of these problems arise with preconceptional sex selection. Whereas this would allow maximizing the benefits of adding sex selection to PGD or NT for mtDNA disorders, extra costs are the single proportionality-limiting factor. Currently, there are no fail-safe methods of preconceptional sex selection. For selection of Y-bearing sperm, the maximum yield of the most promising method is about 80%. This may be considered important enough as it would at least considerably increase the chances of obtaining male embryos, thereby also providing a much better starting position for conditional (two-step) sex selection in the context of PGD. Given remaining uncertainties about the long-term safety of sperm sorting by flow cytometry, follow-up of any children born after adding this element to the procedure would be morally imperative, as it is for NT itself.

Although adding sex selection to avoid the transgenerational health risks and related reproductive burdens that might otherwise result from a clinical application of PGD or NT for mtDNA disorders is morally recommendable in principle, there are important hurdles affecting the proportionality of this idea and therefore also the moral acceptability of putting it in practice. The only cases where this does not apply are the (sparse) situations in which after PGD for mtDNA disorders (i) no extra steps are needed for sex determination and (ii) sufficient healthy and good quality embryos are available for transfer. In those situations, we recommend to actively select male embryos. With regard to the possible clinical application of NT, these situations may only occur if PGD already serves as a back-up. If not, sex selection in the context of NT (for the purpose under consideration) will be a morally defendable proposition only if effective and safe methods for preconceptional sex selection become available against limited costs. Of course, this will then also be relevant for sex selection in the context of PGD, at least with a view of increasing the chances of selecting suitable male embryos through preselection of Y-bearing sperm.

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