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Review Article

Preimplantation genetic diagnosis and screening: Current status and future challenges

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Preimplantation genetic diagnosis (PGD) is a clinically feasible technology to prevent the transmission of monogenic inherited disorders in families afflicted the diseases to the future offsprings. The major technical hurdle is it does not have a general formula for all mutations, thus different gene locus needs individualized, customized design to make the diagnosis

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accurate enough to be applied on PGD, in which the quantity of DNA is scarce, whereas timely result is sometimes requested if fresh embryo transfer is desired. On the other hand, preimplantation genetic screening (PGS) screens embryo with aneuploidy and was also known as PGD-A (A denotes aneuploidy) in order to enhance the implantation rates as well as livebirth rates. In contrasts to PGD, PGS is still under ferocious debate, especially recent reports found that euploid babies were born after transferring the aneuploid embryos diagnosed by PGS back to the womb and only very few randomized trials of PGS are available in the literature. We have been doing PGD and/or PGS for more than 10 years as one of the core PGD/PGS laboratories in Taiwan. Here we provide a concise review of PGD/PGS regarding its current status, both domestically and globally, as well as its future challenges.

Historical aspect

Preimplantation genetic diagnosis (PGD) was first introduced in 1990 by selecting female embryos in order to prevent the birth of male patients affected with X-linked recessive disorders.[1] It is well recognized by the clinical community that is indicated in preventing monogenic inherited disorders with severe morbidity and mortality.[2] Moreover, it is also well recognized that is indicated in couples carrying balanced chromosomal translocation, since about half of the embryos would be unbalanced and contribute to implantation failure, early abortion, and even fetal anomalies. Fluorescence *in situ* hybridization (FISH) was then used to screen the balanced embryos.[3] There is little controversy of PGD since it is well accepted that to prevent the known transmissible condition from generation to generation, except from the ethical aspects in which what kind of the inheritable conditions are severe and debilitating enough to be enrolled, is justified. However, the flourish of genotyping of preimplantation embryos since 1990s is also attributed to the development of screening embryos for aneuploidy in otherwise normal couples based on the fact that the risk of trisomy disorders in humans is associated with advanced maternal age. Such strategy to combine screening aneuploidy embryos with the routine *in vitro* fertilization (IVF) is therefore called preimplantation genetic screening (PGS) or preimplantation genetic screening of aneuploidy (PGD-A).[4] Initially the Day 3 cleavage-stage embryos were most frequently used for embryo biopsy whereas more recently the trophectoderm biopsy of Day 5/6 blastocyst-stage embryos are more popular for there is evidence showing the implantation potential of the biopsied embryos is less affected if the biopsy is taken at blastocyst stage.[5] In some European countries (*e.g.* Germany) where the legal regulation of PGD/PGS is more strict, polar body biopsy remains a viable option since such biopsy does not affect the embryo integrity despite it is only able to diagnose the maternally inherited balanced translocation instead of the paternally inherited ones.[6] Some recent reports also did a longitudinal study of the embryos being biopsied and diagnosed at polar body, cleavage-stage, and blastocyst stage to elucidate the evolution of genetic complements of the human embryos and found self-correction indeed occurred.[7] PGS was very popular in the 1990s and early 2000s until the famous "Mastenbroek controversy" was published,[8] that the researchers found PGS by FISH actually reduced the livebirth rate in the women with advanced maternal age instead of improving it, and because of that, PGS was under heartily debate since then. FISH was therefore considered an outdated tool after the introduction of newer technologies to achieve the comprehensive chromosome screening, including quantitative polymerase chain reaction (qPCR), array comparative genomic hybridization (aCGH), and next generation sequencing (NGS). It is noteworthy that excellent outcome was reported mainly by qPCR technology[9,10] and the researchers even had one of the very few randomized trials of PGS in which the outcome parameters such as the implantation rate and livebirth rate were significantly improved.[11–14] Conversely, despite aCGH and NGS should have a much better resolution than qPCR, surprising reports were published when normal euploid babies were born after transferring aneuploid embryos diagnosed by IVF + PGS back to the womb in women who had no euploid embryos available for transfer.[15] The debate of the need for PGS in IVF is therefore ongoing.[16–18]

Local status in Taiwan

The efforts of researchers in Taiwan in the field of PGD/PGS started very early, with the first few reports of sex identification and amplification of beta-globin gene in preimplantation embryos, as well as the biopsy techniques back in 1990s.[19–21] However, the real booming of using PGD/PGS in clinical settings did not occur until 2000s, by reporting of utilizing FISH to prevent the unbalanced embryos being transferred from couples carrying balanced translocation (PGD-A),[22] utilizing molecular technologies to tackle monogenic inherited disorders and even did double selection by filtering out mutant-carrying and filtering in HLA-matched embryos to produce a rescue baby whose cord blood was used to treat the sibling affected with beta thalassemia major,[23–26] and adopting newer technologies such as aCGH or NGS.[27–29] Some patented inventions regarding the methodology used for PGD/PGS were also reported in recent years.[10,28,30–32]

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