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Mini Review

Who Benefits From PGS?

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Abstract

Whilst new generation sequencing techniques of blastocyst biopsies give rapid response times and are more accurate, we question whether counting chromosomes can lead to an improvement in pregnancy rates and if the cost of trophectoderm biopsy outweighs the benefit in PGS. NGS does not define embryo viability or health, as it does not guarantee that genes are free from DNA breaks/errors, or that they will be expressed/transcribed correctly at the appropriate time in preimplantation development. In addition, PGS cannot detect embryos whose health has been jeopardized by metabolic malfunctions due to epigenetic effects resulting from inherent gamete physiology or sub-optimal *in vitro* culture and handling.

Keywords: Blastocyst; PGS; Trophectoderm biopsy; Mosaicism; Epigenetics; Defective signalling

Introduction

Recent advances in new generation sequencing have been hailed as a major breakthrough in same-day analysis for selection of embryos in ART procedures [1]. While we can only admire the technological improvements and rapid response times we would like to question whether counting chromosomes can truly lead to an improvement in pregnancy rates; we are also concerned that the benefit of trophectoderm biopsy may be outweighed by the potential cost to embryonic health. Pressure from industry, competition between professionals and sometimes inflexible scientific logic have created fierce 'for or against' stances that do not help patients to make an informed choice [2].

We begin by affirming that in our opinion a uni-variate approach to ART is not practical. The causes of infertility are multiple, each stimulation cycle creates cohorts of gametes that differ from the previous cycle(s), and both clinicians and embryologists should tailor each programme of treatment to the individual couple. IVF Centres should make it clear to patients that gametes and embryos cannot be improved *in vitro,* although sub-optimal embryos may be rescued by co-culture or improved culture conditions [3]. The role of the embryologist is to minimise damage while these cells are *extra corporeo* and to select the most viable embryo. It has been estimated that 95% of oocytes in IVF programmes do not give rise to a live birth [4,5].

Whether embryo selection by counting chromosome numbers (Preimplantation Genetic Screening, PGS) is actually effective in improving pregnancy rates and live births has now been the subject of controversy for some years [1,6-11]. While those advocating its use have admitted that early attempts using day 3 embryo biopsies were indeed not convincing, the same authors now promote rapid detection techniques and blastocyst biopsy as the reasons for the most recent improvement/breakthrough. In any medical treatment, the benefit must outweigh the cost. Preimplantation Genetic Diagnosis (PGD) represents a clear-cut case of benefit, where biopsy, a highly invasive surgical technique, is essential in order to eliminate embryos carrying a defective gene from transfer, allowing the selection and transfer of a healthy embryo and the birth of a disease-free child. In contrast, PGS involves the same surgical techniques, but arguably can only eliminate aneuploid embryos that would probably either fail to implant or be spontaneously lost; it may however be used to decrease the number of viable embryos transferred, reducing multiple pregnancies [12]. In both cases there is a valid alternative: the progressive transfer of all embryos over consecutive cycles, sorted by standard criteria, until a pregnancy is achieved.

Which patient group might benefit from PGS?

Biological considerations: A correct chromosome number does not guarantee a live birth, nor indeed, successful implantation. It is becoming increasingly clear that non-genomic factors, whether they be mitochondrial activity, methylation patterns, cytoplasmic glutathione levels, or a myriad of biochemical and physiological parameters are necessary for a viable embryo and a healthy birth [2,13]. For example, it has been estimated that up to 2 million DNA repair processes are carried out at the time of the first cell cycle [14]. Homeostasis in oocytes, as in all cells, depends on a myriad of cell signalling pathways which in turn are fuelled by metabolic pathways, both aerobic and anaerobic [15-18]. Defective signalling leads to cytoskeletal deficiencies which lead, amongst many other cellular effects, to aneuploidy. A correct chromosome number in any cell (ploidy) is a reflection of normal cytoplasmic processes that contribute to correct cytoskeletal alignment and function, allowing the chromosomes to be evenly divided during meiosis/mitosis. Any malfunction in cell signalling/metabolic systems due to upstream cytoplasmic factors can jeopardize cytoskeletal function and result in aneuploidy; in other words, chromosome number is the gross morphological expression of cellular dysfunction – not its cause. Finally, we need to know more about the heterogeneity of cells in the trophectoderm, since it is well known for large farm animals that this tissue is composed of cells of varying ploidy [19] and confined placental mosaicism (different karyotype of the placenta and the foetus), albeit quite low, is manifest in human development [20]. Of course, PGS only offers a static estimate of chromosome number; mitotic inconsistency can arise at any time after the biopsy [21].

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Although the new next generation sequencing techniques have apparently reached a new level of diagnosis [1], they are orders of magnitude away from defining embryo viability, since they do not detect cellular activities at the molecular level. The presence of the correct number of chromosomes as diagnosed by PGS does not guarantee that all of the genes are free from DNA breaks/errors, that all of the genes will be expressed/transcribed correctly, at the appropriate time in preimplantation development - i.e., PGS cannot detect embryos whose health has been jeopardized by metabolic malfunctions due to epigenetic effects resulting from inherent gamete physiology or sub-optimal *in vitro* culture and handling.

Cost and benefit of TE biopsy

Blastocyst formation is a fundamental step in mammalian embryogenesis [22]. An amazing complex structure with clear developmental purpose, it is subject to regulation at the morphological, cellular, transcriptional and epigenetic levels [23,24]. Trophectoderm (TE) biopsy is a radical intervention involving an essential layer of cells that leads to collapse of the blastocyst cavity at a delicate moment in preimplantation development, with presumably modification of epithelial elements important in cellular communication and differentiation such as gap junctions, ionand water pumps [25,26]. The trophectoderm plays a fundamental part in cross-talk with the endometrium and the production of enzymes for hatching and it has been shown in the bovine that implantation may be improved by adding trophectoderm tissue to the blastocyst [27]. Ifblastocyst stage PGS screening were to be introduced across the board as some authors may suggest, a sizeable part of the trophectoderm would be eliminated in all biopsied healthy embryos that lead to birth. More than 5 million children today would have been born with an essential part of their pre-implantation development compromised by dissection. Although the pre-implantation mammalian embryo is highly regulative and may recover from such surgery we do not know the long-term consequences of trophectoderm biopsy.

Heterogeneous patients

The gold standard in IVF today is probably to be found in donor IVF programmes, where pregnancy rates with fresh oocytes from young donors approach 80% with conventional ART and selection procedures. Thus, without the new wave of high- tech selection procedures such as time lapse, PGS or indeed estimation of mitochondrial activity [28], the probability of success is extremely high and in our opinion does not warrant further invasive technology.

At the other end of the spectrum, let us consider a typical 40-year old patient undergoing ART, generically classified as a poor prognosis patient. It has been suggested that live birth rate is correlated with the number of oocytes retrieved, with maximum efficiency reached at 15 oocytes [29]. In many IVF programmes today, we have seen a decline (to less than 20%) in good prognosis patients aged <38 yrs who produce more than 10 oocytes. Oocytes from older patients are of course defined as not only at greater risk of aneuploidy, but also less metabolically fit owing to mitochondrial inadequacies [17]; this alone questions the usefulness of chromosome counting. In a growing proportion of patients today, the number of viable embryos produced may be less than three, excluding any kind of selection procedures. Soft protocols and natural cycle protocols automatically exclude selection procedures whether invasive (PGS) or less invasive (Time lapse). It would thus appear that the patient groups that might benefit from PGS is rather small, perhaps being those with recurrent IVF failure [30] and others defined as c.35yrs old, generating more than 5oocytes. In the latter population, the only obvious reason for PGS would be to avoid multiple pregnancy [31].

Reproductive success and chance

If an algorithm for reproductive success were to be created, it would need to take into account not only patient age, gamete quality, laboratory and clinical competence and uterine receptivity but all genetic and epigenetic processes. Somatic mutations, for example are stochastic events that occur by chance in the aetiology of cancer [32]. Perhaps it is time in ART to recognise that success depends not only on technology, but also on chance.

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