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ASSISTED REPRODUCTION TECHNOLOGIES

Review of 10 years of preimplantation genetic diagnosis in South Africa: implications for a low-to-middle-income country

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Abstract

Purpose To evaluate the preimplantation genetic diagnosis (PGD) service, for the period of January 2006 to December 2016, through a South African academic and diagnostic Human Genetics Unit, and to assess the outcomes and cost of PGD.

Methods A retrospective review of PGD files available at the Human Genetics Unit was performed. Data was collected from genetic counseling, fertility, and PGD-specific records.

Results Amongst the 22 couples who had PGD, 42 in vitro fertilisation cycles were completed with 228 embryos biopsied and included in the analysis. Most (59%) of the conditions for which PGD was requested were autosomal recessive. Of the biopsied embryos, 71/228 (31.1%) were suitable for transfer and 41/71 (57.7%) were transferred. Of these, 14/41 (34.0%) successfully implanted and 11/14 (78.6%) resulted in a liveborn infant. The clinical pregnancy rate per embryo transfer was 29.3%. Overall, 10/22 (45.5%) couples had a successful cycle resulting in a liveborn infant. On average, one cycle of PGD costs USD 9525.

Conclusions This is the first study to assess the success rates and the cost of PGD in South Africa and provides evidence for the feasibility in a low-to-middle-income country. The success rates in this sample are comparable to those achieved globally. South Africa has the infrastructure and expertise to provide PGD; the limiting factor is the lack of funding initiatives for PGD. Although the sample size was small, the findings from this study will enable genetic counselors to offer couples in South Africa evidence-based and locally accurate information regarding outcomes, success rates, and costs.

Keywords Assisted reproductive techniques · Human genetics · Low-to-middle-income country · Genetic counseling · Preimplantation genetic diagnosis · Reproductive techniques

Introduction

Although preimplantation genetic diagnosis (PGD) (now referred to as PGT-M) has been in existence since 1990 [1], in South Africa (SA), a low-to-middle-income country (LMIC), it is still a relatively new and limited service. The first known PGD case managed through our South African academic and diagnostic Human Genetics Unit was in 2006. The PGD process has evolved over the years and significant changes in the timing of embryo biopsy and techniques used have been made.

The stage at which the embryo biopsy is performed influences the outcome of the in vitro fertilisation (IVF) process and the accuracy of genetic testing [2]. If the specific familial mutation is unknown, a diagnostic workup, in a reputable genetics laboratory, is initiated to identify the familial mutation(s). Once the mutation(s) has been identified, the reproductive genetics laboratory optimises the PGD test. Currently, PGD laboratories are using genome-wide karyomapping [3] as the assay of choice. Patients who are undergoing PGD may opt to have preimplantation genetic screening (PGS) (now referred to as PGT-A) performed simultaneously to increase the pregnancy success rate by decreasing the rate of aneuploid embryos transferred [4]. Preimplantation genetic diagnosis and PGS together offer parents an opportunity to have a child unaffected with a molecularly confirmed familial genetic condition, or any other chromosomal abnormality for which they

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may be at risk. These procedures significantly reduce the likelihood of having to terminate an affected pregnancy.

Unlike the situation in Italy, France, and the UK, for example, where there are strict regulatory policies that guide the use of PGD [5], the South African legislative framework lacks such regulation [6]. South Africa is governed by three acts which address various reproductive issues: The Human Tissues Act No. 65 of 1983, the National Health Act No. 61 of 2003, and the Children's Act No. 38 of 2010 (https://www.gov.za/documents/acts). There is no direct reference to PGD in these acts; however, the content is broad enough to permit the use of PGD for genetic conditions, as well as for human leukocyte antigen (HLA) matching for donor siblings [6]. The National Health Act No. 61 of 2003 does, however, state that sex selection for family balancing is not permitted. Furthermore, unlike the government-funded PGD initiatives in several European countries, there are no such initiatives available for South African couples. In France, for example, the government funds up to four IVF cycles per couple [5]. In South Africa, approximately 17.4% of the population is covered by private medical insurance [7], but it generally does not cover the cost of PGD, and couples are therefore obliged to pay for the procedure themselves. The remaining 82.6% of the population is dependent on the government-funded healthcare system which does not currently offer PGD as a service. The high cost of PGD, coupled with the lack of medical insurance coverage, is a limiting factor locally, making this procedure only accessible to few individuals of higher socioeconomic status.

During PGD-related genetic counseling, queries that are often raised by South African couples centre around the perceived high costs involved, the length and complexity of the entire PGD process, and the relatively low success rates. In order to make an informed decision about whether to undergo PGD, couples need to understand all the limitations involved and the possible outcomes that they may experience. Current PGD-related genetic counseling in South Africa can only provide information on PGD outcomes and expenses based on the published experiences of other countries. We therefore aimed to evaluate the PGD service facilitated through a local Human Genetics Unit and private reproductive centre to provide accurate data to local couples, and to assess the feasibility of PGD in a LMIC.

Methods

Study sample

A retrospective file review was undertaken. The target population consisted of 33 couples who consulted the selected Human Genetics Unit between January 2006 and December 2016 for PGD-related genetic counseling (with a registered medical geneticist, genetic counselor, or genetic nurse). These couples were at risk of having a child with a monogenic condition. Only couples seen at a single genetic counseling centre and selected reproductive centre were included, allowing for ease of accessibility and consistency of processes. Couples who had PGS without PGD, or who had PGD for a chromosomal abnormality, were excluded. After all exclusions, the files of 22 couples were available for data extraction and analysis.

Study design

This was a descriptive study that involved an assessment of the genetic counseling, IVF/intracytoplasmic sperm injection (ICSI), and PGD/PGS records of couples requesting PGD. Documented information included the types of genetic conditions, family and obstetric history, IVF/ICSI outcomes, the time elapsed until a successful pregnancy was achieved or the process was terminated, and the number of successful pregnancies achieved. Couples signed consent at the time of PGD initiation allowing for the anonymous use of their data. Ethics clearance was obtained from the Human Research Ethics Committee (Medical) of the University of the Witwatersrand (Ethics Clearance Certificate no. M170257 27/02/2017).

Data analysis

The data analysis and statistical software package STATA version 12 (StataCorp. 2011. College Station, TX: StataCorp LP.) was used to analyse the data in this study. All data were checked for normality using the Shapiro-Wilk test. Continuous variables that were normally distributed were reported as means (standard deviations, SD). Continuous variables that were not normally distributed were reported as medians (interquartile ranges). Categorical variables were described as frequencies and percentages.

Results

Participant demographics

Of the 22 couples included in the sample, 19/22 (86.4%) were Caucasian of European ancestry and 3/22 (13.6%) were Indian. There were no Black or Mixed Ancestry couples. Altogether, 7/22 (31.8%) of the couples were of Ashkenazi Jewish ancestry. The mean (SD) age of the female and male partners at their initial PGD genetic counseling consultation was 31 (4.08) and 34.5 (3.73) years, respectively. Of the female partners, 6/22 (27.3%) were of advanced maternal age (> 35 years of age). There was no mention of medical insurance coverage at the time of PGD enrolment in the files of two couples. All other couples had medical insurance coverage.

Preimplantation genetic diagnosis was requested for a range of monogenic conditions as shown in Table 1.

Family and reproductive histories of PGD couples

There was a single consanguineous couple (third-cousin union) in the study sample who requested PGD for an autosomal recessive condition. Regarding the family histories, there was a median of 1 (1–2) individual affected with the familial monogenic condition in each case. Prior to PGD enrolment, there was a total of 41 pregnancies amongst the 22 couples in the sample. Of these pregnancies, 9/41 (17.1%) had prenatal testing. All nine of these prenatal tests were positive for the various monogenic conditions. In total, 8/9 (88.9%) affected pregnancies were terminated. Furthermore, 13/22 (59.1%) couples had at least one affected liveborn child each.

PGD indications

Couples' reasons for seeking PGD are reported in Table 2; indications were inferred from family and reproductive histories, as well as notes recorded in patient files. Some couples had more than one indication for undergoing PGD. All of the couples chose PGD to avoid having an affected child; with 13/22 (59.1%) couples having at least one affected child already and 11/22 (50%) couples either had a previous termination of pregnancy or wanted to avoid terminating a pregnancy.

PGD cycle outcomes

A total of 45 PGD cycles were initiated amongst the 22 couples in the timeframe of the study. Out of 45 cycles, three cycles resulted in failed oocyte harvesting and were therefore discontinued. Outcomes for the remaining 42 cycles were analysed at different stages of the PGD process as indicated in Tables 3 and 4. A median of 2 (1–2) cycles per couple was completed. Of the transferred embryos, 14/41 (34.0%) successfully implanted (indicated by positive beta-human chorionic gonadotropin (β-hGG) tests) and 11/14 (78.6%) of the implanted embryos resulted in a liveborn infant. The clinical pregnancy rate per embryo transfer was 29.3%. Overall, 10/22 (45.5%) couples in this study sample had a successful cycle resulting in a liveborn child by the end of the study period. One couple had a successful twin pregnancy.

Table 1 Genetic conditions for which PGD was requested

Mode of inheritance	Genetic conditions[a]
Autosomal recessive *N* = 13 (59%)	Beta-thalassaemia (*n* = 3) Congenital disorder of glycosylation Cystic fibrosis (*n* = 3) Familial dysautonomia Joubert syndrome Krabbe disease Stargardt disease Von Willebrand disease Zellweger syndrome
Autosomal dominant *N* = 6 (27%)	Achondroplasia Autosomal dominant polycystic kidney disease Bullous congenital icthyosiform erythroderma Familial adenomatous polyposis Facioscapulohumeral muscular dystrophy Tuberous sclerosis
X-linked recessive *N* = 3 (14%)	Duchenne muscular dystrophy Haemophilia B Hypohidrotic ectodermal dysplasia

[a] Each condition represents one case unless otherwise stated

Table 2 Couples' reasons for undergoing PGD (*N* = 22)

Indication[a]	Number of PGD couples
To avoid having an affected child	22
Previous affected child	13
HLA-matching for donor sibling	2
Previous failed sex selection for X-linked condition	1
Poor fertility history	3
To avoid termination of pregnancy	5
Previous termination of pregnancy	6

[a] Couples may have had more than one indication for undergoing PGD

HLA human leukocyte antigen, *PGD* preimplantation genetic diagnosis

Time to complete the PGD process

On average, during the study timeframe, it took 21 months from the initial PGD genetic counseling consultation to complete the PGD process, i.e. achieve a biochemical pregnancy or discontinue the process. Furthermore, it took an average of 17.5 months from the initial fertility consultation until completion of the PGD process, and an average of 10 months from the initiation of IVF/ICSI (hormone stimulation) until completion of the PGD process. The time it took couples to complete the process was, however, variable. For example, one couple took 40 months to complete two PGD cycles, which resulted in a single successful pregnancy. Contrastingly, another couple took 35 months in which seven cycles were completed, but there was no successful pregnancy.

Cost assessment of one PGD cycle

The cost analysis included costs involved from the initiation of PGD until the completion of a PGD cycle, as shown in Table 5. Seven cycles with insufficient financial records were omitted from the cost evaluation. The cost assessment was divided into two analyses: the first considered the average cost of all included cycles (*n* = 35). On average, the total cost was USD 9525 (as per exchange rate on 25/08/2017) per cycle.

Table 3 Pooled data of cycle outcomes at various stages of the PGD process for 22 couples over a period of 10 years from 2006 to 2016

Stage of the PGD process	Outcome	*n*/*N* (%)
Total number of cycles	Failed cycles (failed oocyte harvesting)	3/45 (6.7)
	Completed IVF/ICSI cycles (from oocyte harvesting to embryo biopsy/implantation)	42/45 (93.3)
IVF/ICSI	Oocytes retrieved[a]	532
	Oocytes fertilised/inseminated	343/532 (64.5)
Embryo biopsy	Embryos biopsied	220/343 (64.1)
	Embryos re-biopsied	8/220 (3.6)
	Day 3 biopsies	88/228 (38.6)
	Day 5/6 biopsies	132/228 (57.9)
	Unknown embryo stage	8/228 (3.5)
Testing of biopsied embryos	Embryos tested (PGD)	222/228 (97.4)[b]
	Embryos tested (PGS)	137/228 (60.1)
Biopsy results[c]	Unaffected embryos (PGS and PGD) suitable for transfer	71/228 (31.1)
	Total number of affected embryos	117/228 (51.3)
	Affected embryos with abnormal karyotype only (PGS)	42/137 (30.7)
	Affected embryos with monogenic condition only (PGD)	67/222 (30.2)
	Affected embryos with abnormal karyotype and monogenic condition (PGS and PGD)	8/228 (3.5)
	Inconclusive results (PGD/PGS/Both)	47/228 (20.6)[d]
Embryo transfer	Embryos transferred	41/71 (57.7)
Final pregnancy outcome	Embryos implanted (positive β-hCG)	14/41 (34.1)
	Prenatal genetic tests recorded	1/14 (7.1)
	Miscarriages	2/14 (14.3)
	Clinical pregnancies	12/14 (85.7)
	Liveborn babies recorded	11/14 (78.6)
	Postnatal genetic tests recorded	2/11 (18.2)

β-hCG beta-human chorionic gonadotropin, *HLA* human leukocyte antigen, *ICSI* intracytoplasmic sperm injection, *IVF* in vitro fertilisation, *PGD* preimplantation genetic diagnosis, *PGS* preimplantation genetic screening

[a] Number of oocytes retrieved and fertilised were taken to be the same as the number of embryos biopsied for four cycles where this information was missing from records

[b] Some embryos were tested for chromosome abnormalities prior to PGD. Six of these embryos were chromosomally abnormal (detected by PGS) and therefore did not have PGD

[c] There were 66 embryos that were also tested for HLA-matching. Of these, 8/66 (12.1%) were HLA matches but were unsuitable for transfer. The majority of the HLA testing was requested by one couple included in the study sample

[d] Eight of these were re-biopsied, of which seven were reclassified and are therefore also represented in the affected/unaffected category

The second analysis only included couples' most expensive cycles. On average, the total cost per cycle was USD 10,283 (as per exchange rate on 25/08/2017). Two different analyses were done because of the variability of the costs involved during each cycle.

The costs reflected here do not include the cost of the molecular genetic diagnostic workup to identify the familial mutation(s), which is required prior to the initiation of PGD. These costs were excluded because of their variability. The cost for the molecular testing will be influenced by the type of genetic test performed, the laboratory used (local or international), when testing was performed, and the number of people in the family who need to be tested to identify the familial mutation(s).

Discussion

PGD outcomes

This is the first study to report on PGD outcomes in South Africa. The data show a clinical pregnancy success rate of 29.3%, comparable with the clinical pregnancy success rate of 29.0% per embryo transfer reported from a much larger sample in 2012 by the European Society of Human Reproduction and Embryology (ESHRE) PGD consortium [8]. Despite our significantly smaller sample size, our findings are comparable to previously reported global PGD outcomes, which is encouraging. The results will be useful in providing evidence-based genetic counseling in the local context.

Table 4 Average outcomes per cycle at various stages of the PGD process for the 42 cycles completed by the 22 couples in this study sample

Number of events per cycle	Mean (SD)[a]	Median (IQR)
Oocytes retrieved	–	12 (11–14)
Oocytes fertilised/inseminated	8.2 (4.59)	–
Embryos biopsied	5.2 (2.72)	–
Unaffected embryos (PGS and PGD) suitable for transfer	–	1 (1–2)

IQR interquartile range, *PGD* preimplantation genetic diagnosis, *PGS* preimplantation genetic screening, *SD* standard deviation

Preimplantation genetic diagnosis is changing constantly. In recent years, changes in the timing of embryo biopsy, new testing strategies and methodologies, embryo vitrification technologies, and the introduction of PGS appear to have improved the IVF/ICSI pregnancy success rates. The use of next generation sequencing (NGS) and array comparative genomic hybridisation (aCGH) for PGS, and karyomapping for PGD, have led to an increase in the accuracy and efficiency of testing, with fewer false-negative and false-positive results reported [3, 4]. Also, embryo biopsy on day 5 and day 6 is associated with increased success rates compared with biopsy on day 3 embryos [2, 4]. Although karyomapping is currently the PGD technique employed, the majority of the cases included in this study had their PGD cycles prior to the introduction of karyomapping, and therefore, family-specific PCR-based approaches were used. With the introduction of new, robust vitrification technology in 2015, there has been an improvement in the pregnancy success rates in patients who have a frozen thawed transfer cycle where centres vitrify rather than slow-freeze the embryos [9, 10]. One would expect to see higher pregnancy success rates in a PGD couple cohort, compared with an IVF for infertility cohort, since many would be expected to have normal fertility. Most of the PGD couples included in the present study sample had PGD before 2015. With a general increase in IVF/ICSI success rates, we expect to see a concomitant rise in the PGD pregnancy success rates in the coming years.

Couple's reasons for seeking PGD

The main indications for PGD in this study sample was to avoid having an affected child, having a previous affected child, and wanting to avoid termination of pregnancy (some having had previous pregnancy terminations). A systematic literature review conducted by Cunningham et al. (2015) showed that avoiding termination of pregnancy was a main advantage of PGD in studies conducted in the UK, Spain, the USA, Australia, and the Netherlands. These studies included participants who had a previous affected child, had previous terminations of affected pregnancies, multiple miscarriages,

Table 5 Cost assessment of the PGD process per cycle given in USD, excluding molecular genetic testing costs

Stage of PGD process	Costs involved	Average cost of all cycles (n = 35)	Range	Average cost of couple's most expensive cycles (n = 20)[a]	Range
Pre-PGD enrolment	Genetic Counseling	35	0–64	36	0–64
IVF/ICSI	Fertility Assessments[b]	189	0–648	47	0–648
	Medication	741	28–1514	803	38–1514
	IVF/ICSI[c]	3782	573–7878	4501	1582–7878
	Total	4712	1525–9189	5351	2748–9189
Testing	PGD	3025	1033–4575	3094	2115–3668
	PGS	1474	992–2209	1511	992–2209
	Courier fees	250	0–561	248	0–561
	Other fees[d]	29	0–379	43	0–379
	Total	4778	2025–7724	4896	3107–6817
Grand total of PGD cycle		9525	4052–14,554	10,283	6577–14,554

ICSI intracytoplasmic sperm injection, *IVF* in vitro fertilisation, *PGD* preimplantation genetic diagnosis, *PGS* preimplantation genetic screening, *USD* United States Dollar

[a] Some couples only had one cycle, which was included

[b] Includes, but may not be limited to, fertility screening, blood tests, follicle counts, semen analysis, hysteroscopy, and doctor's consultation

[c] Includes ovarian stimulation, oocyte retrieval procedure, fertilisation by IVF/ICSI, embryo culturing, embryo biopsy, embryo vitrification, embryo transfer, embryo storage, fertility specialist and embryologist fees, facility fees, and laboratory fees

[d] Other fees include antenatal consultation fees, ultrasound fees, and other non-routine medical procedures that may have been necessary

and infertility due to a genetic condition [11]. The main indications for PGD in this study sample are therefore comparable to those in high-income countries.

Time to complete the PGD process

This is the first study to comment on the time it takes couples to complete the PGD process. Data were not available on couples who initiated PGD discussion, but then did not proceed with PGD. The variable timing of the PGD process amongst these couples may be influenced by many factors. This study only considered the time to complete the PGD process and did not investigate the factors contributing to the timing. Follow-up qualitative research will aim to identify the factors that contribute to the timing of the PGD process.

The cost of PGD

The cost of PGD, coupled with the lack of medical insurance coverage, is currently a limiting factor to uptake for many couples. A previous study found that couples in the USA felt that using PGD to avoid having affected children was worth the financial burden; however, couples also stressed that the cost of PGD was a major barrier to its use [12]. In 2013, the cost range of one IVF cycle in the USA was USD 9226–12,513 whilst PGD cost an additional USD 2500–6000 per cycle [12]. A fertility centre in Chicago estimated the cost of one PGD cycle to amount to USD 20,895 [13]. We estimated the cost of one PGD cycle (including PGS) to be approximately USD 9525. As the median number of cycles per couple in this sample was 2 (1–2), the average cost of PGD in South Africa can be estimated at USD 19,050. The costs reflected here are likely to be underestimates of the total cost, as the evaluation did not consider discounts that may have been offered, and medical insurance that may have covered some of the costs for which couples were then not invoiced. For example, some medical insurance companies may provide some financial cover for consultation fees, medication, and other aspects. Medical aid schemes with comprehensive cover may cover some IVF costs.

The cost of PGD limits access for many local couples and is an area that requires attention to increase its availability. The Malka Ella Fertility Fund is a charity which assists South African Orthodox Jewish couples. This organisation will fund up to two IVF/ICSI cycles per couple per year and will also fund PGD and PGS [14]. There was an overrepresentation of Ashkenazi Jewish couples in this study sample (31.8%), which could be explained by their access to assisted funding for PGD and suggests that more couples would opt for PGD if financial support were available. No other such services exist for South African couples who are not Ashkenazi Jewish. The Malka Ella Fund is driven solely by financial donations made by the South African Ashkenazi Jewish population. Similar organisations that offer funding to broader population groups should be established.

Benefits of PGD

Whilst the costs of PGD are high, the financial burden of caring for a child with a genetic condition is significant. As reviewed in Anderson et al. (2007), children with disabilities utilise healthcare services at a significantly higher rate compared with children without disabilities, and therefore incur higher healthcare expenditure. The cost of caring for a child with disabilities varied between USD 108 to USD 8742 per year, with costs exceeding 5–12% of families' incomes [15]. Cystic fibrosis, one of the most common, and, as a result, most studied, genetic conditions, is also one of the most common conditions for which PGD is requested globally [16]. Davis et al. (2010) performed a cost-benefit analysis of PGD for carrier couples of cystic fibrosis (CF) compared with the alternative of natural conception followed by prenatal testing and termination of affected pregnancies. When used for women younger than 35 years of age, the net benefit of PGD over natural conception was USD 182,000; for women aged 35–40 years, the net benefit of PGD over natural conception was USD 114,000. Furthermore, the medical costs for the treatment of cystic fibrosis are reported to be in the range of USD 15,000 per year. The authors concluded that for women aged 40 years and younger, PGD provides substantial net economic benefits relative to natural conceptions followed by prenatal testing and termination of affected pregnancies and we believe this would apply locally [17]. This study was done prior to the introduction of mutation-directed drugs, which further increase the cost of care. A study conducted in the USA investigating the economic burden of paediatric patients suspected of having a genetic disease found that these patients make up only 2.6–14% of all hospital discharges, but make up 11–46% of all aggregate total charges of the national bill, corresponding to an increase of total costs ranging from USD 12,000–USD 770,000 per discharge compared with patients without a genetic condition [18]. Based on these findings, we hypothesise that PGD would therefore provide net economic benefit for most genetic conditions.

The data from the present study suggest that an important indirect benefit of PGD is avoiding termination of a desired but affected pregnancy. Besides the financial cost implications of prenatal testing and termination of pregnancy, there are the added emotional, psychological, and physical costs, particularly when termination occurs later in the pregnancy, which cannot be assigned a monetary value. The potential cost-benefit of PGD compared with prenatal testing and termination of pregnancy, or caring for an affected child, is therefore an important consideration.

It is also important to note that whilst PGD is initially expensive, the costs of further cycles may be significantly reduced

if there are frozen embryos from previous cycles that are available to implant. This cost should be weighed against the cost of multiple prenatal tests and termination of pregnancies in successive pregnancies. In this sample, 11/22 (50%) couples requested PGD to avoid terminating a pregnancy, or because they had a previous termination of pregnancy for an affected foetus and were not prepared to undergo another termination of pregnancy. This finding highlights the significance of avoiding a termination of pregnancy as an indication for PGD.

Low-income families are particularly vulnerable to the financial burden of caring for a child with disabilities or severe medical problems. Furthermore, caring for a child with a genetic condition who may have physical and intellectual disability, or may need continuous medical intervention and care, can carry a significant emotional burden. The psychological effects of terminating an affected pregnancy are also significant [19]. South Africa is a resource-limited country. The unemployment rate was reported as 27.7% in the third quarter of 2017 [20], leaving many citizens dependent on government-funded healthcare, which at present does not provide any funding towards PGD. The cost-saving benefit of PGD compared to caring for an affected child should be used to promote the establishment of PGD services in state centres. Current legislative frameworks lack appropriate regulation regarding the use and accessibility of PGD, and this needs to be addressed.

Access to equal healthcare is a basic human right. The ESHRE argue that the decision to have children should not be dependent on income as this is considered part of basic healthcare, and PGD provides an equal opportunity for parents to have an unaffected, yet genetically related, child [21]. PGD should thus be assessed as a cost-effective procedure in LMIC.

Study limitations

Limitations of this study include omitted and incomplete information in records which impacted on the validity of the data presented. Meticulous record keeping in healthcare is of utmost importance to ensure the quality of future research in the field. Although the sample size was limited, it reflects the uptake of PGD in this centre. Furthermore, the success rate achieved in this sample is comparable to what has been achieved globally, despite the smaller sample size. Data regarding the number of couples who inquired about PGD and then ultimately declined could not be analysed as this type of information is not routinely or consistently recorded.

Research recommendations

Future research should focus on collecting larger data sets over a longer period to assess the success rates of PGD more accurately over time. The authors of this paper are currently conducting a qualitative study assessing couples' experiences of the PGD process. The results from this second study, together with the information from the present study, are important in guiding PGD-related practices in SA.

Practice implications

This evaluation of the experiences of PGD of 22 couples shows that the success rates achieved in our South African centre are comparable to those achieved globally. South Africa has the infrastructure and the expertise to provide PGD as a service; the limiting factor is the lack of government-funded or medical insurance-funded PGD initiatives, despite the financial burden children affected with genetic conditions place on healthcare resources and the financial burden of prenatal diagnosis and termination of pregnancy. Furthermore, this study provides preliminary evidence for the feasibility of PGD in a LMIC.

Artificial reproductive technology (ART) is generally well accepted in Africa [22]. There were eight assisted conception centres in sub-Saharan Africa by 2001. Despite structural challenges; scarce resources; and the instability of infrastructure, political systems and legal guidelines, African countries have found ways to overcome these barriers to offer these services whilst aligning to international recommendations. Whilst ART in many sub-Saharan African countries is still relatively new, the African experience of ART shows similarities to European centres when they first started. It took a period of 40 years before regulations and laws as well as best-practice guidelines were developed and implemented in these centres [23]. Performing ART in the African context has unique challenges, with different societal norms, religious, and cultural practices. South Africa has the skills available to establish PGD, but it is important that we develop our own regulations, laws and best-practice guidelines. To our knowledge, other reproductive centres in South Africa use the same techniques and there is a single laboratory service that offers PGD and PGS, so all the reproductive centres work in conjunction with them. As a result, we would expect the results of this study to be generalizable to other centres in South Africa. Further, we would expect that similar successes would be achievable in other LMIC. Many already offer some ART so extension to PGD services should be achievable. The challenge is in ensuring broad access to these technologies.

We propose that the potential benefits, both financial and emotional, that can be garnered using PGD as a prevention mechanism for monogenic disorders outweigh the cost implications and recommend that the South African government and private healthcare insurance consider increasing public access to PGD. We also advocate for the essential inclusion of genetic counseling services as a standard part of the PGD process. Couples need such counseling to address the PGD process, its limitations, and potential outcomes. Couples also

need to be aware of other reproductive options available to them, for example adoption, prenatal testing, or gamete donation, so that they can make informed decisions. Genetic counselors are equipped with the necessary skills to convey this information in a non-directive manner and can assist with the adaptation process.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee (Human Research Ethics Committee (Medical) of the University of the Witwatersrand no. M170257 27/02/2017) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

References

1. Handyside AH, Kontogianni EH, Hardy K, Winston RML. Pregnancies from biopsied human preimplantation embryos sexed by Y-specific DNA amplification. Nature. 1990;344(6268):768–70.
2. Scott RT, Upham KM, Forman EJ, et al. Cleavage-stage biopsy significantly impairs human embryonic implantation potential while blastocyst biopsy does not: a randomized and paired clinical trial. Fertil Steril. 2013;100(3):624–30.
3. Natesan SA, Bladon AJ, Coskun S, Qubbaj W, Prates R, Munne S, et al. Genome-wide karyomapping accurately identifies the inheritance of single-gene defects in human preimplantation embryos in vitro. Genet Med. 2014;16(11):838–45.
4. Dahdouh EM, Balayla J, Audibert F, Wilson RD, Brock JA, Campagnolo C, et al. Technical update: preimplantation genetic diagnosis and screening. Obstet Gynecol Surv. 2015;70(9):557–8.
5. Bayefsky MJ. Comparative preimplantation genetic diagnosis policy in Europe and the USA and its implications for reproductive tourism. Reprod Biomed Online. 2017. https://doi.org/10.1016/j.rbms.2017.01.001 Accessed 10 July 2017.
6. Strode A, Soni S. Pre-implantation diagnosis to create 'saviour siblings': a critical discussion of the current and future legal frameworks in South Africa. S Afr Med J. 2012;102(1):21–4.
7. Statistics South Africa 2017. Media release: general household survey, 2016. 2017. http://www.statssa.gov.za/?p=9922 Accessed 22 Aug 2017.
8. Harper JC, Wilton L, Traeger-Synodinos J, Goossens V, Moutou C, SenGupta SB, et al. The ESHRE PGD consortium: 10 years of data collection. Hum Reprod Update. 2012;18(3):234–47.
9. Sherbahn R. Frozen Embryo Transfer, FET cycles after IVF. 2017. http://www.advancedfertility.com/fet-cycle.htm Accessed 13 July 2017.
10. Advanced Fertility Center of Chicago. IVF success rates: in vitro fertilization statistics. 2017. http://www.advancedfertility.com/ivf-success-rates.htm. Accessed 13 July 2017.
11. Cunningham J, Goldsmith L, Skirton H. The evidence base regarding the experiences of and attitudes to preimplantation genetic diagnosis in prospective parents. Midwifery. 2015;31(2):288–96.
12. Drazba KT, Kelley MA, Hershberger PE. A qualitative inquiry of the financial concerns of couples opting to use preimplantation genetic diagnosis to prevent the transmission of known genetic disorders. J Genet Couns. 2014;23(2):202–11.
13. Sherbahn R. PGD and IVF Costs - what is the cost for preimplantation genetic diagnosis - PGD and PGS, preimplantation genetic screening? 2017. http://www.advancedfertility.com/pgd-costs.htm. Accessed 13 July 2017
14. Ella M. Apply for Funding. 2017. https://malkaella.co.za/funding/ Accessed 27 July 2017.
15. Anderson D, Dumont S, Jacobs P, Azzaria L. The personal costs of caring for a child with a disability: a review of the literature. Public Health Rep. 2007;122(1):3–16.
16. Geraedts JP, De Wert GM. Preimplantation genetic diagnosis. Clin Genet. 2009;76(4):315–25.
17. Davis LB, Champion SJ, Fair SO, Baker VL, Garber AM. A cost-benefit analysis of preimplantation genetic diagnosis for carrier couples of cystic fibrosis. Fertil Steril. 2010;93(6):1793–804.
18. Gonzaludo N, Belmont JW, Gainullin VG, Taft RJ. Estimating the burden and economic impact of pediatric genetic disease. Genet Med. 2018;20:1.
19. Asplin N, Wessel H, Marions L, Öhman SG. Pregnancy termination due to fetal anomaly: women's reactions, satisfaction and experiences of care. J Midwifery. 2014;30(6):620–7.
20. Statistics South Africa 2017. Media release: quarterly labour force survey – QLFS Q1:2017. http://www.statssa.gov.za/?p=9960 Accessed 13 Nov 2017.
21. Pennings G, de Wert G, Shenfield F, et al. ESHRE Task Force on Ethics and Law 14: equity of access to assisted reproductive technology. Hum Reprod. 2008;23(4):772–4.
22. Butler P, Khanna J. Assisted reproduction in developing countries-facing up to the issues. Prog Reprod Health Res. 2003;63:1–8.
23. Hörbst V. You cannot do IVF in Africa as in Europe': the making of IVF in Mali and Uganda. Reprod Biomed Soc Online. 2016;1(2):108–15.