

Recurrent miscarriage in translocation carriers: no differences in clinical characteristics between couples who accept and couples who decline PGD

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STUDY QUESTION: Do clinical characteristics of recurrent miscarriage couples with a chromosomal abnormality and who opt for PGD differ from couples that decline PGD after extensive genetic counselling?

SUMMARY ANSWER: No differences in clinical characteristics are identified between recurrent miscarriage couples carrying a structural chromosomal abnormality who opt for PGD compared with those that decline PGD after extensive genetic counselling.

WHAT IS KNOWN ALREADY: Couples who have experienced two or more miscarriages (recurrent miscarriage) are at increased recurrence risk if one of the partners carries a structural chromosomal abnormality. PGD can be offered to avoid (another) miscarriage or pregnancy termination when (invasive) prenatal diagnosis shows an abnormal result. To date, no reports are available that describe reproductive decision-making after genetic counselling on PGD in these specific couples.

STUDY DESIGN, SIZE, DURATION: Retrospective cohort study of 294 couples carrying a structural chromosomal abnormality seeking genetic counselling on PGD between 1996 and 2012.

PARTICIPANTS/MATERIALS, SETTING, METHODS: Participants were recurrent miscarriage couples carrying a structural chromosomal abnormality. They had been referred for genetic counselling to the only national licensed PGD centre. Clinical characteristics analysed included couple associated characteristics, characteristics concerning reproductive history and external characteristics such as type of physician that referred the couple for genetic counselling and the clinical geneticist performing the counselling on PGD.

MAIN RESULTS AND THE ROLE OF CHANCE: Of 294 couples referred for counselling on PGD, 26 were not accepted because they did not meet the criteria for IVF-PGD. The remaining cohort of 268 couples consisted of two-thirds female and one-third male carriers. Main PGD indications were reciprocal translocations (83.9%) and Robertsonian translocations (16.7%). Following genetic counselling, 76.9% of included couples chose PGD as their reproductive option, the others declined PGD. Reproductive choice is not influenced by sex of the translocation carrier ($P = 0.499$), type of chromosomal abnormality ($P = 0.346$), number of previous miscarriages ($P = 0.882$), history of termination of pregnancy (TOP) because of an unbalanced fetal karyotype ($P = 0.800$), referring physician ($P = 0.208$) or geneticist who performed the counselling ($P = 0.410$).

LIMITATIONS, REASONS FOR CAUTION: This study only included recurrent miscarriage couples carrying a structural chromosomal abnormality, who were actually referred to a PGD clinic for genetic counselling. We lack information on couples who were not referred for PGD. Some of these patients may not have been informed on PGD at all, while others were not referred for counselling because they did not opt for PGD to start with.

WIDER IMPLICATIONS OF THE FINDINGS: This study shows that reproductive choices in couples with recurrent miscarriage on the

basis of a structural chromosomal abnormality are not influenced by characteristics of the couple itself, nor by their obstetric history or external characteristics. These findings suggest that a couples' intrinsic attitude towards PGD treatment is a major factor influencing their reproductive choice. Future research will focus on these personal motives that seem to push reproductive decision-making following genetic counselling in a given direction.

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Introduction

Couples who have had two or more miscarriages (recurrent miscarriage) are at increased risk of a structural chromosome abnormality in one of the partners. The incidence of balanced structural chromosome abnormalities is 0.7% in the general population and increases to 2.2% after one miscarriage, 4.8% after two miscarriages and even 5.2% after three miscarriages (De Braekeleer and Dao, 1990). Low maternal age and a history of recurrent miscarriages in siblings or parents increase the probability of carrier status. Structural chromosomal abnormalities mainly consist of reciprocal translocations (61%), Robertsonian translocations (16%), pericentric inversions (8%) and paracentric inversions (8%). Other structural chromosomal abnormalities are rare (Franssen *et al.*, 2005).

An unbalanced karyotype in the conceptus of a couple with a structural chromosomal abnormality in one of the partners may result in failure to implant, early or late miscarriage, or an ongoing pregnancy of an unbalanced fetus, resulting in physical and/or mental disabilities in the child. The risk of an unbalanced fetus varies according to the type of rearrangement and the chromosomes involved. Once a structural chromosome abnormality has been discovered in one of the partners, prenatal chromosomal analysis may be performed in subsequent pregnancies to prepare for the birth of an affected child or to allow for termination of the pregnancy in case of an unbalanced fetal karyotype. IVF with PGD has been used to avoid (recurrent) miscarriage and as an alternative to traditional prenatal diagnosis plus termination of pregnancy (Braude *et al.*, 2002; Munné, 2002; Sermon *et al.*, 2004; Verlinsky *et al.*, 2004). Fluorescence *in situ* hybridization (FISH) has been the technique most commonly used in PGD for the detection of structural chromosomal abnormalities (Scriven *et al.*, 1998; Harper *et al.*, 2012).

Although at present PGD is widely available for and utilized by recurrent miscarriage couples carrying a structural chromosomal abnormality, little is known about how these couples make their reproductive choices. Several studies have dealt with couples' motives and considerations of PGD, however those concern mostly couples with monogenic or X-linked disorders and not structural chromosomal abnormalities (Musters *et al.*, 2010; Hershberger *et al.*, 2012). Only one study with a prospective design and a relatively large sample size has been carried out in the general PGD population that included couples with structural chromosomal abnormalities. The authors reported that couples with a history of miscarriages expressed a stronger intention to use PGD (odds ratio (OR) 3.0, 95% confidence interval (CI) 1.5–5.8). However, the effect of miscarriages lost its significance when looking at the actual PGD use. In contrast, the experience of a termination of pregnancy only moderately increased the intention to use PGD, but in time, actual PGD use was significantly increased (OR 3.1, 95% CI 1.5) (van Rij

et al., 2011). The present study addresses reproductive choice after genetic counselling on PGD in recurrent miscarriage couples with a structural chromosomal abnormality. We investigated factors possibly influencing reproductive choice in these couples, such as sex of the carrier, number of previous pregnancies, miscarriages, pregnancy terminations and unbalanced ongoing pregnancies. In addition, the physician that referred the couple and the clinical geneticist performing the counselling were taken into account.

We aimed to identify factor(s) that influence these couples' decision whether or not to proceed with PGD. This information would enable clinicians to provide better guidance of and support to couples during the process of reproductive decision-making.

Materials and Methods

Study population

This retrospective cohort study included prospectively collected data and chart review data of all couples with recurrent miscarriage carrying a structural chromosomal abnormality that were referred for genetic counselling on PGD in the Netherlands between February 1996 and October 2012. The study was carried out at the Maastricht University Medical Centre+ (MUMC+), the only licensed centre for PGD in the Netherlands. PGD-related IVF treatment was conducted in a national collaboration with the University Medical Centre Utrecht and the University Medical Centre Groningen called 'PGD the Netherlands'.

Couples that were not accepted for IVF (and thus PGD) treatment were excluded. Reasons were maternal age over 40 years, BMI above 30 kg/m² and/or poor ovarian reserve, defined as an FSH > 15 IU in the early follicular phase. Also couples were excluded if PGD was not possible because of technical limitations of the FISH technique for their specific indication.

Genetic counselling was performed in a standardized way following the department protocol and included, amongst others, explanation of all procedures, complications, and risk of misdiagnosis. Couples were informed that live birth rate per started cycle is 15–20% and that not all oocyte retrievals lead to a transfer due to chromosomal imbalance in all embryos examined (Harper *et al.*, 2012). In the study period, there were six different genetic counsellors.

Outcomes

The couple's first choice after genetic counselling was recorded. Reasons to refrain from PGD after genetic counselling were categorized into different groups. When multiple reasons were listed, couples' foremost reason to refrain from PGD was listed as main reason. Most couples decided immediately after genetic intake if they wanted to proceed with PGD or not. Others needed more time and were contacted by telephone after 1 month to record their choice. All other data were collected in retrospect from couples'

medical charts. We compared clinical characteristics, including sex of the carrier, parental age and type of structural chromosomal abnormality, of the couples that chose PGD with the cohort that declined PGD. Furthermore, we analysed reproductive history, including number of previous pregnancies, miscarriages, births, termination of pregnancies (TOP) and unbalanced ongoing pregnancies. Miscarriage was defined as spontaneous pregnancy loss before 24 weeks of gestation, and biochemical pregnancies were excluded. Ongoing unbalanced pregnancy was defined as a pregnancy beyond 24 weeks of gestation with an unbalanced karyotype. Reasons for TOP were registered as 'unbalanced fetal karyotype' or 'other therapeutic or elective reasons'. Lastly, we analysed external factors such as the type of physician that referred the couple for genetic counselling on PGD. This could be their general practitioner, a clinical geneticist, a gynaecologist, or another medical specialist. Also the clinical geneticist performing the counselling on PGD in these couples was recorded. All couples who actually started PGD treatment were first seen by a reproductive specialist to whom they gave written informed consent for the IVF-PGD treatment and the follow-up

of reproductive outcome. Couples' medical data were collected by chart review. Permission for this study was not required from the institute ethical review board.

Statistical analysis

For statistical analysis categorical variables were expressed as percentage and compared using chi square tests and Fisher's exact test. Continuous variables were expressed as mean with range and compared using the independent t-test. *P*-values of <0.05 were considered to be statistically significant. Predictive Analysis Software (PASW) version 18.0 for windows (SPSS, Inc., Chicago, IL, USA) was used for the analysis.

Results

In total 294 couples with recurrent miscarriages carrying a structural chromosomal abnormality visited our PGD centre for genetic

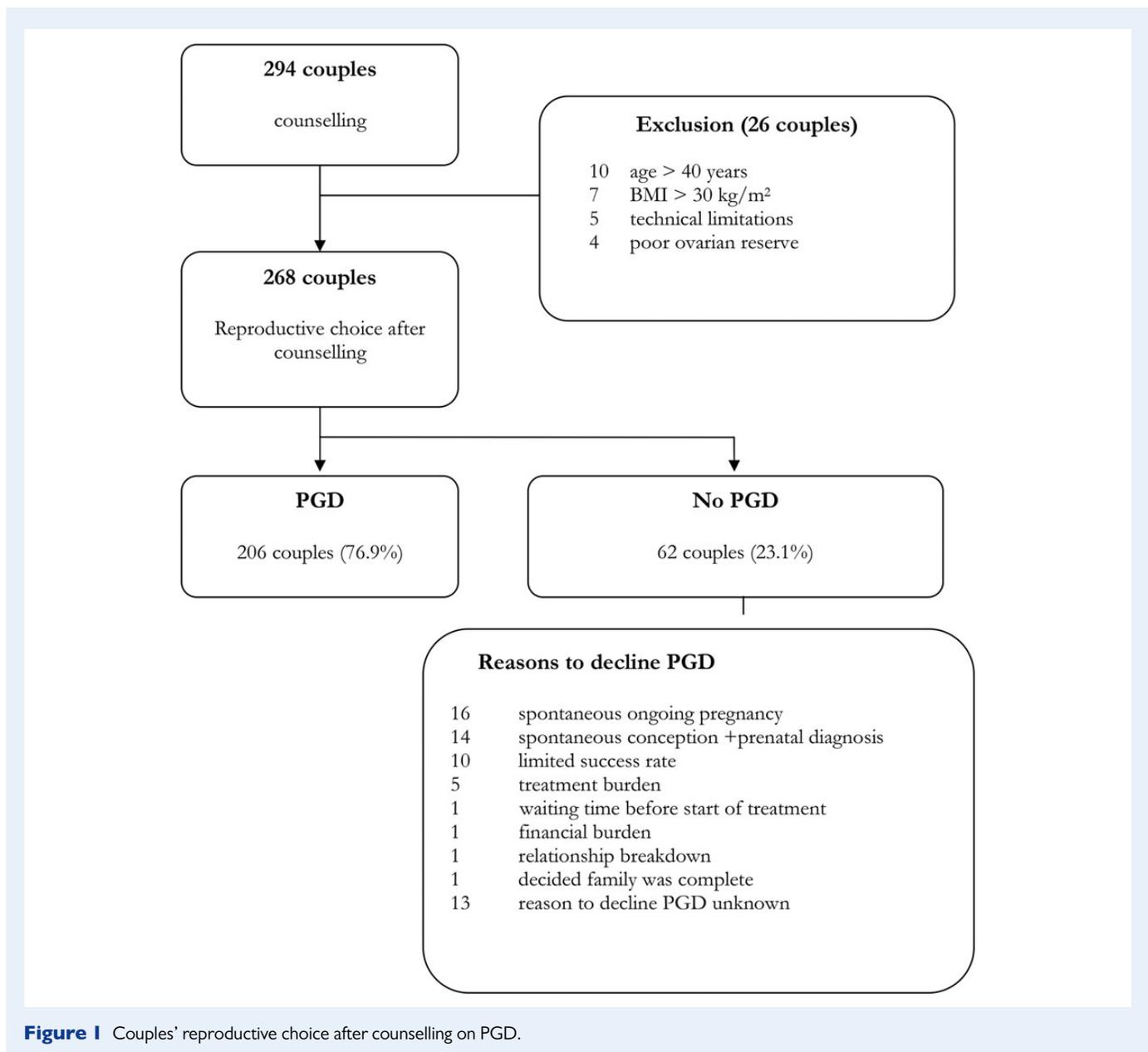


Figure 1 Couples' reproductive choice after counselling on PGD.

counselling during the study period. Of these, 21 couples were excluded because of female age ≥ 40 years ($n = 10$), BMI ≥ 30 ($n = 7$) and/or anticipated poor ovarian reserve ($n = 4$). Five couples were rejected because of the technical inability of the FISH technique to detect their specific chromosomal abnormality. Of the remaining 268 couples, two-thirds had a female ($n = 172$) and one-third a male carrier ($n = 94$). In two couples both partners carried a structural chromosomal abnormality. The structural abnormalities were reciprocal translocations (83.9%), Robertsonian translocations (16.7), inversions (2.0%) and other structural chromosomal abnormalities (one insertion, one ring chromosome, two translocations combined in one carrier).

Following genetic counselling 76.9% of couples ($n = 206$) chose PGD as their reproductive option, the other 23.1% ($n = 62$) refrained from PGD (Fig. 1). The main reasons for couples to refrain from PGD were a spontaneous intercurrent ongoing pregnancy ($n = 16$) or a preference to conceive spontaneously followed by prenatal diagnosis in case of an ongoing pregnancy ($n = 14$). Other reasons are depicted in Fig. 1.

Table I shows a comparison between couples that opted for PGD and couples that refrained from PGD after genetic counselling. There was no significant difference concerning sex of the translocation carrier ($P = 0.499$), type of chromosomal abnormality ($P = 0.346$), number of previous pregnancies ($P = 0.337$), number of births ($P = 0.124$), number of previous miscarriages ($P = 0.882$), number of TOP ($P = 0.800$), number of ongoing pregnancies with an unbalanced karyotype ($P = 0.494$) or physician that referred the couple for genetic counselling on PGD ($P = 0.208$) between both groups. Table II shows that there is no difference in reproductive choice between couples that experienced an ongoing unbalanced pregnancy (> 20 weeks of gestation) in their reproductive history compared with couples that did not ($P = 0.383$). Table III shows a comparison between the clinical geneticist that performed genetic counselling on PGD and couples' reproductive choice, and there is no significant difference ($P = 0.445$).

Discussion

PGD is offered to avoid (another) miscarriage in couples with a structural chromosomal abnormality in one of the partners and thus to increase the chance of an ongoing pregnancy. It can also be offered as an alternative to traditional prenatal diagnosis (PND) with possible pregnancy termination in case of an abnormal result. In this study we investigated whether clinical characteristics such as couple associated characteristics, reproductive history and external factors of a given couple differ in the cohort of couples that opt for PGD compared with the cohort that declines PGD after extensive genetic counselling.

Our findings that there were no significant differences between groups, may suggest that most couples with recurrent miscarriage due to a structural chromosome abnormality have already made up their mind before they visit a clinical geneticist for PGD counselling. One could presume that the majority of patients who visit a PGD clinic will opt for PGD as their way of becoming pregnant. To further investigate this hypothesis we are currently conducting a study that aims to provide an integral qualitative account of the decision-making process among these couples. Motives and considerations regarding opting for or against PGD will be studied, as well as the reproductive alternative of spontaneous conception with or without PND.

In line with the study of van Rij *et al.* we expected that couples with more miscarriages or less live born children would show the tendency

Table I Clinical characteristics of the couples who choose PGD compared with the couples that decline PGD.

	PGD (n = 206)	No PGD (n = 62)	P-value
Couple associated characteristics			
Sex translocation carrier – no. (%)			
Male	75 (36.4)	19 (30.6)	0.499*
Female	129 (62.6)	43 (69.4)	
Both partners carrying a translocation	2 (1.0)	0 (0)	
Type of chromosomal abnormality – no. (%)			
Reciprocal translocation	164 (79.6)	45 (72.6)	0.346*
Robertsonian translocation	36 (17.5)	13 (21.0)	
Inversion	3 (1.5)	3 (4.8)	
Other	2 (1.0)	0 (0)	
Combined	1 (0.5)	1 (1.6)	
Reproductive history			
Obstetric history – mean [range]			
Pregnancies	4.17 [2–12]	4.44 [2–10]	0.337 [†]
Births	0.49 [0–3]	0.65 [0–3]	0.124 [†]
Spontaneous abortion	3.59 [2–12]	3.63 [2–10]	0.882 [†]
Termination of pregnancy because of an unbalanced fetal karyotype	0.07 [0–3]	0.08 [0–3]	0.800 [†]
Ongoing pregnancy of a fetus with an unbalanced karyotype	0.07 [0–2]	0.10 [0–1]	0.494 [†]
External factors			
Referred by – no. (%)			
Clinical geneticist	127 (61.7)	45 (72.6)	0.208*
Gynaecologist	71 (34.5)	15 (24.2)	
General practitioner	5 (2.4)	0 (0)	
Paediatrician	1 (0.5)	0 (0)	
Own initiative	2 (1.0)	2 (3.2)	

*Chi square test.
[†]T-test.

to opt for PGD more often (van Rij *et al.*, 2011). However this could not be confirmed in the present study. Van Rij *et al.* included a subgroup of 64 couples with a structural chromosomal abnormality in their study. We investigated a larger group ($n = 294$) of couples carrying a structural chromosomal abnormality during a longer period (1996–2012). Besides, we expected couples who experienced an unbalanced ongoing pregnancy in their reproductive history would be more likely to choose PGD as their reproductive choice than couples who did not. However our results did not confirm this. We do not have a reasonable explanation for this, but it could be due to coincidence because of

the small number of couples that experienced an ongoing unbalanced pregnancy.

As PGD treatment is fully reimbursed by the insurance system in the Netherlands we do not expect financial burden to play a role in couples' choice. In countries where PGD treatment is not covered, cost aspects could play an important factor in couples' decision-making process.

We found a disproportion in sex of the translocation carriers, with two-thirds female versus one-third male carriers (Table I). Several studies have reported an increased frequency of balanced chromosomal abnormalities in infertile men (De Braekeleer and Dao, 1990; Gekas *et al.*, 2001). We only included fertile couples that experienced at least two miscarriages. This could explain the underrepresentation of male translocation carriers in our study. Another possible explanation might be that females carriers are more often referred for PGD for (psycho)emotional reasons. However, our study was not suitable to give information on this suggestion.

Previous studies have been performed regarding the decision-making process in couples genetically at risk (Musters *et al.*, 2010; Hershberger *et al.*, 2012). They found that couples experience a complex, dynamic and iterative decision-making process where multiple, sequential decisions are made (Hershberger *et al.*, 2012). And when informed, most couples prefer PGD over PND. However these studies mainly focus on couples with monogenic or X-linked disorders (Musters *et al.*, 2010). Couples with a balanced rearrangement with a high risk of recurrent miscarriage usually have a low risk of an unbalanced ongoing pregnancy, which is in contrast with the risk of 25 or 50% of affected offspring in monogenic disorders (Franssen *et al.*, 2006). The main reason to choose for PGD in our couples is therefore not the risk for

an affected child, but the problem of achieving an ongoing pregnancy. These couples may expect that by using PGD they can increase their reproductive fitness and decrease their time to pregnancy. Most of them will not refrain from a spontaneous pregnancy during the PGD preparation period, explaining the high number of couples that decline PGD treatment because of a spontaneous intercurrent pregnancy. Therefore the conclusions from these previous studies regarding the decision-making process on PGD in couples genetically at risk are not directly applicable to our recurrent miscarriage couples carrying a structural chromosomal abnormality.

The study of van Rij *et al.* found that the reproductive decision of couples changes over time (van Rij *et al.*, 2011). In their study 53% of couples in the overall PGD population chose PGD as their reproductive option and 47% refrained from PGD as their first choice directly after genetic counselling. In our study we found that only 23.1% of couples choose not to start PGD treatment after genetic counselling, the main reason being a spontaneous intercurrent ongoing pregnancy. This suggests these couples use PGD as a way to increase their reproductive fitness and decrease their time to pregnancy. To our knowledge this has not been shown before. Future research will have to elucidate how these spontaneous pregnancies proceeded and which decisions these couples have made in later reproductive life.

Although large for a PGD cohort, the study population of 294 couples is from a statistical point of view still rather limited and we only have information about couples with recurrent miscarriage, on the basis of a structural chromosomal abnormality, that were referred to our PGD clinic for counselling on PGD. Some patients may not be informed on PGD and others do not wish to consider PGD and are therefore not referred for counselling. It is plausible that couples willing to undergo genetic counselling in our PGD clinic already had a positive attitude towards PGD and are therefore more likely to choose PGD treatment as their reproductive option.

Understanding couples' motives and considerations when making a decision on PGD may help to improve genetic counselling and clinical care in these couples. In further research we will provide an integral qualitative account of the decision-making process motives and considerations among recurrent miscarriage couples carrying a structural chromosomal abnormality who consider PGD.

Reproductive choice in couples with recurrent miscarriage on the basis of a structural chromosomal abnormality seems not to be influenced by their clinical characteristics such as couple associated characteristics, characteristics concerning reproductive history and external characteristics. It might be influenced by the couples wish to increase their reproductive fitness and reduce time to pregnancy.

Table II Reproductive choice and presence of an unbalanced ongoing (>20 weeks of gestation) pregnancy in reproductive history.

	None (n = 250)	Present (n = 18)	P-value
Reproductive choice – no. (%)			
PGD	194 (77.6)	12 (66.7)	0.383*
No PGD	56 (22.4)	6 (33.3)	

*Fisher's exact test.

Table III Reproductive choice and genetic counsellor.

	Counsellor 1 (n = 69)	Counsellor 2 (n = 84)	Counsellor 3 (n = 31)	Counsellor 4 (n = 35)	Counsellor 5 (n = 28)	Counsellor 6 (n = 21)	P-value
Reproductive choice – no. (%)							
PGD	49 (71.0)	62 (73.8)	26 (83.9)	28 (80.0)	22 (78.6)	19 (90.5)	0.445*
No PGD	20 (29.0)	22 (26.2)	5 (16.1)	7 (20.0)	6 (21.4)	2 (9.5)	

*Fisher's exact test.

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Authors' roles

G.K., Y.H.J.M.A., R.J.T.G., C.E.M.D. participated in the conception and design of the study. G.K. collected the data, managed the data base, analysed the data. G.K., Y.H.J.M.A., R.J.T.G., C.E.M.D. contributed in the interpretation of the data. J.L.H.E., C.E.M.D., M.M., C.M.A.R., E.C. provided their expertise in the critical reading of the manuscript. All contributors reviewed and edited the manuscript and gave their final approval of the version to be published.

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Conflict of interest

None declared.

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