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Review

Does preimplantation genetic diagnosis improve reproductive outcome in couples with recurrent pregnancy loss owing to structural chromosomal rearrangement? A systematic review

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KEY MESSAGE
Despite the purported benefits of preimplantation genetic diagnosis among patients with structural chromosomal rearrangements and a history of recurrent miscarriage, this systematic review demonstrates that natural conception offers similar pregnancy outcomes compared with IVF–PGD. Hence, these patients should be counselled that assisted reproduction technologies should not be offered first-line given the cost and unproven benefits.

A B S T R A C T

Recurrent pregnancy loss (RPL) is a common, yet elusive, complication of pregnancy. Among couples at high risk of RPL, such as those carrying a structural chromosomal rearrangement, preimplantation genetic diagnosis (PGD) has been proposed as a tool to improve live birth rates and reduce the incidence of miscarriage; however, no clear consensus has been reached on its benefits in this population. This systematic review summarizes existing published research on the effect of PGD on pregnancy outcomes among carriers of chromosomal abnormalities with RPL. A comprehensive search of common databases was conducted, which yielded 20 studies. Meta-analysis was precluded owing to significant heterogeneity between studies. The primary outcome of interest was live birth rate (LBR), and a pooled total of 847 couples who conceived naturally had a LBR ranging from 25–71% compared with 26.7–87% among 562 couples who underwent IVF and PGD. Limitations of the study include lack of large comparative or randomized control studies. Patients experiencing RPL with structural chromosomal rearrangement should be counselled that good reproductive outcomes can be achieved through natural conception, and that IVF–PGD should not be offered first-line, given the unproven benefits, additional cost and potential complications associated with assisted reproductive technology.

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Introduction

Human reproduction is an intricate process that requires a synchronous dialogue between a myriad of genetic, anatomic and environmental factors. Naturally, this results in frequent errors, with an estimated 15–25% of human conceptions failing to achieve viability and resulting in early pregnancy loss (El Hachem et al., 2017). As an extension, recurrent pregnancy loss (RPL) is a distinct disorder defined by two or more failed clinical pregnancies and affects 2–5% of couples (Practice Committee of the American Society for Reproductive Medicine, 2012). Among many different causes, structural chromosomal rearrangements substantially increase the incidence of RPL and ultimately contribute to a significant cause of physical and psychological distress. Consequently, significant efforts are being made to improve treatment modalities, reduce the risk of miscarriage and decrease the time needed to achieve a successful pregnancy among carriers of structural chromosome rearrangements (Zidi-Jrah et al., 2015).

Epidemiologic and pathologic studies suggest that structural chromosomal rearrangements, such as reciprocal and Robertsonian translocations, contribute to 3–4% of cases of RPL (De Braekeleer and Dao, 1990). Hence, among known carriers of chromosomal abnormalities, technologies such as preimplantation genetic diagnosis (PGD) to screen and prevent the transfer of genetically inherited unbalanced embryos have been shown in several small observational studies to improve live birth rates (LBR) and reduce the incidence of unfavourable sequelae such as miscarriage (Munne et al., 1998; Munné et al., 2000). More recent prospective studies (Franssen et al., 2011; Platteau et al., 2005) and a prior systematic review (Hirshfeld-Cytron et al., 2011), however, found no overall differences in LBR compared with natural conception. In addition, a cost-analysis by Murugappan et al. (2015) provided insight into the significant cost differences between IVF–PGD and expectant management despite similar pregnancy outcomes in women with unexplained RPL of whom one of the partners is a carrier of a structural chromosomal rearrangement. Hence, given the invasive and costly nature of IVF–PGD, as well as potential complications associated with ovarian stimulation, the value of such a procedure is less clear.

No clear evidence-based consensus has been reached on whether the benefits of PGD outweigh the costs among couples with known structural chromosomal rearrangement and a history of recurrent pregnancy loss. This is because results are conflicting and well-controlled prospective studies are lacking.

To further elucidate the evidence in support of and against the routine use of PGD in this population group, we systematically reviewed the literature on live birth and miscarriage rates among known carriers of structural chromosomal rearrangement with a history of RPL.

Materials and methods

This systematic review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines (Liberati et al., 2009).

Search strategy and allocation of studies

We systematically searched the following electronic databases: *EMBASE* (Ovid), *MEDLINE* (Ovid), *Cochrane Central Register of Controlled Trials* and *Grey Literature Database* from inception to July 2017, as well as the reference lists of the selected articles.

We used the following search terms in each of the databases: 'recurrent or repeated or habitual or pregnancy loss or miscarriage or spontaneous abortion or fetus wastage, combined with translocation, reciprocal translocation, Robertsonian translocation, Inversion, chromosomal structural rearrangement or abnormality or aberration or preimplantation genetic diagnosis'.

Eligibility criteria and data extraction

All randomized, non-randomized and cohort studies that reported reproductive outcome after natural conception or PGD for structural chromosomal rearrangement in couples with a history of recurrent pregnancy loss were reviewed. In this case, RPL was defined as a history of two or more clinical pregnancy losses at less than 20 weeks' gestation. Additional studies were extracted from the references in the full-text articles. Articles were restricted to English language only. We also considered published abstracts from conferences but excluded review articles, case reports and case series.

Studies were grouped according to three categories: studies dealing with medical management or natural conception only; studies dealing with PGD only; and studies comparing natural conception and PGD.

Two reviewers (MI and SA) independently searched and reviewed the retrieved articles and results were compared. Any disagreement was resolved by discussion. The final decision was taken by the senior investigator (MB).

The primary outcome of interest was live birth rate per couple, defined as the percentage of couples achieving a live birth after 24 weeks' gestation. Secondary outcomes of interest included miscarriage rate per couple and time to successful pregnancy.

Results

A flow chart of the search strategy and studies included in our systematic review is presented in **Figure 1**. Most of the studies were retrospective and case-controlled. Unfortunately, there were no randomized controlled trials (RCT), but two comparative studies were identified, one of which was an abstract. A search of studies describing reproductive outcomes after natural conception and IVF with PGD resulted in 285 publications. After rejecting articles that did not address our research question, 20 studies were included for our analysis. Specifically, 10 studies evaluated reproductive outcomes after natural conception, eight studies after IVF and PGD (**Figure 2**), and two studies directly compared differences in live birth rates between couples conceiving naturally compared with after IVF and PGD (**Figure 2**).

Reproductive outcomes after natural conception

A detailed summary of the 10 studies that investigated reproductive outcomes after attempted natural conception among couples with a known chromosome rearrangement and a history of recurrent pregnancy loss is presented in **Table 1** (Carp et al., 2004; Desjardins and Stephenson, 2012; Dong et al., 2014; Flynn et al., 2014; Franssen et al., 2006; Kabessa et al., 2017; Kochhar and Ghosh, 2013; Pal et al., 2009;

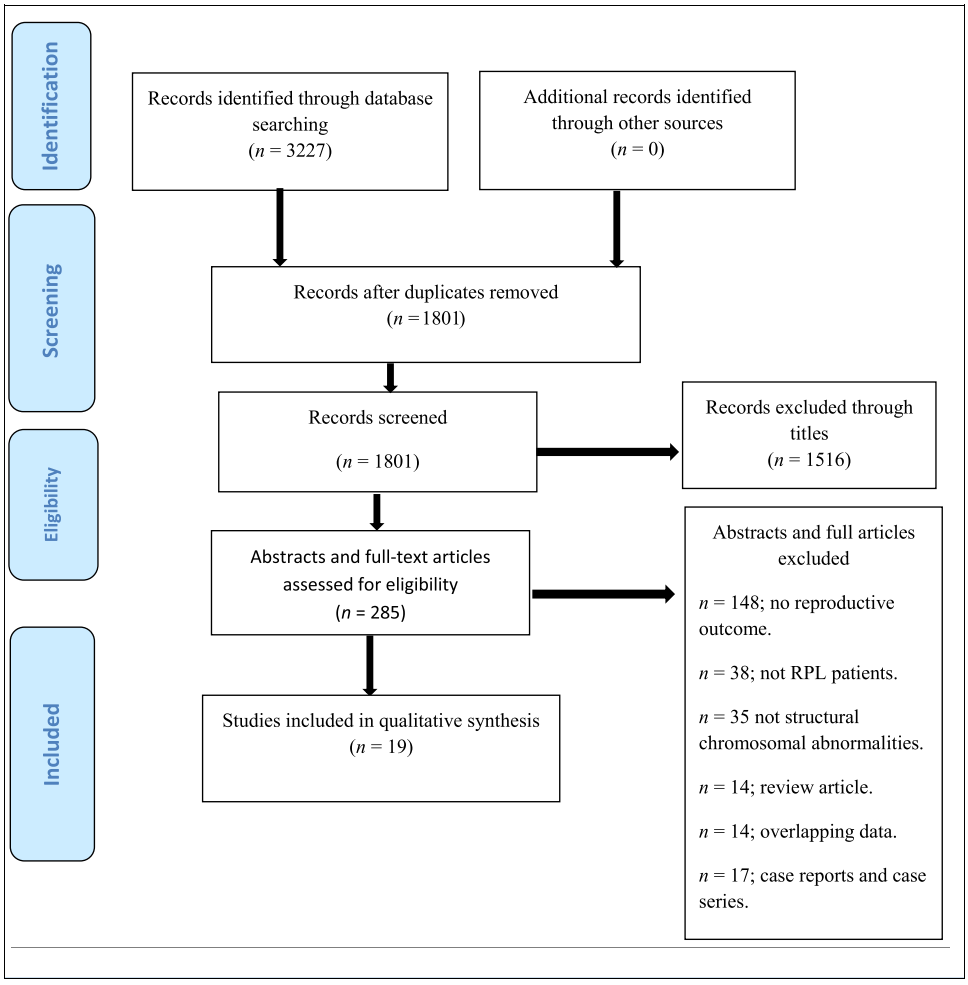

Figure 1 – Flow chart of included studies and search strategy.

Stephenson and Sierra, 2006; Sugiura-Ogasawara et al., 2008). Across all studies, the cumulative number of couples included was 772. Average maternal age ranged from 29.8 to 33.6 years, with an average of 2.6 to 4.2 miscarriages before chromosome analysis and mean follow-up period ranging from 12 to 146 months. The distribution of structural chromosome rearrangements between patients is outlined in **Table 2**. As shown in **Table 1**, there reproductive outcomes seem to vary substantially between studies of LBR after chromosome analysis. Among studies (Carp et al., 2004; Desjardins and Stephenson, 2012; Dong et al., 2014; Flynn et al., 2014; Franssen et al., 2006; Stephenson and Sierra, 2006; Sugiura-Ogasawara et al., 2008) that compared reproductive outcomes between paternal and maternal abnormal chromosome carriers, a consistent negligible incidence of viable unbalanced offspring was observed (data not shown).

The time to conception was reported either in months or cycles and varied substantially from 2 to 11.7 months, with a LBR ranging from 25–71% compared with 55–78.7% among patients with a history of recurrent miscarriage and normal chromosome analysis (**Table 1**). The miscarriage rate was 25–55.6% in patients with structural chromosome rearrangements compared with 21–45.8% in chromosomally normal patients. Although LBR and miscarriage rates were similar between cases and controls in most studies, Franssen et al. (2006) reported a lower live birth rate and higher miscarriage rate in patients with structural chromosome rearrangements compared with chromosomally normal patients after natural conception.

Reproductive outcomes after IVF–PGD

A summary of the studies reporting outcomes after IVF–PGD is presented in **Table 2** (Chang et al., 2012; Farahmand et al., 2016; Fischer et al., 2010; Kato et al., 2016; Keymolen et al., 2012; Kyu Lim et al., 2004; Otani et al., 2006; Pundir et al., 2016). A total of 512 couples were included and all of the studies were retrospective cohorts. The mean maternal age was 31.05 to 36.5 years, and the mean number of previous miscarriages before IVF–PGD ranged from 3.3 to 4. A total of 964 IVF with PGD cycles were carried out, and live birth rates varied from 26.7–87%, with associated miscarriage rates ranging from 5.3–39% (**Table 2**). It is important to note that Keymolen et al. (2012) and Chang et al. (2012) reported live birth rates per embryo transfer compared with other studies that reported cumulative pregnancy rates. Similarly, Lim et al. (2004) reported pregnancy rates per assisted reproductive technology (ART) cycle started compared with cumulative or pregnancy rates per embryo transferred. Variations were observed with live birth; some studies reported mean or median time in months, whereas others reported time in number of cycles. This greatly limited the comparability of these data between studies.

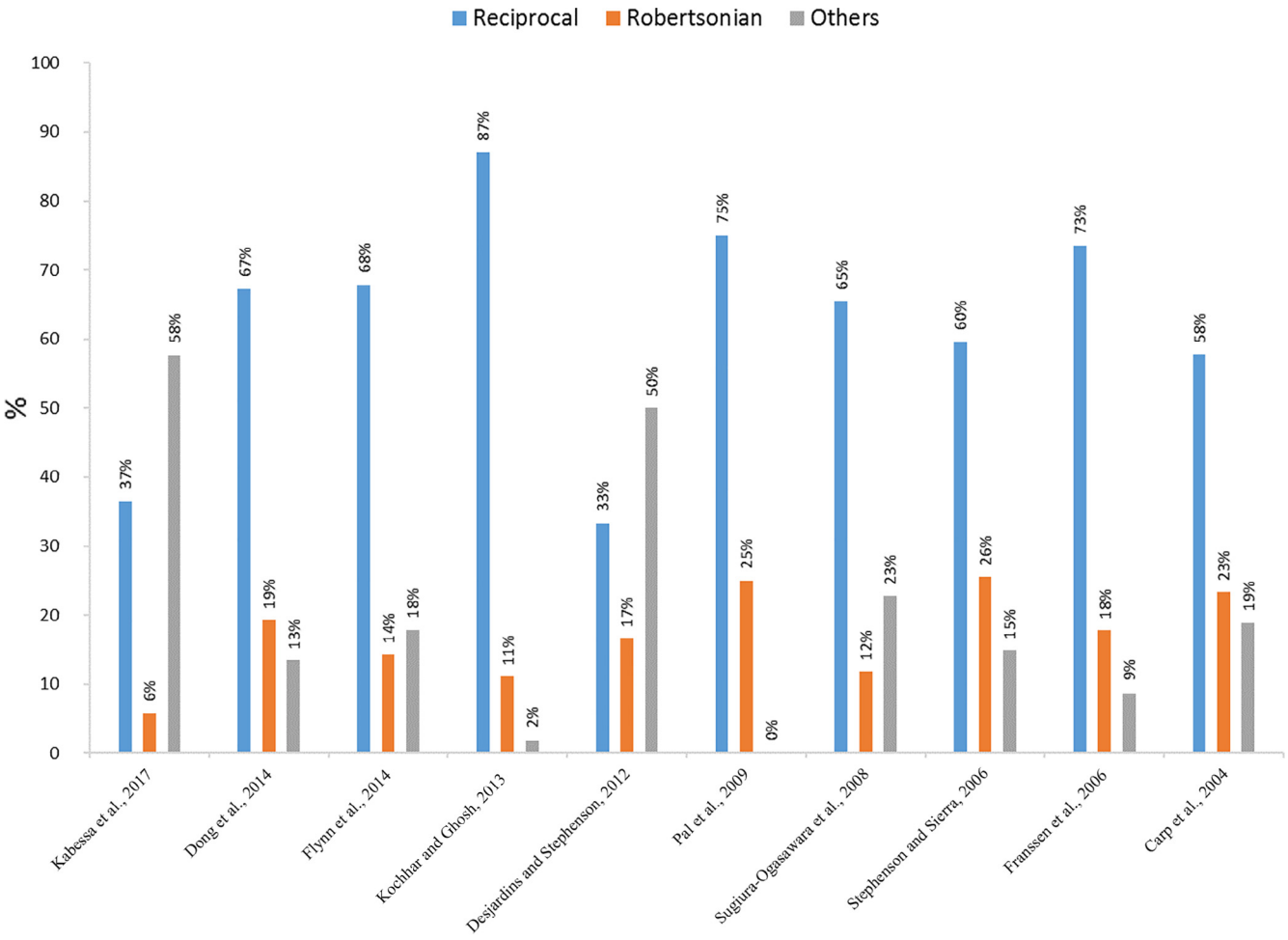

Figure 2 – Proportional distribution of structural chromosomal abnormalities among natural conception studies.

Studies comparing reproductive outcomes after IVF–PGD versus natural cycle

A summary of studies comparing PGD and natural conception is presented in **Table 3** (Bedaiwy et al., 2016; Ikuma et al., 2015). A total of 50 couples were included in the IVF–PGD group and 75 couples in the natural conception group. One of the studies was an abstract (Bedaiwy et al., 2016). The mean age was similar between groups: 30.9 and 31.8 years in the natural conception group compared with 30.6 and 31.6 years in IVF–PGD cases. Previous miscarriages were also similar in the two studies, with mean values of 2.8 and 3.1 in the natural conception women versus 3.2 and 3.4 in the IVF–PGD groups. Regarding reproductive outcomes, the LBR were 66.6 and 67.6% in the IVF–PGD groups compared with 55.8 and 65.4% in the natural conception groups (**Table 3**). Time to live birth varied greatly being 12.4 and 23.3 months in the IVF–PGD groups compared with 11.4 and 17.5 months in the natural conception groups.

Discussion

Despite its relatively common occurrence, spontaneous pregnancy loss remains an exceptionally traumatic event for many couples (Lee and Slade, 1996). Particularly in cases of recurrent pregnancy loss, common symptoms include a sense of desperation, vulnerability and powerlessness; these symptoms can be further exacerbated by unnecessary tests and investigations that fail to enhance their reproductive outcomes (Speraw, 1994). In this way, it is imperative that clinical and diagnostic tests focus on optimizing three main outcomes: maximizing the chances of live birth, minimizing the risk of further miscarriage and optimizing the time required to achieve pregnancy.

Munne et al. (1998) proposed the clinical utility of ART with PGD among parental carriers of structural chromosomal rearrangement, ushering in a new generation of genetic diagnostics and therapeutics for infertility patients with genetic abnormalities such as Robertsonian translocations or reciprocal translocations. As these couples are at increased risk of recurrent loss owing to the production of chromosomally unbalanced gametes, it seems logical that screening of embryos through IVF–PGD would improve live birth rates and reproductive outcomes. No RCT, however, have been conducted to directly validate the benefits of such technology, and most studies in this domain have been limited by their retrospective nature. Franssen et al. (2011) first systematically reviewed the evidence among 595 couples, and concluded that the paucity of available data, including a large proportion of patient series and case reports, precluded any conclusive benefit of PGD over natural conception in this subgroup.

Table 1 – Basic clinical characteristics of patients in studies reporting pregnancy outcomes from natural conception.

Author	Design	Study period	Follow-up (months)	Couples, (n)	Maternal age (years) (mean ± SD)	Number of prior miscarriages (mean ± SD)	Miscarriage rate	Live birth rate (mean) (%)	Mean time to conception (months)
Kabessa *et al.*, 2017	Case-control	1996–2015	NA	52	30.92 ± 5.81	4.02 ± 1.65	NA	54.16	NA
Dong *et al.*, 2014	Case-control	2007–2011	12	52	31.6 ± 6.1	2.6 ± 0.9	25	46	NA
Flynn *et al.*, 2014	Case-control	1992–2011	NA	28	29.9 ± 6.1	3.0	55.60	64.30	NA
Kochhar and Ghosh, 2013	Prospective cohort	2006–2009	24	54	30[a]	3.4	29.60	67	NA
Desjardins and Stephenson, 2012	Prospective cohort	2004–2011	NA	25	33.6 ± 5.4	2.76	30	63	1.7 ± 1.3 cycles
Pal *et al.*, 2009	Prospective cohort	2005–2006	12–24	4	(24–32)[b]	NA	50	25	NA
Sugiura-Ogasawara *et al.*, 2008	Prospective cohort	2003–2005	60	129	31 ± 3.9	3.1 ± 1.2	37	63	10.1 ± 7.7
Stephenson and Sierra, 2006	Prospective cohort	1992–2005	146	51	29.8 ± 5.0	3.43	29	71	NA
Franssen *et al.*, 2006	Case-control	1992–2000	24	278	31.8 ± 4.3	3.0	48	59	NA
Carp *et al.*, 2004	Retrospective cohort	1984–2001	24	99	32.8 ± 5.8	4.2 ± 1.6	54.80	45	11.7 ± 13.6

[a] Maternal age reported as a median.
[b] Maternal age was reported as a range.
NA, not available.

Significantly more robust and reliable evidence, however, has now been published; hence, the goal of this study was to exclusively focus on examining more rigorously designed retrospective and prospective studies that assess the clinical benefits of PGD for this select cohort of patients. On the basis of our systematic review of 1409 couples, which included two recently published prospective comparative studies, it seems that IVF–PGD offers no clear benefit to reproductive outcomes over natural conception. Despite the ongoing heterogeneity among studies on this topic, several relevant and practical conclusions can be drawn to inform clinical practice.

First and foremost, it is important to note that several published studies have shown that good reproductive outcomes may be achieved through natural conception among couples who have experienced RPL who are thoroughly evaluated and treated for reversible concomitant factors (**Table 1**). For example, Stephenson and Sierra (2006) found a cumulative live birth rate of 71% after natural conception over a 146 month follow-up in a Canadian RPL cohort. Similarly, Sugiura-Ogasawara et al. (2008) reported a 63% LBR with natural conception over a 60-month period and Kochhar and Ghosh (2013) reported that two-thirds of couples with a parental carrier of a structural chromosome rearrangement are likely to have a live birth within 2 years. Flynn et al. (2014) reported a cumulative LBR of 64.3% in this group and found no differences in LBR between pregnancies with maternal or paternal carriers as well as those with balanced reciprocal compared with Robertsonian translocations. Finally, Franssen et al. (2011) also demonstrated that 73.5% of couples with RPL and structural chromosome rearrangement achieved a live birth through natural conception, compared with 64–84% cumulative LBR after PGD in a pooled review of case reports. Hence, current evidence suggests that good reproductive outcomes can be achieved through natural conception alone among patients who are evaluated and treated for other reversible causes of RPL.

Beyond live birth rates, another purported benefit of IVF–PGD in this subgroup is an overall reduction in the risk of recurrent miscarriage and time to live birth owing to the ability to selectively screen and transfer genetically normal embryos, particularly as this subgroup is at an increased risk of producing gametes with either unbalanced translocations that are non-viable or paracentric inversions, which can result in live born children with birth defects (Morin et al., 2017). Indeed, Chang et al. (2012) found that PGD significantly reduced the rate of pregnancy loss (6.6%) and shortened the average time from cycle start to positive serum HCG (3.3 months or 1.6 cycles) compared with the same couples' histories before PGD (mean duration of infertility of 3.2 years), thereby proposing that PGD may be beneficial in this cohort. This is consistent with the time scale reported in other studies (Fischer et al., 2010; Keymolen et al., 2012; Otani et al., 2006) for couples with RPL undergoing ART–PGD, with an average time to conception of 1.4 cycles of ART and a median of 15.5 months to live birth. Patients in the study by Chang et al. (2012), however, were not evaluated and treated for immunological disorders and luteal phase defects, which are likely to bias the reported results. Conversely, Desjardins and Stephenson (2012) showed, in a similar carrier cohort, that evaluation and management of concomitant factors of RPL without PGD resulted in an index LBR of 63% and an average time to conception of 1.7 natural cycles. Furthermore, their study showed that only a minority of miscarriages and no live births were found to have an unbalanced chromosomal aberration, which is consistent with other studies (Carp et al., 2004; Dong et al., 2014; Flynn et al., 2014; Franssen et al., 2006; Stephenson and Sierra, 2006;

Table 2 – Basic clinical characteristics of studies reporting pregnancy outcomes of IVF and preimplantation genetic diagnosis cycles.

Author	Design	Couples, (n)	Maternal age at PGD (mean ± SD)	Type of rearrangement (n)	Previous miscarriages (mean ± SD, mean ± range or range)	Duration of the study	Cycle started	Embryo transfer cycles	Outcomes of IVF–PGD cycles			
									Mean pregnancy rate (%)	Mean Live birth rate per couple (%)	Mean miscarriage rate (%)	Time to live birth
Pundir *et al.*, 2016	Retrospective cohort	91	34.5 ± 4	All Reciprocal	4 ± 2	2000–2012	171	107	44	32	39	Mean 28 months (range 12–79 months)
Kato *et al.*, 2016	Retrospective cohort	52	36.5 ± 3.8	Reciprocal (46) Robertsonian (6)	(2–7)	2007–2013	239	71	60.6[a] per embryo transfer 18% per oocyte retrieval	76.9	7.0	Median 2 years
Farahmand *et al.*, 2016	Retrospective cohort	21	31.05 ± 3.56	Reciprocal (14) Robertsonian (1) Others (6)	NA	2008–2014	26	24	73.07[a]	61.54	6.84	NA
Keymolen *et al.*, 2012	Retrospective cohort	40	32.8	All Reciprocal	NA	1997–2007	79	39	17.9 per embryo transfer	26.7 per embryo transfer	27.3	Mean 15.5 months (range 9–76 months)
Chang *et al.*, 2012	Retrospective cohort	34	32.04 ± 3.5	All Robertsonian	2.87 ± 0.86	2000–2009	66	57	26.3[a] per embryo transfer	41.2	6.6	Time to positive serum HCG[c] 3.3 months (1.6 cycles)
Fischer *et al.*, 2010	Retrospective cohort	192	34	Structural chromosomal abnormalities[b]	3.8 (3–7)	2008	272	NA	25	87	13	Time to successful pregnancy <4 months
Otani *et al.*, 2006	Retrospective cohort	33	32.7	Reciprocal (29) Robertsonian (4)	3.5 ± 1.9	2004–2006	41	NA	46.3[a]	47.2 (ongoing pregnancy rate)	5.3	Time to successful pregnancy 1.24 IVF cycles
Lim *et al.*, 2004	Retrospective cohort	49	31.4 ± 3.9	Reciprocal (43) Robertsonian (6)	2.9 (0–8)	2001–2002	70	64	40.8%[a]	30.6	15	NA
Total number		512				1997–2014	964					

[a] Clinical pregnancy.
[b] The type of structural chromosomal abnormality not included.
[c] For pregnancies that resulted in a third trimester ongoing pregnancy or a live birth.
NA, not available; PGD, preimplantation genetic diagnosis.

Table 3 – Basic clinical characteristics of studies comparing pregnancy outcomes from IVF and preimplantation genetic diagnosis versus natural conception.

Author	Design	Number of patients		Patient history			Outcomes		Mean time to live birth (months)
				Age (mean ± SD)	Previous miscarriage (mean ± SD)	Previous live birth (mean ± SD) (%)	Mean live birth rate (%)	Mean Miscarriage rate (%)	
Ikuma et al., 2015	Retrospective comparative study	PGD	37	30.6 ± 3.0	3.37 ± 1.26	0.14 ± 0.35	67.6	15.7	12.4
		Natural conception	52	30.9 ± 3.8	3.10 ± 1.07	0.15 ± 0.36	65.4	38.3	11.4
Bedaiwy et al., 2016	Retrospective comparative study	PGD	13	31.6 ± 1.9	3.23 ± 1.0	0.08 ± 0.28 (2.1)	66.6	33.3	23.3
		Natural conception	23	31.8 ± 4.0	2.81 ± 0.85	0.40 ± 0.50 (11.0)	55.8	47.7	17.5

PGD, preimplantation genetic diagnosis.

Sugiura-Ogasawara et al., 2008), and most likely reflects the body's natural mechanism to identify and prevent the implantation and development of chromosomally abnormal embryos (Morin et al., 2017). In this way, the miscarriage rate and overall time to live birth does not seem to be consistently improved through the use of IVF–PGD over natural conception.

In perhaps the most reliable data to date, our systematic review included two comparative studies by (Ikuma et al., 2015) and (Bedaiwy et al., 2016). Ikuma et al. (2015) recruited 52 patients considering natural conception and compared the live birth rate with 37 patients undergoing IVF–PGD. They reported a similar LBR and time to pregnancy, although the miscarriage rate was significantly lower in the PGD cohort. This is consistent with previously reported miscarriage rates with PGD that range from 0–10% (Chang et al., 2012; Farahmand et al., 2016; Fischer et al., 2010; Kato et al., 2016; Keymolen et al., 2012; Kyu Lim et al., 2004; Otani et al., 2006; Pundir et al., 2016), whereas miscarriage rates in patients with natural conception are in the range of 25–55.6% (Carp et al., 2004; Desjardins and Stephenson, 2012; Dong et al., 2014; Flynn et al., 2014; Franssen et al., 2006; Kochhar and Ghosh, 2013; Pal et al., 2009; Stephenson and Sierra, 2006; Sugiura-Ogasawara et al., 2008). Conversely (Bedaiwy et al., 2016) reported a similar LBR and miscarriage rate in patients who did or did not undergo PGD but also found no reduction in miscarriage with PGD. Despite their limited sample size, these studies offer a more direct and reliable comparison between natural conception and IVF–PGD than the aforementioned observational studies, and reinforce the conclusions that IVF–PGD offers no pregnancy outcome benefits over natural conception among patients with RPL and structural chromosomal rearrangement.

A major strength of this systematic review is the breadth and scope of the included studies. A total of 20 studies encompassing a diverse range of ethnic and geographic cohorts were included, which reduces the risk of selection bias. Furthermore, a total of 1409 couples with pure structural chromosomal rearrangement and their associated reproductive outcomes were analysed with solid inclusion and exclusion criteria. Most notably, individual case reports and case series were excluded owing to significant heterogeneity, risk of bias and lack of generalizability of this type of data. Generally, the data presented were more reliable and based on clear hypothesis generation compared with a previous systematic review (Franssen et al., 2011) Nevertheless, our analysis demonstrates that the quality of evidence on this topic remains suboptimal and precludes any definitive comparisons between PGD and natural conception in relation to reproductive outcomes in this population cohort.

The studies included in this systematic review have several limitations. First, most were retrospective, not randomized, and lacked a well-defined population. As a result, direct comparison was challenging owing to inherent differences in patient cohorts. For instance, most studies offered limited background information about the populations in question, such as specific health variables and prior investigations that may influence reproductive outcomes. In fact, few studies even emphasized that appropriate investigation and treatment of concomitant factors was carried out before couples proceeded with IVF–PGD over natural conception. Furthermore, many studies did not explicitly investigate the genetics of the conceptuses or stratify patients based on primary or secondary RPL, which is clinically important, as distinctive differences in cytogenic findings, aneuploidy rates and morphologic defects have been characterized for each group (Feichtinger et al., 2017). As reproductive outcomes and treatment approaches can vary significantly between patients with primary and

secondary RPL, the heterogeneity between population cohorts ultimately limits the potential for any definitive comparisons.

Second, terminology, study design and reported outcomes among the included studies were heterogeneous; in particular, RPL was defined as either two or three prior losses with varying gestational age cut-offs. Similarly, outcomes of interest and length of follow-up varied widely, with some studies reporting pregnancy outcomes based on conception rates, whereas others followed patients for up to 146 months and reported more clinically relevant live birth rates.

Among studies that included LBR outcomes after ART, most publications reported LBR per embryo transfer, which can significantly overestimate the reproductive outcomes in this cohort compared with outcomes reported per cycle started (Fischer et al., 2010). For instance, (Stephenson and Goddijn, 2011) noted that a re-interpretation of results by Fischer et al. (2010) based on cycles started yielded a far lower LBR of 22% per cycle started compared with the natural conception LBR of 63% reported by Desjardins and Stephenson (2012). In fact, the above findings support the conclusion drawn by Franssen et al. (2011) that IVF–PGD yielded significantly poorer LBR compared with natural conception among couples with RPL and structural chromosome rearrangement.

The included studies span over 2 decades; therefore, inherent differences and evolution of PGD techniques are likely to contribute to the heterogeneity of results observed between studies. The inherent complexity of controlling for a myriad of factors that may influence PGD outcomes, including sex of the carrier, type of translocation and type of biopsy or analysis method, has led to the significant development of more accurate and reliable PGD techniques over the past 25 years based on new high-resolution platforms that are able to detect small segmental imbalances. In this systematic review, most reported studies used fluorescent in-situ hybridization, which has a limited ability to detect translocations across all 24 chromosomes simultaneously. Conversely, Fiorentino et al. (2011) used single nucleotide polymorphism and comparative genomic hybridization, which has been shown to detect translocations more accurately and hence improve overall pregnancy rates (Alfarawati et al., 2011; Velilla et al., 2002). Most recently, next-generation sequencing has been used for whole chromosome screening, and further improves the resolution of PGD to detect segmental abnormalities associated with chromosome rearrangements (Morin et al., 2017).

To improve the quality of evidence, prospective randomized studies should encompass a unified cohort of patients, use standardized PGD protocols based on accurate comparative genomic hybridization or next-generation sequencing platforms, and include a sufficiently long follow-up to accurately report meaningful reproductive outcomes. Furthermore, future studies should also report adverse outcomes related to patients undergoing IVF–PGD, including the significant cost of treatment and associated health risks such as OHSS. Murugappan et al. (2015) demonstrated a 100-fold difference in cost ($45,300 versus $418 per live birth) between IVF–PGD and expectant management in a RPL population, although not specifically studying couples with structural chromosomal rearrangements. A follow-up intention-to-treat analysis was able to attribute the radically different costs to a high incidence of cancelled cycles in the IVF–PGD group (Murugappan et al., 2016). Ultimately, these findings are particularly relevant to patients, and clinicians should take treatment cost into account when counselling patients about the risks and benefits of different treatment options.

In conclusion, this systematic review demonstrates that similar LBR, time to subsequent conception and miscarriage rates are observed through natural conception and IVF–PGD in couples experiencing recurrent miscarriage and carrying a structural chromosome rearrangement. Well-controlled randomized controlled trials are still needed to directly compare reproductive outcomes after PGD compared with natural conception in this subgroup of patients. At present, patients should be informed of the risk and significantly higher cost associated with IVF–PGD, as well as the lack of available evidence regarding its benefits. As with all cases of RPL, couples with a known carrier of a structural chromosome rearrangement should first be thoroughly evaluated for all possible causes of PRL and treated accordingly. These couples should also be fully informed of all possible treatment options and reassured that they have a good prognosis for successful pregnancy. Ultimately, a judicious approach to invasive and costly treatment is advisable, as our systematic review demonstrates insufficient data are available to recommend IVF–PGD over natural conception in couples with structural chromosomal rearrangement experiencing RPL.

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