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# Reproductive outcome after PGD in couples with recurrent miscarriage carrying a structural chromosome abnormality: a systematic review

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## ABSTRACT

**BACKGROUND** Preimplantation genetic diagnosis (PGD) has been stated to improve live birth rates compared with natural conception in couples with recurrent miscarriage (RM) carrying a structural chromosome abnormality. It is unclear to what extent this claim can be substantiated by evidence. A systematic review of the literature was performed on the reproductive outcome of these couples after natural conception or after PGD.

**METHODS** MEDLINE, EMBASE and the Cochrane database were searched until April 2009. Trials, patient series and case reports describing reproductive outcome in couples with RM carrying a structural chromosome abnormality after natural conception and/or after PGD were included. Since no randomized controlled trials or non-randomized comparative studies were found, separate searches for both groups were conducted. Primary outcome measure was live birth rate per couple. Secondary outcome measure was miscarriage rate per couple.

**RESULTS** Four observational studies reporting on the reproductive outcome of 469 couples after natural conception and 21 studies reporting on the reproductive outcome of 126 couples after PGD were found. After natural conception, live birth rate per couple varied between 33 and 60% (median 55.5%) after parental chromosome analysis; miscarriage rate ranged from 21

to 40% (median 34%). After PGD, live birth rate per couple varied between 0 and 100% (median 31%) after parental chromosome analysis; miscarriage rate ranged from 0 to 50% (median 0%).

**CONCLUSIONS** Currently, there are insufficient data indicating that PGD improves the live birth rate in couples with RM carrying a structural chromosome abnormality.

## **INTRODUCTION**

Couples with two or more miscarriages are at increased risk of either of the partners carrying a structural chromosome abnormality (Tharapel et al., 1985; de Braekeleer et al., 1990). In couples with recurrent miscarriage (RM), the incidence of either of the partners being a carrier of a structural chromosome abnormality is 3–4%, mainly consisting of reciprocal translocations (61%) and Robertsonian translocations (16%) (Clifford et al., 1994; Franssen et al., 2005). Other abnormalities include pericentric inversions and paracentric inversions. The karyotype of the products of conception in these carrier couples can be normal, balanced or unbalanced, the latter leading to miscarriage, stillbirth or a child born with major congenital defects and severe mental handicaps. In view of these consequences, most guidelines advise prenatal chromosome analysis in future pregnancies to make termination of pregnancy possible in case of an unbalanced fetal karyotype (ACOG, 2002; RCOG, 2003; Jauniaux et al., 2006; NVOG, 2007).

Nowadays, preimplantation genetic diagnosis (PGD) is an established alternative to invasive prenatal diagnosis and as such may avoid termination of pregnancy in couples with a high risk of transmitting genetic disorders such as X-linked diseases, various monogenic diseases and also for structural chromosome abnormalities (Handyside et al., 1990; Geraedts et al., 2001; Sermon et al., 2004). PGD has also been proposed to improve live birth rates in couples with RM who carry a structural chromosome abnormality (Munne et al., 2000; Otani et al., 2006). The rationale behind the use of PGD for this purpose is that relatively more live births will be achieved and that the number of miscarriages will be reduced by eliminating the transfer of unbalanced embryos. Since PGD is invasive and requires IVF-ICSI, the claim that PDG increases live birth rates should be substantiated before this technique is introduced into daily clinical practice. To improve informed decision-making, we systematically searched the literature on live birth rates and miscarriage rates after natural conception and after PGD, in couples with a history of two or more miscarriages and carrying a structural chromosome abnormality.

## **METHODS**

### **Search strategy**

EMBASE (Ovid, 1980 to April 2009), MEDLINE (Ovid, 1950 to April 2009) and Cochrane Central Register of Controlled Trials (Central, April 2009) were systematically searched as well as the reference lists of the selected articles.

Initially, a search was conducted for randomized controlled trials (RCTs) and/or non-randomized comparative studies comparing natural conception with PGD in couples with RM carrying a structural chromosome abnormality. Since no such RCTs or non-randomized comparative studies were found, two separate searches were conducted; one for all study designs reporting on the reproductive outcome after attempting natural conception, using the keywords 'recurrent miscarriage' and 'structural chromosome abnormalities', and one for the reproductive outcome after PGD, using the keywords 'preimplantation genetic diagnosis', 'recurrent miscarriage' and 'structural chromosome abnormalities'. The searches were performed by a clinical librarian (J.L.)

The appendix shows the search strategies in EMBASE, and adapted for MEDLINE, which were used to investigate the reproductive outcome after natural conception and after PGD in couples with RM and carrying a structural chromosome abnormality.

### **Study selection and data extraction**

All cohort studies, patient series and case reports describing the reproductive outcome after attempting natural conception or after PGD for structural chromosome abnormalities and in which couples with a history of at least two miscarriages could be identified were eligible for this review. Structural chromosome abnormalities were classified according to the recommendations of The International Standing Committee

for Human Cytogenetic Nomenclature (ISCN, 2005). RM was defined as the loss of two or more pregnancies before the 20th week of gestation regardless of the outcome of intervening pregnancies. The intervention was PGD by polar body biopsy or by blastomere biopsy. The primary outcome measure was live birth rate per couple, defined as the percentage of couples achieving a live birth. Secondary outcome measure was miscarriage rate per couple.

Data were extracted by four independent investigators (M.T.M.F., J.C.K., M.G. and A.M.M.), and results were compared. Any disagreement was resolved by discussion.

## RESULTS

### RESULTS OF THE SEARCH

The flow chart of study inclusion is presented in Fig. 1. There were no RCTs or non-randomized comparative studies comparing reproductive outcome after attempting natural conception to reproductive outcome after PGD. The search on studies describing reproductive outcome after attempting natural conception resulted in 945 publications. After rejection of articles not addressing the research question, four articles were included. The search for studies reporting on the reproductive outcome in couples with RM carrying a structural chromosome abnormality after PGD resulted in 359 publications. After rejection of articles not addressing the research question, 21 articles were included.

#### [FIGURE 1]

##### Reproductive outcome after natural conception

The main characteristics of the four studies on reproductive outcome after attempting natural conception in couples with RM carrying a structural chromosome abnormality are presented in Table I (Carp et al., 2004; Franssen et al., 2006; Stephenson and Sierra, 2006; Sugiura Ogasawara et al., 2008). These were two prospective cohort studies and two retrospective cohort studies. The total number of couples included was 469. The average number of miscarriages prior to parental chromosome analysis varied between 2.9 and 4.3 and the average maternal age varied from 29.8 to 32.8 years. In one of these studies, 21 couples were mosaic for a numeric chromosome abnormality (Carp et al., 2004). The reproductive outcome of these couples could not be distinguished from couples with structural chromosome abnormalities. Data on live birth rate and miscarriage rate per couple after parental chromosome analysis are summarized in Table II. Studies are divided into those reporting on reproductive outcome of the first pregnancy after parental chromosome analysis and studies reporting on the cumulative reproductive outcome of pregnancies after parental chromosome analysis (0–12 pregnancies). In total, 12% (range: 3–26%) of all couples failed to conceive. Live birth rate per couple varied between 33 and 60% (median 55.5%) after parental chromosome analysis; miscarriage rate ranged from 21 to 40% (median 34%). In none of the first pregnancies after parental chromosome analysis were viable unbalanced offspring reported.

#### [TABLE 1]

#### [TABLE 2]

In the two studies reporting on the cumulative reproductive outcome of all reported pregnancies after parental chromosome analysis, at least one healthy child was documented in 64% and in 83% of the couples, respectively and at least one miscarriage was documented in 21% and in 49% of the couples in these two studies, respectively (Franssen et al., 2006; Stephenson and Sierra, 2006). In one study, two fetuses with an unbalanced karyotype were detected at prenatal diagnosis (0.4%) and two children with an unbalanced karyotype were born (0.4%) (Franssen et al., 2006).

### REPRODUCTIVE OUTCOME AFTER PGD

The main characteristics of the 21 studies presenting results after PGD are listed in Table III (Conn et al., 1998; Munne et al., 1998a, b, c; Conn et al., 1999; Van Assche et al., 1999; Willadsen et al., 1999; Coonen et al., 2000; Escudero et al., 2000; Lee and Munne, 2000; Munne et al., 2000; Durban et al., 2001;

Escudero et al., 2001; Fridstrom et al., 2001; Scriven et al., 2001; Emiliani et al., 2002; Pujol et al., 2003; Simopoulou et al., 2003; Kyu Lim et al., 2004; Sampson et al., 2004; Otani et al., 2006). In total, these studies included 164 couples receiving PGD for structural chromosome abnormalities, among whom 126 couples with a history of two or more miscarriages prior to PGD were identified. Baseline characteristics of these 126 couples are listed in Table III. The average number of miscarriages prior to PGD varied between 2.0 and 7.7, and the average maternal age varied between 29.0 and 37.5 years. In 104 couples, one of the partners carried a reciprocal translocation, in 20 couples a Robertsonian translocation and in two couples a pericentric inversion. The results after PGD in these 126 couples are presented in Table IV. One of the studies (Otani et al., 2006) only reported ongoing pregnancies and miscarriages after PGD, and did not detail the number of live births: since this study presents one of the largest series of couples with RM carrying a structural chromosome abnormality who had undergone PGD, it was decided not to exclude these data but to consider these ongoing pregnancies as live births. Live birth rate per couple varied between 0 and 100% (median 31%) after parental chromosome analysis; miscarriage rate ranged from 0 to 50% (median 0%). Live birth rate per started cycle varied between 0 and 100% (median 17%) after parental chromosome analysis; miscarriage rate per started cycle ranged from 0 to 50% (median 0%). No studies reported that viable unbalanced offspring occurred after PGD.

[TABLE 3]

[TABLE 4]

[TABLE 5]

## DISCUSSION

In couples trying to conceive, RM causes tremendous grief, feelings of insecurity and ambivalence about each subsequent pregnancy. Once a structural chromosome abnormality is detected in one of the partners, couples are confronted with difficult choices, such as whether or not to try to conceive again, to undergo prenatal diagnosis in future pregnancies and to terminate a pregnancy once an unbalanced fetal karyotype is found. Although PGD might seem an attractive alternative for couples desperately seeking help to carry a pregnancy to term, its benefits should be clear before introducing this technique into daily clinical practice.

We found that little information was available addressing our specific research question. This review deals with the specific subgroup of couples with RM carrying a structural chromosome abnormality and not with couples with RM in general or with couples carrying a structural chromosome abnormality without RM in their obstetric history. Unfortunately, in larger series describing the reproductive outcome after PGD in carriers of structural chromosome abnormalities in general, such as the data from the European Society of Human Reproduction and Embryology PGD Consortium, details on obstetric history are not presented or not provided by case (Goossens et al., 2009). The obstetric history, including the previous number of miscarriages, cannot be extracted from these data.

The absence of RCTs and non-randomized comparative studies makes a direct comparison between PGD and natural conception in couples with RM carrying a structural chromosome abnormality impossible. The best outcome measures to directly compare the reproductive outcome of these groups would be the time required to obtain a healthy live birth or the live birth rate in a fixed time period. None of the studies carried out thus far have included these details. Data can only be derived from observational studies or even from case reports. Considering the poor quality and the heterogeneity of these studies, performing a meta-analysis was considered inappropriate. Describing the results of two separately performed systematic reviews, as presented in this paper, is therefore the best alternative for investigating the potential benefits of PGD over natural conception. Other weaknesses of the individual studies reporting on the reproductive outcome after PGD were that none of them reported on the costs of PGD, or complications related to the IVF-ICSI procedure, such as ovarian hyperstimulation syndrome.

The results after PGD might be inflated as these data are based upon small series and case reports that are notorious for being prone to publication bias. Also, one of the studies included in this review (Otani et al., 2006) only reported on ongoing pregnancies, not number of live births: in this study subsequent miscarriage or stillbirth might have occurred, leading to a lower live birth rate.

Little is known on the karyotype of miscarried conceptuses in couples with RM carrying a structural chromosome abnormality, since karyotyping miscarriage tissue in these couples is not routine practice. It has been described that after natural conception in carrier couples with RM, ~25% of the miscarried conceptuses has an unbalanced karyotype (Carp et al., 2006; Stephenson and Sierra, 2006). In addition, it has been reported that after PGD in carrier couples, only 25% of the embryos with a diagnostic result were transferable, confirming the high level of chromosomally abnormal embryos in these patients (Goossens et al., 2009). This might explain why the results of PGD in these couples are rather poor. For unbalanced products of conception, miscarriage serves as a natural selection mechanism which, to date, cannot be improved by clinical interventions.

In theory, offering PGD to couples with RM and carrying a structural chromosome abnormality might be beneficial to prevent the birth of children with an unbalanced karyotype and to reduce the number of miscarriages. We know, however, that the risk of viable unbalanced offspring in these couples is very low after natural conception (Franssen et al., 2006). The finding of a low miscarriage rate after PGD was to be expected since PGD selects for the replacement of unbalanced embryos. It has been reported that couples with RM and carrying a structural chromosome abnormality are at a higher risk of repeat miscarriages compared with non-carrier couples (Carp et al., 2004; Franssen et al., 2006; Stephenson and Sierra, 2006; Sugiura Ogasawara et al., 2008). In unbalanced products of conception, miscarriage serves as a natural selection mechanism.

In some of the studies included in this review, preimplantation genetic screening (PGS) for aneuploidies (or PGD-S) had been conducted as well as PGD for structural chromosome abnormalities, which might contribute to a lower miscarriage rate. However, PGD for aneuploidies in couples of advanced maternal age has been shown to be not beneficial (Mastenbroek et al., 2007). The low miscarriage rate found in this review could also be the result of publication bias.

## CONCLUSION

In conclusion, at present there are insufficient data indicating that PGD improves the live birth rate in couples with RM carrying a structural chromosome abnormality. More research on this topic is urgently required. We would welcome future attempts to perform RCTs and to present details on obstetric history so that it might become clear whether subgroups of carrier couples exist that might benefit from PGD. To date, it remains a matter of debate whether a lower miscarriage rate after PGD in these couples would justify its use in light of the limited change in live birth rate, the high costs and procedure-related complications, given the scarce data. It is our opinion that, currently, there are insufficient arguments to introduce PGD, with its high costs and potential complications related to the IVF procedure, into the daily clinical practice for couples with RM carrying a structural chromosome abnormality.

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## APPENDIX

Search strategies used in systematic review of literature:

Natural conception:

- (1) recurrent abortion/or Spontaneous Abortion/((habitual\* or recurr\* or multiple or repeat\* or repetit\* or consecutive or unexplained or spontaneous\*) adj4 (Abortion\* or miscarriage\*)).tw.
- (2) ((habitual\* or recurr\* or multiple or repeat\* or repetit\* or consecutive or unexplained or spontaneous\*) adj4 ((pregnanc\* or fetal or fetal or fetus\* or fetus\* or embryo\* or intrauterine or intrauterine or in-utero) adj2 loss\*)).tw.
- (3) ((habitual\* or recurr\* or multiple or repeat\* or repetit\* or consecutive or unexplained) adj4 ((fetal or fetal or fetus\* or fetus\* or embryo\* or intrauterine or intrauterine or in utero) adj2 death\*)).tw.
- (4) ((three or "3" or two or "2" or frequent or previous or more) adj2 (Abortion\* or miscarriage\* or ((pregnanc\* or fetal or fetal or fetus\* or fetus\* or embryo\* or intrauterine or intrauterine or in-utero) adj2 loss\*) or ((fetal or fetal or fetus\* or fetus\* or embryo\$ or intrauterine or intrauterine or in-utero) adj2 death\*)))).tw.
- (5) ((IRM or RSA or RM or RPL) and (pregnan\* or abortion\*)).tw.
- (6) or/1–6
- (7) exp human/
- (8) 7 and 8
- (9) structural chromosome aberration/or chromosome duplication/ or chromosome insertion/or double minute chromosome/or partial monosomy/or ring chromosome/or exp chromosome deletion/or chromosome inversion/or exp chromosome translocation/

- (10) genetic recombination/
  - (11) (Structural adj2 chromosom\* adj2 (abnormal\* or aberra\* or anomal\* or defect\* or error\*)).tw.
  - (12) translocation\*.tw.
  - (13) (chromosom\* and (deletion\* or inversion\*)).tw.
  - (14) (chromosom\* adj2 rearrangement\*).tw.
  - (15) robertson\*.tw. and (chromosom\* or transloc\*).mp.
  - (16) or/10–16
  - (17) 9 and 17
  - (18) ((preimplant\* or pre-implant\*) and (diagn\* or screen\*)).mp.
  - (19) ((Preimplant\* or pre-implant\*) adj10 (testing or tests or test)).tw.
  - (20) (pgd\* or (pgs and screen\*)).mp.
  - (21) ((preimplant\* or pre-implant\*) and genetic\*).tw.
  - (22) (aneuploid\$ adj10 (diagn\$ or screen\$)).mp.
  - (23) or/19–23
  - (24) 18 and 24
  - (25) exp controlled clinical trial/or double blind procedure/or single blind procedure/or randomization/or placebo/
  - (26) (randomized and controlled and trial).ti,ab.
  - (27) ((controlled adj (trial or study)) or (controlled adj clinical adj (trial or study))).ti,ab.
  - (28) or/26–28
  - (29) 18 and 24 and 29
  - (30) from 30 keep 1
  - (31) from 18 keep 1–568
  - (32) from 32 keep 1–10
- PGD:
- (1) ((preimplant\$ or pre-implant\$) adj4 (diagnos\$ or testing or tests)).mp.
  - (2) ((prenatal\$ or antenatal\$) adj2 genetic adj2 (diagnos\$ or testing or tests)).mp.
  - (3) pgd.mp.
  - (4) or/1–3
  - (5) ((habitual\$ or recurr\$ or multiple or repeat\$ or repetit\$ or three or "3" or two or "2") adj4 (((pregnanc\$ or fetal or fetal or fetus) adj2 loss\$) or (Abortion\$ or miscarriage\$))).ti,ab.
  - (6) ((IRM or RSA or RM or RPL) and (pregnan\$ or abortion\$)).ti,ab.
  - (7) recurrent Abortion/
  - (8) or/5–7
  - (9) structural chromosome aberration/or chromosome duplication/or chromosome insertion/or double minute chromosome/or partial monosomy/or ring chromosome/or exp chromosome deletion/or chromosome inversion/or exp chromosome translocation/
  - (10) (structural adj2 chromosom\$ adj2 (abnormal\$ or aberra\$ or anomal\$ or defect\$ or error\$)).tw.
  - (11) exp chromosome translocation/or translocation\$.mp.
  - (12) chromosom\$ and (deletion\$ or inversion\$)).mp.
  - (13) or/9–12
  - (14) 4 and (8 or 13)

TABLES AND FIGURES

Figure 1

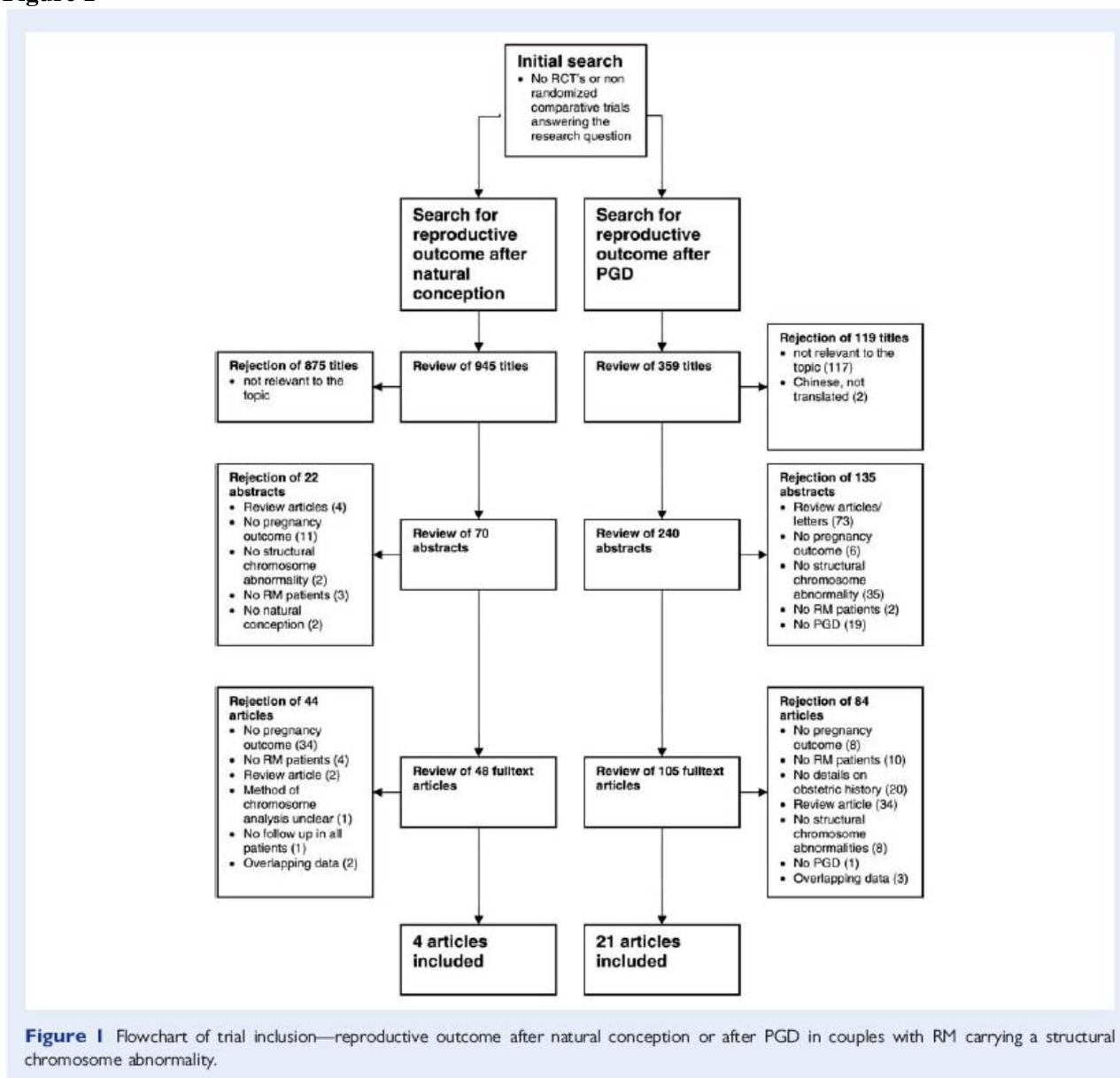


Figure 1 Flowchart of trial inclusion—reproductive outcome after natural conception or after PGD in couples with RM carrying a structural chromosome abnormality.

**Table 1**

**Table I** Characteristics of the four included studies on reproductive outcome after attempting natural conception in couples with RM carrying a structural chromosome abnormality.

	Design	No. of couples	Patient characteristics			Follow-up	
			Average maternal age (years) $\pm$ SEM	Average no. of previous miscarriages	Average no. of previous live births	Data on first pregnancy only or long-term follow-up	Mean follow-up (years)
Carp <i>et al.</i> (2004)	Single centre retrospective cohort	99	32.8 $\pm$ 5.8	4.3 $\pm$ 1.6		First pregnancy	1.0 $\pm$ 1.1
Sugiura Ogasawara <i>et al.</i> (2008)	Single centre prospective cohort	71	31.4 (23–42)	2.9 (2–6)	0.2 (0–1)	First pregnancy	0.8 $\pm$ 0.6
Stephenson and Sierra (2006)	Single centre prospective cohort	52	29.8 $\pm$ 5.0	3.4		Long-term	Duration not mentioned 0–3 pregnancies
Franssen <i>et al.</i> (2006)	Multicentre retrospective cohort	247	32.1 $\pm$ 4.3	3		Long-term	5.9 (2.0–11.4) 0–12 pregnancies

Number of couples per study varied from 52 to 247.

**Table 2**

**Table II** Live birth rate and miscarriage rate per couple after natural conception in couples with RM carrying a structural chromosome abnormality.

Study	No. of couples	Live births after parental chromosome analysis n (%)	Miscarriages after parental chromosome analysis n (%)	No. of (potential) viable unbalanced offspring
(a) Reproductive outcome in the first pregnancy after parental chromosome analysis (including couples with failure to conceive)				
Carp <i>et al.</i> (2004)	99	33 (33%)	40 (40%)	None reported
Franssen <i>et al.</i> (2006)	247	148 (60%)	91 (37%)	0
Stephenson and Sierra (2006)	52	29 (56%)	11 (21%)	0
Sugiura Ogasawara <i>et al.</i> (2008)	71	39 (55%)	22 (31%)	0
(b) Reproductive outcome of all pregnancies after parental chromosome analysis				
Franssen <i>et al.</i> (2006)	247	205 (83%) <sup>a</sup>	120 (49%) <sup>b</sup>	4 2 at PND 2 live births
Stephenson and Sierra (2006)	52	33 (64%) <sup>a</sup>	11 (21%) <sup>b</sup>	0

Studies are categorized by (a) the first pregnancy after parental chromosome analysis and (b) all pregnancies reported after parental chromosome analysis. PND, invasive prenatal diagnosis.

<sup>a</sup>Couples with at least one live birth after parental chromosome analysis.

<sup>b</sup>Couples with at least one miscarriage after parental chromosome analysis.

**Table 3**

**Table III** Characteristics of the 21 included studies reporting on reproductive outcome after PGD in couples carrying a structural chromosome abnormality in which couples with RM could be identified.

		Design	No. of couples with RM	Average maternal age (years)	Average no. of previous miscarriages	Average no. of previous live births
1	Van Assche et al. (1999)	Descriptive	1	29	5	0
2	Conn et al. (1998)	Descriptive	1	37	2	0
3	Conn et al. (1999)	Descriptive	1	32	4	1
4	Coonen et al. (2000)	Descriptive	2	–	6.5 (6–7)	0
5	Durban et al. (2001)	Descriptive	5	35.2 (32–37)	3.2 (5–5)	0
6	Emiliani et al. (2002)	Descriptive	1	37	6	0
7	Escudero et al. (2000)	Descriptive	2	30	2.5 (2–3)	0.5 (0–1)
8	Escudero et al. (2001)	Descriptive	1	33	3	0
9	Fridstrom et al. (2001)	Descriptive	8	–	2.8 (2–4)	1 (1–2)
10	Kyu Lim et al. (2004) <sup>a</sup>	Cohort study	49	31.4 ± 3.9	2.9 (0–8)	0.2 (0–1)
11	Lee and Munne (2000)	Descriptive	1	31	2	1
12	Munne et al. (1998a)	Descriptive	1	32	5	0
13	Munne et al. (1998b)	Descriptive	3	33.7 (28–37)	4.7 (4–5)	0.3 (0–1)
14	Munne et al. (1998c)	Descriptive	2	35 (33–37)	≥6	0
15	Munne et al. (2000)	Descriptive	3	–	7.7 (2–15)	0
16	Otani et al. (2006) <sup>b</sup>	Descriptive	33	32.7 (26–41)	3.5 ± 1.9	0
17	Pujol et al. (2003)	Descriptive	2	37.5 (36–39)	4 (3–5)	0
18	Sampson et al. (2004)	Descriptive	4	29.8 (25–33)	2.3 (2–3)	0.5 (0–2)
19	Scriven et al. (2001)	Descriptive	1	34	4	0
20	Simopoulou et al. (2003)	Descriptive	3	33.7 (32–36)	3.7 (2–5)	0
21	Willadsen et al. (1999)	Descriptive	2	34 (31–37)	≥2	–

Number of couples per study varied from 1 to 49 couples.

<sup>a</sup>Including seven couples without two or more miscarriages prior to PGD, which could not be separated.

<sup>b</sup>Ongoing pregnancies, no live births reported.

**Table 4**

**Table IV** Results of PGD in couples with at least two miscarriages, prior to current PGD, carrying a structural chromosome abnormality.

	No. of couples	Started cycles	Embryo transfer cycles	Transferred embryos	TE per embryo transfer cycle	Pregnancies resulting in live birth n (%)	No. of healthy children	Miscarriages	Other pregnancy outcome
1	Van Assche et al. (1999)	1	3	2	7	3.5 (3–4)	0 (0%)	0	0
2	Conn et al. (1998)	1	3	2	2	1	0 (0%)	0	1 biochemical
3	Conn et al. (1999)	1	2	1	1	1 (1)	0 (0%)	0	1 ongoing
4	Coonen et al. (2000)	2	4	2	3	1.5 (1–2)	1 (50%)	1	0
5	Durban et al. (2001)	5	5	2	3	1.5 (1–2)	0 (0%)	0	1
6	Emiliani et al. (2002)	1	2	2	3	1.5 (1–2)	1 (100%)	2	0
7	Escudero et al. (2001)	1	2	2	6	3 (3)	1 (100%)	1	0
8	Escudero et al. (2000)	2	2	2	2	1 (1)	1 (50%)	2	0
9	Fridstrom et al. (2001)	8	16	9	14	1.6 (1–2)	2 (25%)	3	0
10	Kyu Lim (2004) <sup>a</sup>	49	70	64	169	2.6 (1–4)	15 (31%)	16	3
11	Lee and Munne (2000)	1	1	2	4	2	1 (100%)	1	0
12	Munne et al. (1998a)	1	2	0	0	0 (0)	0 (0%)	0	0
13	Munne et al. (1998b)	3	3	2	3	1.5 (1–2)	1 (33%)	2	0
14	Munne et al. (1998c)	2	2	2	4	2 (2)	1 (50%)	2	1
15	Munne et al. (2000)	3	3	3	6	2 (1–3)	0 (0%)	0	0
16	Otani et al. (2006)	33	–	41	–	Max 3	18 <sup>b</sup> (55%)	–	1
17	Pujol et al. (2003)	2	2	2	2	1 (1)	0 (0%)	0	0
18	Sampson et al. (2004)	4	5	1	1	1 (1)	0 (0%)	0	0
19	Scriven et al. (2001)	1	1	1	3	3 (3)	1 (100%)	3	0
20	Simopoulou et al. (2003)	3	3	3	5	1.7 (1–3)	1 (33%)	1	0
21	Willadsen et al. (1999)	2	2	1	1	1	0 (0%)	0	1 affected child <sup>c</sup>

ET, embryo transfer; TE, transferred embryos.

<sup>a</sup>Including seven couples without two or more miscarriages prior to PGD, which could not be separated.

<sup>b</sup>Only ongoing pregnancies, no live births reported.

<sup>c</sup>Child with 46,XX karyotype and severe ventricular septal defect with complications.

**Table 5**

**Table V** Summary of live birth rate and miscarriage rate per couple after natural conception and after PGD in couples with RM carrying a structural chromosome abnormality.

	No. of studies	No. of couples	Started cycles	No. of live births (%)	No. of miscarriages (%)
Natural conception					
First pregnancy after natural conception	4	469	NA	249 (range: 33–60%, median: 55.5%)	164 (range: 21–40%, median: 34%)
All pregnancies after natural conception <sup>a</sup>	2	299	NA	238 <sup>b</sup> (range: 64–83%, median: 73.5%)	131 <sup>c</sup> (range: 21–49%, median: 35%)
PGD	21	126	133	44 (range: 0–100%, median 31%) <sup>d</sup>	6 (range: 0–50%, median: 0%)

NA, not applicable.

<sup>a</sup>0–12 pregnancies.

<sup>b</sup>Couples with at least one live birth.

<sup>c</sup>Couples with at least one miscarriage.

<sup>d</sup>Including 18 ongoing pregnancies.