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Pregnancy outcome after preimplantation genetic screening or natural conception in couples with unexplained recurrent miscarriage: a systematic review of the best available evidence

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The objective of this systematic review was to assess live birth rates and miscarriage rates after preimplantation genetic screening or natural conception for unexplained recurrent miscarriage. There were no randomized controlled trials or comparative studies found on this topic. Until data from randomized controlled trials become available, this review summarizes the best available evidence of the efficacy of preimplantation genetic screening vs. natural conception.

Recurrent miscarriage (RM), defined as two or more miscarriages, affects approximately 5% of all couples (1). Current diagnostic procedures can identify etiologic factors in approximately 50% of these couples (1). Unexplained RM is a distressing condition for the affected couple and a frustrating problem for the clinician, because there is no effective therapy for these couples as of yet. Some authors have proposed preimplantation genetic screening (PGS) for couples with unexplained RM. The rationale behind the use of PGS in cases of unexplained RM is that aneuploidy of the embryo may be the cause of the RM (2-6) .

Data from the European Society of Human Reproduction and Embryology preimplantation genetic diagnosis consortium shows an increase of PGS cycles for couples with RM, from 285 in 2003 to 990 in 2006 [7] and [8] . The current guidelines from this consortium do not give a recommendation in favor of or against PGS for couples with RM (9). On the other hand, the American Society of Reproductive Medicine guideline states that the available evidence does not support the use of PGS as currently performed to improve live birth rates in patients with recurrent pregnancy loss (10), because randomized control trials are not available. Because PGS is still being performed for this indication worldwide (8), we systemically searched the literature for the best available evidence on live birth rates and miscarriage rates after PGS and natural conception (NC) in couples with unexplained RM.

The following electronic databases were searched: MEDLINE (1950 to December 2009), EMBASE (1980 to December 2009), and the Cochrane Central Register of Controlled Trials (CENTRAL) (December 2009). A search strategy was carried out based on the following terms: recurrent miscarriage, preimplantation genetic screening, natural conception, live birth rate, and miscarriage rate (Supplemental Figure 1, Supplemental Table 1 and Supplemental Table 2, available online). The search was performed by a clinical librarian (J.L.).

Unexplained RM was defined as two or more preceding—not necessarily consecutive— miscarriages (≤20 weeks' gestational age) without an identified underlying cause (i.e., women with normal uterine cavities, negative for antiphospholipid syndrome, and normal parental karyotypes) (11).

We first searched for randomized control trials and/or comparative studies comparing PGS with NC in couples with unexplained RM. Subsequently, if these could not be found, a secondary search was performed in which we searched for cohort studies or randomized studies in which PGS or NC were compared with an intervention other than the one under investigation in this study. For NC, studies were only selected if the study included nonpregnant patients, to allow for a fair comparison with data from PGS studies. In addition, because PGS cycles are usually completed within as restricted a time frame as 1 year, we included NC studies with a follow-up duration of 1 year. Outcome measures were live birth rate per couple, defined as the percentage of couples for whom the pregnancy resulted in live birth, and miscarriage rate per couple, defined as the loss of a pregnancy before the 20th week of gestation.

As a first step, titles were screened. In addition, we hand-searched the reference lists of selected studies, of recent reviews on the subject, and the abstract books of the annual meetings of the American Society of Reproductive Medicine and the European Society of Human Reproduction and Embryology. The abstracts of the included titles were read. Next, full articles of the approved abstracts were read. The final selection of the studies was reached by consensus of two separate reviewers (A.M. and M.G.) after they had read the full articles. Any disagreement was settled by a third investigator (S.R.). In case published data was incomplete, corresponding authors were contacted for clarification.

We found no randomized controlled trials, nor did we find nonrandomized comparative studies in which PGS was directly compared with NC (primary search, Supplemental Fig. 1).

Because the aim of our review was to find the best available evidence, we performed a secondary search in which we searched for cohort studies or randomized studies in which PGS was compared with an intervention other than the one under investigation in this study. This search resulted in 196 publications on women with unexplained RM receiving PGS (secondary search, Supplemental Fig. 1 ([12-23, 26-63]}(192 from electronic searchers, 3 from abstract books searched manually, 1 from reference lists of relevant publications). Of these, 157 were excluded because it was clear from the title that they did not fulfill the selection criteria. From the remaining 39 articles, 20 were excluded on the basis of the abstract. For the remaining 19 articles we obtained the full manuscripts; 15 were excluded (Supplemental Fig. 1). The total number of studies included in the review was therefore four (5, 6, 24 and 25) (Table 1).

The secondary search, in which we searched for cohort studies or randomized studies in which NC was compared with an intervention other than the one under investigation in this study, resulted in 2,272 publications (Supplemental Fig. 1) (2,272 from electronic searchers, 0 from reference lists of relevant publications). Of these, 2,187 publications were excluded because it was clear from the title that they did not fulfill the selection criteria. From the remaining 85 articles, 39 were excluded on the basis of the abstract. We obtained the full manuscripts of the remaining 46 articles; 39 articles were excluded. Therefore, a total of seven studies on NC were included (64-70) (Table 1).

The exact reasons for exclusion of the titles, abstracts, and full manuscripts are shown in Supplemental Fig. 1.

In the four observational studies concerning unexplained RM and PGS, the number of included couples was 181 and varied from 10 to 58 per study. The mean number of previous miscarriage varied between 2.8 and 4.7, and the mean maternal age varied from 35.4 to 37.6 years. In all studies the embryos were biopsied at day 3 of development, and one or two blastomeres were aspirated and analyzed. The fluorescence in situ hybridization (FISH) probes used for aneuploidy screening differed in each study (minimum of three and maximum of nine probes). Additionally, the number of embryos transferred varied per study; from single-embryo transfer to five embryos per transfer. There was an average of 1.3 cycles (range, 1.2–1.6 cycles) per couple in the four studies.

Live birth rate per couple varied between 19% and 46% (mean 35%; median 40%), and miscarriage rate ranged from none to 10% (mean 9%; median 9%).

In the seven studies found for NC in RM couples the control arms of randomized controlled trials (comparing NC with any intervention other than PGS) and prospective cohorts were included. The patients in six of the seven studies received placebo treatment (64-67, 69,70) . This varied from autologous blood

injections to vaginal placebo pessaries to saline injections. In one study, patients used expectant management (68). The number of included couples was 261 and varied from 19 to 85. The mean number of previous miscarriages varied between 3.0 and 5.6, and the mean maternal age varied from 25.1 to 34.6 years. The live birth rate ranged from 11% to 61% (mean 41%; median 36%), and the miscarriage rate ranged from 14% to 52% per couple (mean 28%; median 25%).

Our systematic search of the literature revealed no randomized controlled trials or nonrandomized comparative studies directly comparing the efficacy of PGS with NC for couples with unexplained RM. The need for randomized controlled trials on this topic is evident, considering the increasing numbers of PGS performed for this indication worldwide [7] and [8] .

A secondary search strategy, for the best available evidence, allowing other study comparisons or cohort studies on PGS and NC, provided data on a total of 442 couples (181 PGS and 261 NC).

The studies that were finally included have a number of limitations. The quality of the available data was low, owing to the limited number of observational studies, small sample sizes, and heterogeneity between studies. The heterogeneity among the PGS studies was considerable; the mean RM rate varied between 2.8 and 4.7; chromosomes tested per blastomere varied from three to nine, and the number of embryos transferred per cycle varied between one and five. There was also heterogeneity among the NC studies. The mean maternal age varied from 25.1 to 34.6 years, and in six of the seven included studies placebo treatment was administered to the patients because of the randomized controlled design of these studies. The heterogeneity between the two study groups, apart from receiving PGS or expectant management, was also apparent. The mean maternal age within studies varied almost 10 years; in the PGS studies maternal age varied between 35.4 and 37.6 years, whereas in the NC studies mean maternal age varied between 25.1 and 34.6 years.

Because of the above-mentioned heterogeneity between the PGS and NC studies, no meta-analysis could be performed, and as a result we can only summarize the data by tabulation and listing of ranges. When focusing on the data at hand, keeping in mind their low quality, a similar live birth rate is reported for PGS and NC (35% and 42%, respectively). The miscarriage rate for the PGS group (9%) seems to be lower than in the NC group (28%).

This review summarizes the best available evidence of the efficacy of PGS vs. NC. Live birth rates for PGS and NC groups are not very far apart, and the miscarriage rate after PGS may be lower. The need for comparative studies of high quality is urgent.

[TABLE 1]

[FIGURE 1]

[TABLE 2]

[TABLE 3]

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TABLES AND FIGURES

Table 1

TABLE 1

Main results of included studies in fertile couples with unexplained recurrent miscarriages receiving PGS or conceiving naturally.

Study (reference)	Couples, n	Started cycles, n	OPU cycles, n	ET cycles, n	TE per cycle, mean	Live births, n (% per couple)	Miscarriages, n (% per couple)
PGS							
Wilding et al.[a] (24) 3 FISH probes: 13, 18, 21	16	—	26	—	2.9	3 (19)	—
Wilding et al.[a] (24) 5 FISH probes: 13, 16, 18, 21, 22	48	—	62	—	3.8	22[b] (46)	—
Platteau et al. (25) FISH probes 13,16,18, 21, 22, X, Y	49	—	69	49	2	10 (20)	5 (10)
Munne et al. (5) FISH probes: 13, 15, 16, 17, 18, 21, 22, X, Y	58	69	69	60	2.3	25 (43)	5 (9)
Mantzouratou et al. (6) FISH probes: 13, 15, 16, 18, 21, 22	10	12	12	12	1.7[c]	4 (40)	0
Total	181	—	238	121	—	64 (35)	10 (9)
NC							
Christiansen et al. (64)	26	NA	NA	NA	NA	10 (39)	11 (42)
Clifford et al. (65)	31	NA	NA	NA	NA	19 (61)	7 (23)
Stephenson et al. (66)	30	NA	NA	NA	NA	10 (33)	8 (27)
Ober et al. (67)	85	NA	NA	NA	NA	41 (48)	18 (21)
Ramhorst et al. (68)	37	NA	NA	NA	NA	12 (32)	5[d] (14)
Pandy et al. (69)	19	NA	NA	NA	NA	2 (11)	6 (32)
Scarpellini et al. (70)	33	NA	NA	NA	NA	16 (48)	17 (52)
Total	261					110 (42)	72 (28)

Note: OPU = ovum pick-up cycles; TE = transferred embryos; — = not mentioned; NA = not applicable.

[a] Same article, different probes were used.

[b] Clinical pregnancies, not "live birth events," resulting in 54 children, owing to multiple pregnancies.

[c] Information kindly provided by the author, after e-mail correspondence.

[d] Not clearly stated: unsuccessful pregnancies.

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Figure 1

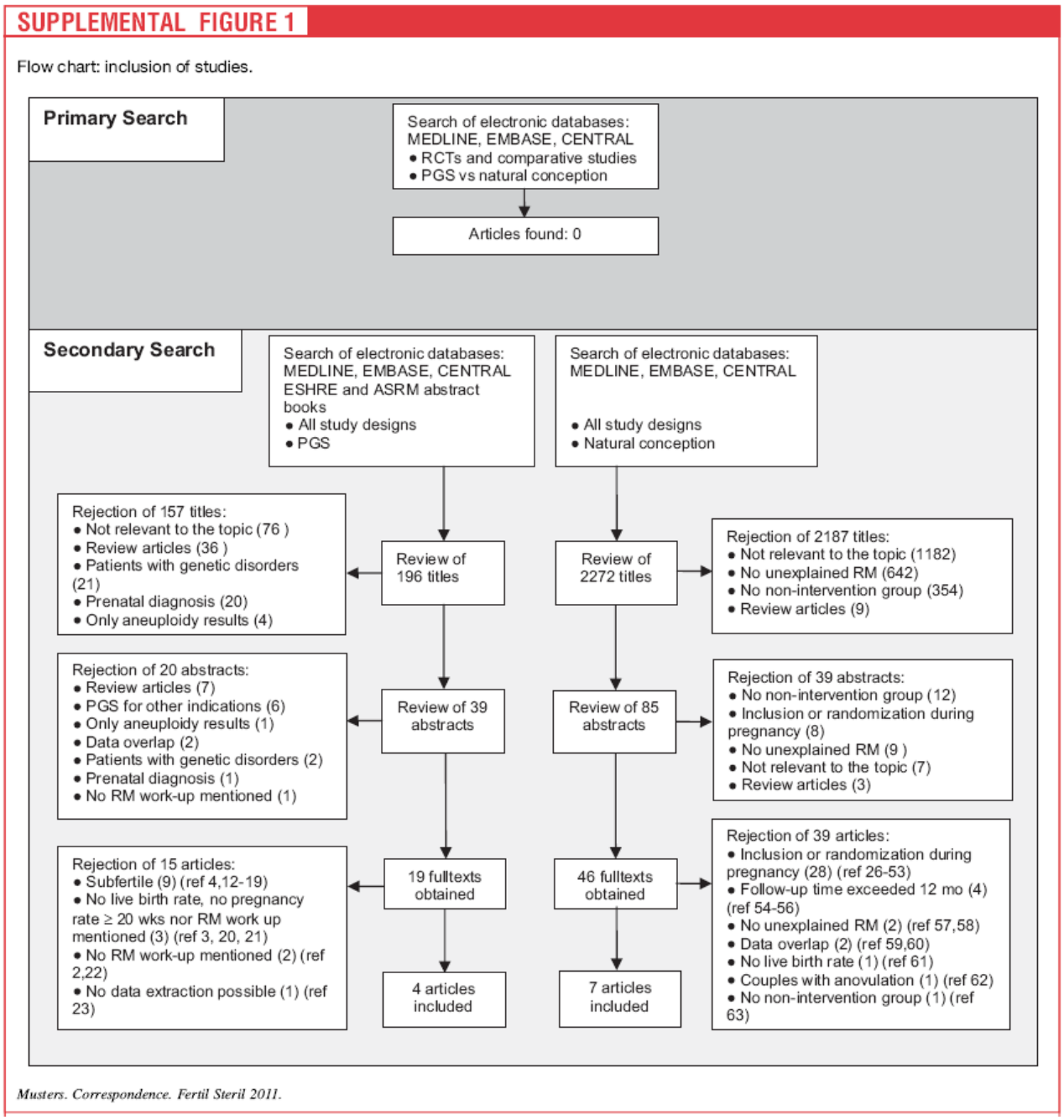

Table 2

SUPPLEMENTAL TABLE 1

Update search: MEDLINE, last update December 22, 2009.

1.	habitual abortion/
2.	((habitual* or recurr* or multiple or repeat* or repetit$ or consecutive or unexplained) adj4 (Abortion* or miscarriage*)).tw.
3.	((habitual* or recurr* or multiple or repeat* or repetit* or consecutive or unexplained) adj4 ((pregnanc* or fetal or foetal or foetus* or fetus* or embryo* or intrauterine or intra-uterine or in-utero) adj2 loss*)).tw.
4.	((habitual* or recurr* or multiple or repeat* or repetit* or consecutive or unexplained) adj4 ((fetal or foetal or foetus* or fetus* or embryo* or intrauterine or intra-uterine or in-utero) adj2 death*)).tw.
5.	((three or "3" or two or "2" or frequent or previous or more) adj2 (Abortion* or miscarriage* or ((pregnanc* or fetal or foetal or foetus* or fetus* or embryo* or intrauterine or intra-uterine or in-utero) adj2 loss*) or ((fetal or foetal or foetus* or fetus* or embryo* or intrauterine or intra-uterine or in-utero) adj2 death*))).tw.
6.	((IRM or RSA or RM or RPL) and (pregnan* or abortion*)).tw.
7.	or/1-6
8.	exp animals/ not (exp animals/ and exp humans/)
9.	7 not 8
10.	preimplantation diagnosis/
11.	((preimplant* or pre-implant*) and (diagn* or screen*)).tw.
12.	((Preimplant* or pre-implant*) adj10 (testing or tests or test)).tw.
13.	(pgd* or (pgs and screen*)).tw.
14.	((preimplant* or pre-implant*) and genetic*).tw.
15.	(aneuploid* adj10 (diagn* or screen*)).tw.
16.	or/10-15
17.	double-blind method/ or random allocation/ or single-blind method/ or Placebos/
18.	((singl* or doubl* or treb* or tripl*) adj (blind*3 or mask*3)).tw.
19.	(randomi?ed or placebo* or randomly or groups or trial or (clinic* adj trial*1) or (allocated adj2 random)).tw.
20.	exp clinical trial/ or exp Clinical Trials as Topic/
21.	or/17-20
22.	9 and 16 and 21
23.	9 and 16
24.	9 and 21
25.	exp cohort studies/ or cohort*.tw.
26.	(consecutive adj2 wom#n).tw.
27.	or/25-26
28.	Birth Rate/ or live birth/ or stillbirth/ or pregnancy outcome/ or pregnancy rate/
29.	((birth*1 adj2 (rate*1 or live or child*)) or livebirth*).ti,ab.
30.	((newborn*1 or child*) adj2 (live or born)).ti,ab.
31.	((viable adj2 pregnanc*) or (ongoing adj pregnanc*)).ti,ab.
32.	(Success* adj (rate* or outcome*)).ti,ab.
33.	((pregnanc* or gestation or reproducti*2) adj2 (achiev*2 or succes* or outcome*1)).ti,ab.
34.	or/28-33
35.	9 and 27 and 34

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Table 3

SUPPLEMENTAL TABLE 2

Update search: EMBASE, last update December 22, 2009.

1.	recurrent abortion/ or ((Spontaneous Abortion/ or fetal wastage/) and Recurrent Disease/)
2.	((habitual* or recurr* or multiple or repeat* or repetit$ or consecutive or unexplained) adj4 (Abortion* or miscarriage*)).tw.
3.	((habitual* or recurr* or multiple or repeat* or repetit* or consecutive or unexplained) adj4 ((pregnanc* or fetal or foetal or foetus* or fetus* or embryo* or intrauterine or intra-uterine or in-utero) adj2 loss*)).tw.
4.	((habitual* or recurr* or multiple or repeat* or repetit* or consecutive or unexplained) adj4 ((fetal or foetal or foetus* or fetus* or embryo* or intrauterine or intra-uterine or in-utero) adj2 death*)).tw.
5.	((three or "3" or two or "2" or frequent or previous or more) adj2 (Abortion* or miscarriage* or ((pregnanc* or fetal or foetal or foetus* or fetus* or embryo* or intrauterine or intra-uterine or in-utero) adj2 loss*) or ((fetal or foetal or foetus* or fetus* or embryo* or intrauterine or intra-uterine or in-utero) adj2 death*))).tw.
6.	((IRM or RSA or RM or RPL) and (pregnan* or abortion*)).tw.
7.	or/1-6
8.	limit 7 to humans
9.	((preimplant* or pre-implant*) and (diagn* or screen*)).tw.
10.	((Preimplant* or pre-implant*) adj10 (testing or tests or test)).tw.
11.	(pgd* or (pgs and screen*)).tw.
12.	((preimplant* or pre-implant*) and genetic*).tw.
13.	(aneuploid* adj10 (diagn* or screen*)).tw.
14.	or/9-13
15.	8 and 14
16.	prenatal diagnosis/ or genetic screening/ or prenatal screening/
17.	exp autosome/ or exp sex chromosome/
18.	fluorescence in situ hybridization/ or FISH.tw.
19.	chromosome aberration/ or aneuploidy/
20.	embryo.mp.
21.	or/17-20
22.	exp controlled study/ or cohort.mp.
23.	birth rate/ or fetus outcome/ or pregnancy outcome/ or pregnancy rate/ or childbirth/ or progeny/
24.	or/22-23
25.	8 and 16 and 21 and 24
26.	15 or 25
27.	exp controlled clinical trial/ or double blind procedure/ or single blind procedure/ or randomization/ or placebo/
28.	(randomized and controlled and trial).ti,ab.
29.	((controlled adj (trial or study)) or (controlled adj clinical adj (trial or study))).ti,ab.
30.	or/27-29
31.	8 and 26 and 30
32.	8 and 30
33.	"parameters concerning the fetus, newborn and pregnancy"/ or birth rate/ or fetus heart rate/ or fetus mortality/ or fetus outcome/ or live birth/ or pregnancy outcome/ or pregnancy rate/ or child birth/ or progeny/
34.	((birth*1 adj2 (rate*1 or live or child*)) or livebirth*).ti,ab.
35.	((newborn*1 or child*) adj2 (live or born)).ti,ab.
36.	((viable adj2 pregnanc*) or (ongoing adj pregnanc*)).ti,ab.
37.	(Success* adj (rate* or outcome*)).ti,ab.
38.	((pregnanc* or gestation or reproducti*2) adj2 (achiev*2 or succes* or outcome*1)).ti,ab.
39.	or/33-38
40.	cohort analysis/ or cohort.tw.
41.	(consecutive wom#n or consecutive nonpregnant wom#n).tw.
42.	longitudinal study/ or prospective study/
43.	or/40-42
44.	8 and 39 and 43
45.	8 and (14 or (16 and 21 and 24))

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