IVF/ICSI with or without preimplantation genetic screening for aneuploidy in couples without genetic disorders: a systematic review and meta-analysis

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Abstract

Purpose To assess the efficacy of preimplantation genetic screening to increase ongoing pregnancy rates in couples without known genetic disorders.

Methods Systematic review and meta-analysis of randomized controlled trials. Two reviewers independently determined study eligibility and extracted data.

Results Ten randomized trials (1,512 women) were included. The quality of evidence was moderate. Meta-analyses using a random-effects model suggest that PGS has a lower rate of ongoing pregnancies (risk ratio=0.73, 95% confidence interval 0.62–0.87) and a lower rate of live births (risk ratio=0.76, 95% confidence interval 0.64–0.91) than standard in vitro fertilization/intracytoplasmic sperm injection.

Conclusions In women with poor prognosis or in general in vitro fertilization program, in vitro fertilization/intracytoplasmic

sperm injection with preimplantation genetic screening for aneuploidy does not increase but instead was associated with lower rates of ongoing pregnancies and live births. The use of preimplantation genetic screening in daily practice does not appear to be justified.

Keywords Meta-analysis · Preimplantation genetic screening · Aneuploidy · IVF/ICSI · Advanced maternal age · Recurrent pregnancy loss · Repeated IVF failure

Introduction

Infertility is regarded as a public health issue and affects approximately every sixth couple in the Western countries [1]. Fertility centers have developed and expanded, together

Capsule Preimplantation genetic screening does not increase pregnancy rates in advanced maternal age, recurrent implantation failure, repeated miscarriages, or in general IVF population.

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with the use of assisted reproductive technologies (ART) in response to an increasing number of couples seeking help for infertility [2]. It is well known that fertility is remarkably reduced with increasing age of women in both natural conceptions and ART. The total oocyte number declines bi-exponentially with age and the loss of follicles accelerates around the age of 37–38 years [3]. Moreover, there is an increasing risk of spontaneous miscarriage with advanced maternal age. On the other hand, women postpone motherhood because they think ART is effective irrespective of the age of women and can compensate fully for the natural decline in fertility with ageing. Unfortunately, even ART cannot compensate for >30–50% of the fecundity that is lost by delaying attempts at conceiving [4]. A marked reduction of embryo implantation rates as a function of female age is the main factor explaining age-related decline in IVF success [5].

Genetic causes have a considerable involvement in infertility. With the introduction of IVF and other forms of ART, it has been possible to diagnose genetic abnormalities in early embryos. The combination of ART and genetic testing is currently being proposed as a suitable option to improve reproduction outcome in women with advanced age. Preimplantation genetic diagnosis (PGD), in most cases an analysis of one or two biopsied cells of a 3-day-old embryo, was developed in an effort to avoid the transfer of affected embryos from couples who carried specific chromosome abnormalities [1]. However, the use of PGD to prevent transmission of serious genetic disorders has largely been overtaken in volume by the use of embryo biopsy to potentially improve IVF outcome in subfertile couples. The application of molecular genetic tests like fluorescence in situ hybridization (FISH) and polymerase chain reaction (PCR) has been extended to detect embryos with major sporadic chromosomal or age-related aneuploidies that may result in failure of implantation or spontaneous miscarriage, and to remove them from the cohort available for transfer [6]. This technique is called preimplantation genetic screening (PGS) according to the European Society of Human Reproduction and Embryology (ESHRE) and the European Society of Human Genetics (ESHG) [1]. In the United States, PGS and PGD are often considered as similar treatments, which inflate the number of preimplantation diagnosis cycles reported from this country [6]. Although the technology used by both PGD and PGS is nearly identical, PGS aims to improve pregnancy rates in subfertile couples undergoing IVF/ICSI treatment, whereas PGD aims to prevent the birth of affected children in fertile couples with a high risk of transmitting genetic disorders [7].

Interestingly, PGS to screen embryos for common aneuploidies using FISH with specific probes for 5 to 9 chromosomes in advanced maternal age, recurrent IVF failure and recurrent pregnancy loss has become the most

common indication of embryo biopsy despite lack of evidence in favor of a true increase in ongoing pregnancy rate [8]. Recently, PGS is being used for increasing pregnancy rates in groups without a poor prognosis in the general IVF population or for selection of the top quality embryos [9–11]. Current guidelines of the ESHRE, ESHG, the American Society for Assisted Reproductive Technology (SART) and the American Society of Reproductive Medicine (ASRM) emphasize that randomized controlled trials with large patient populations are needed before PGS can routinely be recommended as a means of increasing ongoing pregnancy rates in these three groups of patients [1, 5].

A Cochrane review of PGS based on two randomized trials reported no significant difference in ongoing pregnancy rates between women undergoing IVF with and without PGS [12]. One of the trials was published as an abstract and included only 39 patients [13] and in the other trial, an intention to treat analysis was not performed [14]. Because of these limitations and given that further data have been published in the literature, a systematic review and meta-analysis was conducted to assess the effectiveness of PGS as a tool to increase ongoing pregnancy rates in cases of advanced maternal age, repeated IVF failure, repeated pregnancy loss (poor prognosis) but also in the general IVF population in couples without known genetic disorders but doubling the sample size of the previous review [12].

Materials and methods

The study was exempt from Institutional Review Board approval because this was a systematic review and meta-analysis.

Search strategy

We performed an exhaustive electronic search in the following databases (until January 2009): MEDLINE, EMBASE, The Cochrane Central Register of Controlled Trials (CENTRAL), and the Center for Reviews and Dissemination databases (DARE, HTA and NHS EE databases). The search combined terms and descriptors related to in vitro fertilization and the preimplantation genetic screening itself. The complete search strategy is available at request from authors. The search strategy was modified to fit with the syntaxes used in each database consulted. We added validated filters to that strategy to retrieve clinical trials [15, 16]. We electronically-searched the conference proceedings of American Society for Reproductive Medicine (ASRM) and European Society of Human Reproduction and Embryology (ESHRE) association meetings beginning in 2000 until January 2009. We searched for

Table 1 Study eligibility criteria

Target population	IVF/ ICSI with PGS (preimplantation genetic diagnosis for aneuploidy screening) in couples without genetic disorders
Intervention	IVF/ICSI + PGS vs IVF/ICSI
Outcome measure	One or more of the following: <ul style="list-style-type: none"> • Live birth (per woman randomized) • Ongoing pregnancy (per woman randomized) • Clinical pregnancy (per woman randomized) • Preclinical pregnancy or biochemical pregnancy (per woman randomized) • Biochemical loss (per woman randomized) • Miscarriage (per woman randomized) • Multiple pregnancy (per woman randomized)
Design	Randomized controlled trial

on-going trials at www.controlled-trials.com, www.clinical-trials.gov, and the WHO International Clinical Trials Registry Platform (www.who.int/trialsearch/). Reference lists of all identified articles and overviews, and a Science Citation Index Search (SciSearch) of relevant articles, provided additional sources of potentially eligible RCTs. Finally, we contacted first and second authors of the included and ongoing trials to provide any additional trials.

Eligibility criteria

The review included randomized clinical trials of women undergoing in vitro fertilization, receiving embryo transfers with previous PGS compared with women without PGS. Main outcomes of interest for the review were those related with pregnancy (preclinical, clinical, and ongoing) and live births. Multiple pregnancies, miscarriages and biochemical loss rates were assessed as secondary outcomes (Table 1). We assessed trials' methodological quality paying special attention to the generation of the randomization sequence, the allocation concealment adequacy, the blinding of investigators, patients and outcome assessment, and the reporting of follow-up.

Data extraction

Data were collected using standard forms in which characteristics of the study design, participants, intervention, comparisons and main results were recorded. We extracted outcome results per women randomized. Two independent authors (P.A., I.S.) judged study eligibility, assessed quality and extracted relevant data solving discrepancies by agreement, and if needed, reaching consensus with a third author (M.A.C.). Agreement between reviewers was analyzed using the weighted kappa

for each inclusion criterion [17] and kappa with quadratic weighting for the quality components [18].

Analysis

We pooled data for dichotomous outcomes from original studies, to obtain the relative risk (RR) for the occurrence of an outcome event. As we expected some statistical heterogeneity within included studies we employed a random effects model (DerSimonian and Laird) to pool the data, setting statistical significance at a P value < 0.01. We evaluated the degree of variation across studies attributable to heterogeneity with the I^2 statistic [19]. We conducted meta-analyses using Review Manager software. Absolute risk reductions as the difference between the control group risk and the intervention risk were calculated. For two of our main outcomes (live birth and ongoing pregnancy rates), data from large observational studies to estimate the control group risk was used [20]. The quality of the evidence was rated as high, moderate, low, and very low according to the system proposed by the GRADE working group [21] (Table 2).

To provide further insight into the adequacy of the total sample size across all trials, we calculated a posteriori the most desirable information needed for our meta-analysis [22]. To determine the optimal information size (OIS) we assumed a 19.4% for the rate of live birth and 27.1% for the rate of on-going pregnancy (event rate from large observational studies [20] and a 25% relative risk reduction with a power of 95% and a two sided $\alpha=0.01$. Outcomes were defined according to the terminology recommended in the ICMART (International Committee Monitoring Assisted Reproductive Technologies) glossary [23].

Results

A total of 397 studies were identified in the initial electronic search, 28 of which were considered eligible by

Table 2 Quality of evidence and their definitions

Grade	Definition
High	Further research is very unlikely to change our confidence in the estimate of effect
Moderate	Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate
Low	Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate
Very low	Any estimate of effect is very uncertain

one or both reviewers. During the second phase of the inclusion process, 16 studies were excluded because of non-randomized comparisons ($n=14$), the inclusion criteria were not fulfilled ($n=1$) or results were irrelevant for the purpose of the present meta-analysis ($n=1$). Two ongoing trials were retrieved [10, 24], one of which was excluded because it is currently recruiting patients [24], and second one was finally published later as a original paper [11]. The flow chart of the trials included in the meta-analysis is shown in Fig. 1. The two reviewers achieved good agreement in the selection of trials for inclusion (weighted kappa 0.73; 95% confidence interval [CI] 0.58–0.89).

Description of included studies

Ten prospective, randomized, parallel-group, controlled studies evaluating PGS for aneuploidies in IVF/ICSI versus IVF/ICSI met the inclusion criteria [10–14, 25–30].

Their sample sizes ranged from 39 to 408 women, with a total of 1,512 women. PGS was performed for advanced maternal age defined as ≥ 35 or ≥ 37 years [10], 35 to 41 years [26], ≥ 38 years [30] and ≥ 35 years [27]. In one study, PGS was performed for failed IVF cycles and recurrent pregnancy loss [25], whereas in other four studies, PGS was indicated in infertile couples without poor prognosis (general IVF population) [10, 11, 28, 29] or for embryo single transfer [11]. The technique of PGS was broadly similar across the included trials. Characteristics of the studies included in the meta-analysis are shown in Table 3.

Fig. 1 Flow chart for the trial identification and selection process

Interval validity of included trials

Reviewers reached good agreement with the application of validity criteria (weighted kappa 0.75, standard error 0.17). In general, trials provided little detail about methodological aspects, and most had some limitations with the exception of the study of Mastenbroek et al. [26]. Two trials were stopped early for futility [28, 30] (Table 4). One author responded to our request and provided additional information about methodological aspects [13]. The information provided regarding validity showed that authors usually set appropriate safeguards against bias, as pointed out in the available evidence about this issue [31].

Outcomes of interest

Standard IVF/ICSI showed higher rates of live birth, ongoing pregnancy, preclinical and clinical pregnancy than PGS with IVF/ICSI. Statistically significant differences in the number, miscarriages, biochemical losses or multiple pregnancies between the two strategies were not observed (Table 5).

Live birth

Four trials (207 events) showed that live birth rate was significantly lower in the women assigned to IVF/ICSI with PGS than those assigned to IVF/ICSI without PGS in patients with poor prognosis ($RR=0.76$, 95% CI 0.61–0.96) [14, 26, 27, 30]. Three trials (139 events) in general IVF population showed a non-significant deleterious effect ($RR=0.76$, 95% CI 0.59–1.00). The pooled analysis with all seven trials (346 events) showed a lower rate in the PGS group ($RR=0.76$, 95% CI 0.64–0.91) (Fig. 2) This observed effect corresponds to an absolute decrease in the number of live births of 147 per 1,000 women undergoing PGS (95% CI 124–176) in comparison with women undergoing IVF/ICSI alone (Table 5).

Ongoing pregnancy

Four trials with woman with poor prognosis reported ongoing pregnancy outcomes. IVF/ICSI with PGS showed a lower rate of ongoing pregnancies (119 events, $RR=0.68$; 95% CI 0.54–0.85) [13, 14, 26, 30]. When four trials with general IVF population were included [10, 11, 28, 29] still showed a similar, but now not significant result ($RR=0.83$, 95% CI 0.64–1.07) The pooled analysis with all seven trials (370 events) showed a significant worse result ($RR=0.73$, 95% CI 0.62–0.87) and still consistent, effect for women assigned to PGS ($P=0.45$, $I^2=0\%$) (Fig. 3) This accounting for an absolute decrease in the number of ongoing pregnancies of 197 per 1,000 women undergoing PGS for

Table 3 Characteristics of the clinical trials included in the review: IVF/ICSI with PGS for aneuploidy versus IVF/ICSI (control)

Author, year (reference)	Patients (PGS/control)	Age, mean, years PGS/control	Duration of the trial	Diagnosis	Outcomes (per woman randomized)
Werlin 2003 [25]	57 (28/29)		August 2001–August 2002	Advanced maternal age Failed IVF cycles Recurrent pregnancy loss	Preclinical pregnancy or biochemical pregnancy
Staessen 2004 [14]	400 (200/200)	40.1/39.9	March 2000–December 2003	Advanced maternal age	Live birth Ongoing pregnancy Clinical pregnancy Preclinical pregnancy or biochemical pregnancy Biochemical loss Miscarriage Multiple pregnancy
Stevens 2004 [13]	39 (21/28)	39/39	May 2002–March 2004	Advanced maternal age (≥ 35 years)	Ongoing pregnancy Clinical pregnancy Miscarriage
Mastenbroek 2007 [26]	408 (206/202)	38.0/37.9	May 2003–November 2005	Advanced maternal age (35–41 years)	Live birth Ongoing pregnancy Clinical pregnancy Preclinical pregnancy or biochemical pregnancy Miscarriage Multiple pregnancy
Stasessen 2008 [11]	240 (120/120)	29.9/29.9	October 2004–December 2006	Single embryo transfer Maternal age (< 36 years)	Live birth Ongoing pregnancy Preclinical pregnancy or biochemical pregnancy Miscarriage Biochemical loss
Mersereau 2008 [10]	53 (28/25)	35.2/33.5	June 1999–June 2000 interim analysis, ongoing trial	Infertile patients without poor prognosis predictors	Live birth Ongoing pregnancy Preclinical pregnancy or biochemical pregnancy
Hardarson 2008 [30]	109 (56/53)	40.5/40.6	November 2003–February 2007	Advanced maternal age (≥ 38 years)	Live birth Ongoing pregnancy Preclinical pregnancy or biochemical pregnancy Miscarriage Biochemical loss
Meyer 2008 [29]	47 (21/22)	31.6/31.1	June 2004–November 2006	“good prognosis” < 39 years, body mass index < 30 kg/m ² , cycle day-3 follicle-stimulating hormone (FSH) level < 10 mIU/mL, ovarian volume < 3 cc perovary, and < 2 previous failed IVF cycles	Live birth Ongoing pregnancy Clinical pregnancy Miscarriage
Schoolcraft 2008 [27]	62 (32/30)	38.3/38.2	May 2002–March 2004	Advanced maternal age (≥ 35 years)	Live birth Preclinical pregnancy or biochemical pregnancy Clinical pregnancy Miscarriage
Jansen 2008 [28]	101(55/46)	34.5/32.1	August 2004–November 2006	Single embryo transfer Maternal age (< 38 years)	Live birth Preclinical pregnancy or biochemical pregnancy Ongoing pregnancy Miscarriage

Table 4 Methodological data of the clinical trials included in the review

Criterion	Author, year (reference)									
	Werlin 2003 [25]	Staessen 2004 [14]	Stevens 2004 [13]	Mastenbroek 2007 [26]	Merserau 2008 [10]	Staessen 2008 [11]	Meyer 2008 [29]	Jansen 2008 [28]	Hardason 2008 [30]	Schoolcraft 2008 [27]
Explicit eligibility criteria	No	Yes	Unclear	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Sequence generation	Unclear	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Allocation concealed	Unclear	Yes	Yes	Yes	Yes	Unclear	Yes	Yes	Yes	Unclear
Patient blinding	Unclear	Unclear	No	Yes	Yes	No	No	Unclear	No	Unclear
Outcome assessor blinding	Unclear	Unclear	Yes	Yes	Unclear	Unclear	No	Unclear	No	Unclear

aneuploidies (95% CI 168–235) when compared to IVF/ICSI alone (Table 5).

Clinical pregnancy

Four trials (276 events) showed that clinical pregnancy rate was significantly lower in the women assigned to IVF/ICSI with PGS than those assigned to IVF/ICSI without PGS in patients with poor prognosis (RR=0.72, 95% CI 0.60–0.88) [13, 14, 26, 27]. The pooled analysis (303 events), including one additional trial in general population, still

showed a significant lower result (RR=0.72, 95% CI 0.60–0.86) (Fig. 4) This corresponded to an absolute decrease in the number of clinical pregnancy of 368 per 1,000 women undergoing PGS (95% CI 307–440) in comparison with women undergoing IVF/ICSI alone (Table 5).

Preclinical pregnancy

Five trials (368 events) showed that live birth rate was significantly lower in the women assigned to IVF/ICSI with PGS than those assigned to IVF/ICSI without PGS in

Table 5 Summary of outcomes and quality of the evidence of randomized clinical trials of IVF/ICSI with PGS for aneuploidies versus IVF/ICSI (control)

Outcome	No. of participants (trials)	PGS-AS	IVF-ICSI	Effect ^a			Confidence in the estimate of effect ^b
				Relative ^c (95% CI)	Assumed control risk ^d	Corresponding intervention risk ^d	
Live birth	1,419 (7)	151/704 (21.45%)	195/715 (27.27%)	0.76 (0.64 to 0.91)	194 per 1,000 ^e	147 per 1,000 (124 to 176)	+++ ^f Moderate
Ongoing pregnancy	1,398 (8)	160/707 (22.63%)	210/691 (30.39%)	0.73 (0.62 to 0.87)	271 per 1,000 ^e	197 per 1,000 (168 to 235)	+++ ^f Moderate
Clinical pregnancy	952 (5)	129/480 (26.87%)	174/472 (36.86%)	0.72 (0.60 to 0.86)	512 per 1,000 ^e	368 per 1,000 (307 to 440)	+++ ^f Moderate
Pre-clinical pregnancy	1,430 (8)	252/725 (34.76%)	290/705 (41.13%)	0.84 (0.74 to 0.95)	–	–	+++ ^f Moderate
Miscarriage	1,402 (8)	64/711 (9.00%)	69/691 (9.98%)	0.90 (0.66 to 1.22)	–	–	+++ ^{f,g} Moderate
Biochemical losses	749 (3)	22/376 (5.85%)	20/373 (5.36%)	1.09 (0.60 to 1.96)	–	–	+++ ^{f,g} Moderate
Multiple pregnancy	808 (2)	14/406 (3.44%)	20/402 (4.93%)	0.69 (0.35 to 1.35)	–	–	+++ ^{f,g} Moderate

^aARR absolute risk reduction, WMD weighted mean difference, values <0 favor PGS

^bConfidence in the estimate of effect or quality. Rated from 1 (very low quality) to 4 (high quality)

^cRelative Risk, values <1 favor PGS

^dWe calculated absolute risk reductions as the difference between the control group risk and the intervention risk

^eData from reference #20

^gEvidence limited by imprecise data (small sample size or event rate)

^fEvidence limited by study design and implementation

Fig. 2 Effectiveness of IVF/ICSI with PGS versus standard IVF/ICSI for the outcome of live birth

patients with poor prognosis (RR=0.80, 95% CI 0.69–0.94) [14, 25–27, 30]. Three trials of general IVF population also reported results for this outcome showing a non significant differences between the groups (RR=0.91, 95% CI 0.73–1.14) [10, 11, 28]. The pooled analysis with all eight trials (542 events) confirmed a significant lower rate of preclinical pregnancies in the PGS group (RR=0.84, 95% CI 0.74–0.95) (Fig. 5).

Miscarriage

Five trials (114 events) showed similar miscarriage rates in the women assigned to IVF/ICSI with PGS than those

assigned to IVF/ICSI without PGS in patients with poor prognosis (RR=0.87, 95% CI 0.63–1.21) [13, 14, 26, 27, 30]. Three trials of general IVF population also reported results for this outcome showing similar non-significant differences between the groups (RR=1.06, 95% CI 0.44–2.54) [11, 28, 29]. The pooled analysis with all eight trials (133 events) still showed no significant differences (RR=0.90, 95% CI 0.66–1.22) (Fig. 6).

Optimal information size

For the outcome live birth the calculated optimal information size needed for a reliable and conclusive treatment

Fig. 3 Effectiveness of IVF/ICSI with PGS versus standard IVF/ICSI for the outcome of ongoing pregnancy

Fig. 4 Effectiveness of IVF/ICSI with PGS versus standard IVF/ICSI for the outcome of clinical pregnancy

effect is 980 women in each arm. For the outcome measure of on-going pregnancies the calculated optimal information size needed for a reliable and conclusive treatment effect is 647 women in each arm. The current meta-analysis has 1,419 women in total which would suggest the need for additional trials until the 1960 women randomized is reached. In the case of on-going pregnancies the current meta-analysis has reached the size needed for a conclusive result.

Discussion

In this systematic review we aimed to evaluate the effectiveness of PGS for aneuploidy in improving the

ongoing pregnancy and live birth rates in couples without genetic disorders. Despite the biological plausibility of this technique, the present results do not confirm the effectiveness of the procedure, which is in agreement with the opinion of other authors [5, 32]. By contrast, PGS after IVF/ICSI compared to standard IVF/ICSI not only did not increase the outcomes of interest, but also was associated with a significantly lower rate of ongoing pregnancies ($RR=0.71$, 95% CI 0.56–0.89) and live birth ($RR=0.70$, 95% CI 0.54–0.91).

PGS for aneuploidy is a method used to identify the most likely chromosomally normal embryo for transfer in an IVF cycle. At present, this technique is extensively indicated in couples undergoing IVF without any previously

Fig. 5 Effectiveness of IVF/ICSI with PGS versus standard IVF/ICSI for the outcome of pre-clinical pregnancy

Fig. 6 Effectiveness of IVF/ICSI with PGS versus standard IVF/ICSI for the outcome of miscarriage

known familial risk of affected offspring, with the aim to improve IVF results in women of advanced maternal age, in women in which embryos have repeatedly failed to implant and in those with recurrent miscarriages not due to constitutional chromosome aberrations [1]. The hypothesis that PGS may be useful to increase ongoing pregnancy rates in these three populations is justified according to the well known fact of an increased incidence of aneuploidy with increasing age of women. Aneuploidy is a potentially major factor contributing to the low implantation and high miscarriage rates in advanced maternal age, as well as repeated implantation failures in young women even when good quality embryos are transferred [33].

The present results, however, failed to demonstrate a beneficial effect of PGS in these cases. Interestingly, a decrease in the probabilities of achieving ongoing pregnancies and live births per cycle was noted. Mosaicism may be a reason for the lack of pregnancy success. Apparently, most normal embryos with good morphology contain one or more chromosomally abnormal blastomeres [34–36]. Firstly, apoptosis in one cell line is not necessarily lethal for the embryo if a chromosomally normal core persists. Another explanation would be that the aneuploid blastomeres in embryos containing both normal and aneuploid blastomeres either underwent apoptosis or are allocated to the trophectoderm. This could also explain confined placental mosaicism. Finally, a question which remains to be answered is how many normal cells within an embryo are needed in order to establish a normal pregnancy. Therefore, the analysis of only one or two blastomeres for PGS implies the risk of misdiagnosis if the

blastomere used is not representative of the rest of the embryo [34].

Technological limitations may also impair the ability of PGS as a good screening tool for aneuploidy. Although up to 13 chromosome types in single cells can be analysed by FISH [37], PGS usually involves analysis of chromosomes 13, 16, 18, 21, 22, X and Y. The percentage of abnormal embryos derived from oocytes produced by young donors (<35 years of age) has been reported to be as high as 56.5% [38], whereas in studies from the same experienced IVF clinic, the corresponding figures in women with recurrent miscarriage and controls were 71% and 45%, respectively [39]. However, other aneuploidies may be involved in repeated implantation failure and aneuploid miscarriages [7, 40] and, therefore, a full chromosome analysis would reveal that the number of embryos containing at least one aneuploid cell in women with advanced maternal age, repeated implantation failure and recurrent pregnancy loss is almost 100% [33, 41–43]. In these couples, the etiological role of this fact in subsequent events is unknown. On the other hand, false positive and false negative results are also possible due to FISH errors (between 5% and 12%) and mosaicism, in addition to self-correction of chromosomically abnormal embryos in culture [6, 44–47]. Finally, discordance among blastomeres from the same embryo appears to present a significant problem in interpreting results and renders PGS for aneuploidy ineffective [48]. Large studies have shown that among women undergoing IVF, the chances of a live birth are related to the number of eggs fertilized, presumably because of the greater selection of embryos for transfer [49, 50]. The fact that the embryo biopsy inevitably reduces the cohort of normal embryos available for transfer may actually

decrease the chances of pregnancy for some couples [6, 51]. In addition, the possibility that embryo biopsy may damage the embryo, impairing its ability to become implanted and survive cannot be overlooked [51, 52].

The current study has several potential limitations but also some strengths. Systematic reviews have become standard practice in medical research to synthesize the best available evidence but a potential risk for publication bias remains. To avoid drawing biased conclusions from a meta-analysis it is important to identify all relevant primary studies on a given topic. In this regard, we carried out a comprehensive search and contacted authors in order to provide additional information about validity issues. On the other hand, publication bias seems unlikely for two reasons: a) no single study included in the meta-analysis concluded in favor of PGS and b) data of some studies published as abstracts or ongoing trials were identified in our search.

Furthermore, our confidence in the results increases due to the additional information about validity issues. In making health care management decisions, patients and clinicians must trade off the benefits and downsides of alternative strategies, thus they need to know how much confidence they can place in the estimates of effect. In this systematic review the most relevant limitations are those related to the lack of information regarding the design and execution (methodological limitations) of the included studies, some degree of heterogeneity and more importantly a low number of events and hence a low degree of precision. The overall quality of the evidence was therefore considered moderate, which decreases our confidence in the estimate of effect shown by PGS for aneuploidy in comparison with IVF/ICSI. Thus, although we are fairly confident in our results further trials might modify the observed effect.

Nevertheless, an additional insight provided by our calculation of the optimal information size makes it very unlikely that PGS will in the future show a beneficial effect. Our calculation of the OIS suggests that for the outcome of on-going pregnancies the current metanalysis has reached the size needed for a conclusive result. This together with the observed significant and deleterious effect for this outcome, as well as for live births, question the use of this practice outside a clinical trial. Similarly, other authors have recently suggested that it would be unethical to continue randomizing women to this technique [53].

In conclusion, there is moderate quality evidence showing that in women with poor prognosis, or in general IVF populations, IVF/ICSI with PGS for aneuploidy does not increase but instead was associated with lower rates of ongoing pregnancy and live birth rates. In the line of a recent excellent editorial of Fritz [54], the present results provide evidence that further trials to be performed to assess efficacy of PGS to enhance clinical outcomes in IVF/ICSI cycles appear to be clearly unjustified.

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