used a perfect screening instrument, we would have observed a stronger association between prenatal depressive symptoms and the risk of preterm delivery.

With regard to the subtypes of preterm delivery, unfortunately, we did not have such information for that study. However, as with the potential misclassification of depressive symptoms, the effect of potential misclassification of outcomes (i.e., assuming that depression during pregnancy is only related to certain subtype(s) of preterm delivery) is to attenuate the observed association. In other words, had we only included the subtypes that are associated with depressive symptoms during pregnancy, the observed association would have been stronger.

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The importance of good practice in preimplantation genetic screening: critical viewpoints

Sir,

We read with great interest the recent debate entitled ‘What’s next for preimplantation genetic screening (PGS)?’ published in your journal. Most authors concluded that the selection of chromosomally normal embryos for a selected panel of chromosomes does not improve ongoing pregnancy rates per cycle in advanced maternal age (AMA), implantation failure (IF) or ‘good prognosis’ patients undergoing IVF. This is an important message for those practicing reproductive medicine, since we may be over-manipulating the embryos in the IVF laboratories without scientific basis, and therefore increasing the total costs of an IVF cycle without sense. Thus, a critical analysis of the accumulated experience deserves comment, which is the specific objective of this letter.

Regarding AMA patients, four randomized controlled trials (RCTs) have been published so far. In the first of them Staessen et al. (2004) reported high ongoing implantation rates, but without statistical significance in the PGS group and they concluded that there were no arguments in favour of PGS in terms of clinical outcome per initiated cycle. In two other studies, authors stated that PGS has a detrimental effect with significantly reduced live birth rates after three cycles/patient (Mastenbroek et al., 2007) or no improvement in 6–7 weeks clinical pregnancy rates (Hardarson et al., 2008). In the fourth RCT (Schoolcraft et al., 2008), although no superior clinical outcome was observed in the PGS group, lower miscarriage rates and increased delivery rates were reported with PGS. In this study, only 32 and 30 patients were recruited in the PGS and control group, respectively.

In IF patients, only one RCT has been published recently (Blockeel et al., 2008), reporting no significant differences in clinical pregnancies between PGS and control groups, only 72 and 67 cycles were performed in the PGS and control groups, respectively.

In ‘good prognosis’ patients, four RCTs showed contradictory results. In single embryo transfers, two studies showed similar results between PGS and control groups. Staessen et al. (2008) with day-3 embryo biopsy, showed no beneficial effects with PGS, with similar ongoing pregnancy rates. Jansen et al. (2008), with blastocyst biopsy found similar results using an assisted hatching control group, but the study was interrupted with 55 and 46 patients in the PGS and control groups, respectively. In Meyer et al. (2009) with 21 patients in PGS group and 22 in control group, significantly lower live birth rates were reported in the PGS group with a surprisingly high miscarriage rate in the PGS group. Finally, Mersereau et al. (2008) revealed a 34% improvement in live birth rates with PGS, but the study was stopped with a total of 53 patients, due to difficulties in recruiting patients.

There are three major methodological pitfalls in these studies that preclude drawing clear conclusions:

1. Genetic analysis: In one study, the authors reported 20% of non-informative embryos in the PGS group, with only 50% of embryo replacements performed exclusively with informative embryos (Mastenbroek et al., 2007). This is an important pitfall that can be overcome with the reanalysis of non-informative nuclei, using DNA probes directed at different chromosome regions than the previously tested (Rodrigo et al., 2004; Colls et al., 2007). None of the papers introduced the so called non-result rescue analysis which is now common practice in the most experienced PGS programs. Furthermore, not only non-informative embryos can be rescued, but also many false monosomies, mainly those in which centromeric probes are employed in the first panels. Additionally, we are of the opinion that partial and complete non-informative embryos should form a different group for data analysis, since they clearly represent a different category.

Another important issue is the panel of chromosomes selected. Most of the quoted studies did not include chromosomes 15 and/or 22 in their analysis, highly associated with miscarriage with only one out of the nine studies including both chromosomes in the genetic screening (Schoolcraft et al., 2004). And Meyer et al. (2008), who did not test their embryos for chromosome 15, reported a trisomy 15 miscarriage in the PGS group.

Promising results have been recently described with 24-chromosomes analysis either by conventional Comparative Genomic Hybridization (CGH) in AMA/IF/recurrent miscarriage (70% clinical pregnancy rate, Wells et al., 2008) or CGH arrays in IF patients (five out of eight patients with third trimester ongoing clinical pregnancies in Hellani et al., 2008).

2. Embryo biopsy and culture: One of the studies (Staessen et al., 2008) reported relatively low blastocyst rate per biopsied embryos and another one showed incredibly high miscarriage rates after PGS (Hardarson et al., 2008), clearly indicating huge embryo damage during the procedure. These studies should have specified their blastocyst rates in PGS and control groups. Different policies on the day of embryo transfer have been applied in these studies and it is widely accepted that laboratories with difficulties in prolonged embryo culture, choose early embryo transfer rather than day-5 blastocyst transfer. A recent publication has shown the importance of embryo culture media in a PGS program, with an improvement in live birth rates in women ≥40 years with ≤2 previous stimulated IVF cycles after changing embryo culture media (Beyer et al., 2009).
In summary, we consider that standardized methodology should be applied in further RCTs, before concluding whether or not PGS benefits the candidate couples. In this sense, as it appears in the ESHRE PGD Consortium Guidelines, a lack of standardization is detected in PGS compared with other kinds of genetic diagnosis. Recently, various scientific societies (American Society for Reproductive Medicine (ASRM), 2004; The PGD International Society (PGDIS), 2004, 2007; European Society of Human Reproduction and Embryology (ESHRE) Thornhill et al., 2005) have proposed a set of guidelines in order to standardize chromosomal screening in single embryonic cells. Indeed, the validation of the assays and the participation in external quality schemes is radically necessary. Concerning quality assessment, currently there is no clear and comprehensive information regarding the practice of PGS in Europe. Nowadays, we are experiencing the creation of the first pilot program of inter-laboratory quality control in the FISH-based PGD for aneuploidy screening (http://www.ceqa-cyto.eu). In conclusion, there is a lot of work to be done in this field and perhaps we should direct our efforts towards the application of quality criteria before debating over the usefulness of PGS. At present, there may not be arguments in favour of PGS, but neither against, since most of the published studies do not fulfill the proper methodology and expected sample size.

Two other important aspects were not discussed at all in these papers:

(1) Termination of pregnancies (TOP) due to chromosomally abnormal pregnancy: Only two papers mentioned TOP in non-PGS pregnancies: Mastenbroek et al. (2007) reported one TOP with trisomy 18 in the control group and another trisomy 18 in a spontaneous pregnancy occurred in the PGS group and Staessen et al. (2008), one TOP with trisomy 21 in the control group. Surprisingly, no attention has been paid to this important ‘collateral effect’, mainly in AMA patients. A Spanish register that collected IVF/ICSI cycles performed in 2003 and 2005 in Catalonia showed that 16 trisomies 21 after IVF/ICSI cycles could have been avoided with PGS (Servei d’Informació i Estudis: FIVCAT.NET. Sistema d’informació sobre reproducció humana assistida. Catalunya 2005. Barcelona, Departament de Salut, Generalitat de Catalunya, 2008).

(2) Patients’ attitudes towards PGS and the risk of a chromosomally abnormal pregnancy: Twisk et al. (2007) showed patients’ clear preferences towards PGS to prevent Down syndrome. Shahine et al. (2007) also showed that 84% of patients would prefer their embryos to undergo chromosome analysis.

Inclusion criteria: Different maternal ages were included in the four AMA RCTs and we consider that in some of them the patients were too young to be included in this category. For example, in Mastenbroek et al. (2007), female age was 35–41 years old and in Schoolcraft et al. (2008) female age was ≥35 years old. We encourage more comprehensive inclusion criteria in further studies as well as detailed infertility work-up studies in the patients recruited, in order to rule out non-embryonic causes in indications such as IF or recurrent miscarriage. Not to forget that only an appropriate sample size will result in clinically relevant conclusions.

References


Thornhill AR, deDie-Smulders CE, Geraedts JP, Harper JC, Barton GL, Lavery SA, Moutou C, Robinson MD, Schmutzler AG,
Acupuncture and in vitro fertilization: updated meta-analysis

Sir,

We updated our previously published meta-analysis (El-Toukhy et al., 2008), following the recent publication of another randomized controlled study of acupuncture in IVF at the time of embryo transfer (So et al., 2009). Our updated meta-analysis showed no improvement in clinical pregnancy rates with acupuncture at the time of embryo transfer (Fig. 1). A restricted meta-analysis using high quality studies that employed sham acupuncture in the control group also failed to show improvement in live birth rates (Fig. 2).

Despite 14 randomized trials of acupuncture in IVF, some of which are of high quality and nearly 3000 women recruited into these studies, acupuncture has not been shown to improve IVF outcome. Many published studies on the role of acupuncture in IVF recommend that further well designed and sufficiently powered randomized trials to evaluate the impact of acupuncture at the time of embryo transfer on IVF outcome are carried out (Cheong et al., 2008; Pinborg et al., 2008). However, based on current evidence, this recommendation is difficult to justify.

If further research into the effects of acupuncture as an adjunct to IVF treatment is to be carried out, small studies are unlikely to provide a definitive answer. There are currently five ongoing randomized controlled trials of acupuncture and IVF with a sample size ranging from 100 to 600 women (metaRegister of Controlled Trials; Pinborg et al., 2008). It is unclear what these studies will offer over and above the existing studies. For current practice, we believe that women should be advised that there is no evidence that receiving acupuncture during IVF treatment (whether at the time of oocyte collection or embryo transfer) improves IVF outcome.

References


Figure 1 Meta-analysis of the studies evaluating the effect of acupuncture administered around the time of embryo transfer on the clinical pregnancy rate in women undergoing IVF.