

**Human Fertilisation and Embryology Authority
The Scientific and Clinical Advances Group**

Committee:	Scientific and Clinical Advances Group
Meeting Date:	21 st February 2008
Agenda Item:	5
Paper Number:	SCAG(02/08)01
Paper Title:	Preimplantation Genetic Screening
Author:	Hannah Darby
For Information or Decision?	Decision
Resource Implications:	Accounted for in the business plan
Recommendation to the Committee:	<p>Members are asked to consider and approve:</p> <ul style="list-style-type: none"> • the review of literature regarding PGS for advanced maternal age, recurrent implantation failure, recurrent miscarriage and male factor infertility and the conclusions that the Executive have come to • recommendations regarding amendments to the Code of Practice and patient guidance • the literature review regarding the safety of blastomere biopsy and the recommendation that the Authority's policy on tissue typing should remain unchanged

1. Introduction

1.1 Preimplantation genetic diagnosis has only recently been applied to patient populations at high risk of failure with IVF. Practitioners argue that certain patients are failing to get pregnant because of their increased risk for creating aneuploid embryos and that PGD can decrease this risk by selecting for chromosomally normal embryos with a higher chance of successful implantation. This process involves the extraction and analysis of either polar bodies or blastomeres. Analysis of the DNA is conducted with fluorescence in situ hybridisation (FISH), in which DNA probes labelled with fluorochromes are able to identify chromosomal abnormalities in 5-10 chromosomes at a time.

1.2 A number of studies have found that the majority of embryos are chromosomally abnormal, for example Munne et al. (2007)¹ found that out of 6054 embryos analysed 56% were chromosomally abnormal despite 3751 (62%) of them having a good morphology. Similar results have also been found by Munne et al. 1995², Marquez et al. 2000³ and Magli et al. 2007⁴. Therefore morphology is a poor indicator of chromosome

abnormalities. Even though culturing to day 5 or 6 strongly against chromosomally abnormal embryos, extended culture cannot be used as a reliable tool to select against chromosome abnormalities. Sandalinas et al (2001)⁵ found that 37% of trisomic embryos reached the blastocyst stage.

1.3 The number of preimplantation genetic screening (PGS) cycles is increasing at a rapid rate. In 2006 the ESHRE PGD Consortium reported that 1211 PGS cycles were performed in 2002/3, the following years this figure increased to 1722 which represents a 42% increase.^{46 30}

1.4 The Code of Practice outlines requirements for clinics regarding the use of PGS. Guidance and licence conditions limit the use of PGS for aneuploidy to the following categories of patients:

- (i) women over 35 years of age,
- (ii) women with a history of recurrent miscarriage not caused by translocations or other chromosomal rearrangements,
- (iii) women with several previous failed IVF attempts where embryos have been transferred,
- (iv) women with a family history of aneuploidy not caused by translocations or other chromosomal rearrangements,
- (v) male partners whose sperm has higher than normal levels of aneuploidy.

1.5 In addition, centres are required to provide patients with information about the consequences, risks and costs of treatment. These requirements are outlined in full at Annex A.

1.6 In April 2006 SCAG recommended that, due to publication of recent studies suggesting that PGS does not increase success rates, the effectiveness of this technique should be reviewed. This review was then added to the work plan for 2007/8.

1.7 Studies published regarding the use of PGS for advanced maternal age patients, recurrent implantation failure, recurrent miscarriage and male factor infertility have been reviewed in order to come to a conclusion whether the HFEA's current guidance and licence conditions are appropriate. In addition to the text below the table at Annex B outlines details of the trials reviewed. The safety of embryo biopsy in general has also been considered.

2. PGS for advanced maternal age

2.1 The aneuploidy rate is known to increase with maternal age, regardless of embryo morphology, resulting in lower implantation rates and a higher risk of miscarriage. A number of groups have found that 40-80% of embryos derived from older women are aneuploid^{6 28}. The prevalence of aneuploidy increases with the number of chromosome pairs that are examined. Therefore, PGS should reduce the risk of aneuploid embryos being transferred and result in improved implantation, pregnancy and live birth rates.

2.2 To date the majority of studies conducted are not randomised and have been descriptive or observational. The following studies report that PGS has a beneficial effect on implantation or pregnancy rates for women with advanced maternal age (AMA):

- Gianaroli et al (1999)⁷ found a significantly higher implantation rate following PGS compared with assisted hatching (25.8 versus 14.3%) in a series of 157 patients >36 years, who self selected whether or not to have PGS. However, this study has been criticised for using an assisted hatching rather than a no intervention control group.
- A multi centre retrospective study, carried out by Munné et al (1999)⁸, included 117 patients >35 years who underwent PGS and retrospectively matched controls. No difference in implantation rates (13% in each group) were found, but there was a higher proportion of ongoing pregnancies and live births in the PGS group (16.1 versus 10.5%). In a subsequent similar retrospective matched study Munne et al.³¹ found a higher implantation rate of 17.6% in the PGS group compared with 10.6% in the controls. A subsequent study the same group retrospectively compared pregnancy, miscarriage and live birth rates following PGS to non-PGS cycles for 38-42 year olds. They found that PGS significantly increases the chance of a live birth while reducing the risk of miscarriage in 38-42 year olds.¹
- Rubio et al (2003) reported an ongoing pregnancy rate per embryo transfer of 28.8% for a series of 341 PGS cycles¹⁹. Although the control group was aged matched no other details or statistical analysis was provided.
- Two prospective, randomised controlled trials have been carried out by Werlin et al (2003 & 2004)^{25,9}. The first compares 7 advanced maternal age patients who had PGS with 12 advanced maternal age control patients. Three pregnancies were reported in each group. This study was then expanded to include a total of 15 advanced maternal age patients and 13 control patients. 6 of the 15 PGS patients became pregnant (40%), compared to 3 of the 13 controls (23%). However, these are still insignificant figures and information such as number of embryos transferred and implantation rates.
- Verlinky et al (2005)¹⁰ analysed treatment outcome before and after PGS, for 2359 cycles, in the same group of poor prognosis patients (81.2% of which were over 35). 71% of pregnancies resulted in a live birth following PGS. A success rate of 71% for PGS cycles was observed compared to 29% for IVF cycles which did not involve PGS.

2.3 The following studies report that PGS has no beneficial effect for women with advanced maternal age:

- Staessen et al (2004)¹¹ have carried out the largest randomised trial published to date which analysed 289 cycles with oocyte retrieval from 400 patients (however only 121 women reached embryo transfer in the control group, and 81 in the PGS group). There was no significant increase in either the implantation (17.1% PGS vs 11.5% control) or the ongoing implantation rates (17.1% PGS vs 11.5% control). However, this study has been criticised as the number of embryos transferred was not randomised¹². A significantly higher number of embryos were replaced in the

control group which makes the results difficult to interpret and may explain the comparable implantation rates. In addition, this study is the only one which involved removing two blastomeres at day 3, which may compromise the embryos and reduce their implantation potential.

- Stevens et al (2004)¹³, in an ASRM abstract, reported a randomised study which included 39 patients ≥ 35 . PGS was only performed if there were at least 5 good quality embryos on day 3. The ongoing pregnancy rate was 52% in the PGS group and 72% in the control group.
- Mastenbroek et al (2007)¹⁴ carried out a double blind randomised controlled trial which involved 408 women ages 35-41 with no previous IVF failures which underwent up to three cycles with or without PGS. There were 206 women in the PGS group and 202 in the control group. The cumulative ongoing pregnancy and live birth rate was 25 and 24% for the PGS group, which was significantly lower than those observed in the control group (37% and 35%).

However, this study has been criticised for a number of reasons. A commentary on the trial¹⁵ expressed the view that this study suffers from a number of insurmountable inaccuracies and that these are either a direct consequence of the inexperience of the team or of a general disregard of vital guidelines reported in the literature. It is pointed out that the error rate is not presented, shedding doubt on their ability to reliably diagnose the biopsied cells. The commentary concludes that poor biopsy technique (a second biopsy was performed if the first blastomere obtained was not suitable for analysis), substandard fixation and FISH methods, poor IVF outcomes and inappropriate patient selection are the cause of the discouraging results obtained by Mastenbroek et al, rather than problems inherent to PGS. It is speculated that if extensive embryo damage had not occurred, the same study could have possibly shown a beneficial effect of PGS in these patients. In addition, the patients were selected from a population of 35-41 year old women with infertility, however, the majority of these patients had few embryos. Previously published data clearly show that the efficacy of PGS for advanced maternal age is significantly reduced in patients with few embryos (Munné et al, 2003). The British Fertility Society, in their policy and practice guidance on PGS, outlines similar criticisms and points out that some aspects of the study contravene recommendations in the 2007 guideline by the Preimplantation Genetic Diagnosis International Society.¹⁶

- A meta-analysis, which included the Straessen et al and Stevens et al studies, reported no significant difference in the live birth rate, ongoing pregnancy rate and clinical pregnancy rate between PGS and control groups. The analysis concluded more properly conducted randomised controlled trials are needed and until such trials have been performed PGS should not be used in routine patient care.¹⁷

3. PGS for recurrent pregnancy loss

3.1 Recurrent pregnancy loss (RPL) is defined as three or more pregnancy losses before 20 weeks' gestation. As women with recurrent pregnancy loss are more likely to have chromosomally abnormal embryos (50-60%)^{18,19,20} often due to the presence of autosomal trisomies (13, 14, 15, 16, 21 and 22)^{21, 22}, PGS for aneuploidy is used by some clinicians to decrease the risk of conceiving another aneuploid embryo.

3.2 There have been no robust randomised controlled trials to evaluate the clinical use and efficacy of PGS for this group of patients and there are conflicting views. These conflicting views may be due to varying inclusion criteria for studies (e.g. two or three miscarriages and age of women).

3.3 A prospective study, which compared 241 PGS cycles for patients with recurrent pregnancy loss to a control group of PGD cycles performed for sex linked diseases, found similar outcomes for implantation and pregnancy rates (Rubio et al, 2005)²³. This study has been criticised for using an inappropriate control group, because the women did not have recurrent miscarriage.

3.4 In a cohort study by Munné et al (2005)²⁴ the rate of miscarriage in a group of recurrent miscarriage patients undergoing PGS was compared to expected rate (estimated by age and number of previous abortions) and miscarriage rate for a control group of patients undergoing PGS for advanced maternal age. Before PGS 87% of pregnancies in 58 women resulted in miscarriage, whereas after PGS they only lost 17% (compared to an expected rate of 45%). This reduction was particularly significant for patients ≥ 35 .

3.5 One small randomised trial has been carried out which included 19 patients with recurrent pregnancy loss (11 PGS and 8 control) which suggested an improved outcome after performing PGS (pregnancy rate per embryo transfer 63.6% PGS versus 37.5% control) (Werlin et al., 2003)²⁵. However, miscarriage rates were not reported and conclusions cannot be drawn as the patient group was so limited.

3.6 Studies by Garrisi et al.^{26 27} also suggest that PGS can increase success rates in certain groups of patients with recurrent pregnancy loss. In their 2006 study patients with recurrent pregnancy loss and <5 embryos were asked if they wanted to continue with PGS. Outcomes were compared for those who accepted PGS and those who declined. The implantation and delivery rates were significantly higher in the group that received PGS (36.4% and 36.2% vs 5.6% and 13.6%).

In their 2007 study outcomes for 135 patients with histories of easy natural conceptions and multiple consecutive miscarriages who underwent IVF and PGS were compared to those for 144 infertile patients with recurrent pregnancy loss who did not undergo PGS. Previously patients experienced 91.4% miscarriage, after PGS miscarriage rate was improved for patients with 3-5 previous losses (to 19.5% vs predicted 40.9%). The authors claim that this demonstrates for the first time that PGS effectively reduces the rate of pregnancy loss for couples with a history of RPL after easy natural conceptions. Patients with 3-5 previous miscarriages derive the most benefit.

3.7 However, another cohort study, by Platteau et al (2005)²⁸ reported no benefit of PGS in women >37 years (2.7% implantation rate and 5% ongoing pregnancy per transfer). It is likely that these poor results were due to the fact that these older women also had infertility problems and a high number of chromosomally abnormal embryos (66.9%). In addition two cells were biopsied from the embryos, which may be detrimental.

3.8 The ASRM guidelines²⁹ do not support the use of PGS for patient with RPL as they conclude it does not improve ongoing pregnancy or live birth rates and does not

decrease miscarriage rates in such women. However, these conclusions are only supported by one study (Platteau et al, 2005) and make no suggestion that PGS has a negative effect on success rates.

4. PGS for recurrent implantation failure

4.1 Recurrent implantation failure has been defined as three or more unsuccessful IVF cycles or the failure of conception after the replacement of 10 or more good quality embryos (ESHRE PGD Consortium Steering Committee, 2002). Chromosomal abnormalities have been proposed as one cause of implantation failure. There are a limited number of studies regarding PGS for implantation failure and most of them have failed to demonstrate if its use is beneficial for this group of patients.

4.2 The ESHRE PGD Consortium³⁰ have reported an implantation rate of 17% (foetal heartbeats/100 embryos transferred) for cycles carried out in 2003/4. One study³¹ observed a 14% implantation rate in 54 cycles in patients age 35 or older with recurrent implantation failure (two or more failed IVF cycles), compared to 12% in a group of controls matched retrospectively. In addition, PGS demonstrated no benefit to implantation and clinical pregnancy rates (17.3 and 25%) for a series of 54 young patients (mean 32 ± 2.3 years)⁷. The only randomised trial conducted so far evaluated only 19 patients with recurrent implantation failure and concluded that PGS offers no benefit to this patient group.²⁵

4.3 However, some studies have observed better results. One study observed a 34% pregnancy rate after IVF with PGS in a group of patients (mean age of 36.3%±2.5 years) with an average of 4.2 previous failed IVF cycles, compared with a 33% pregnancy rate in a group of women who had IVF for X-linked disease (mean age 31.6±2.5 years)³². A second study found an ongoing pregnancy rate of 30.4% (mean age 30±3.1 years), which was comparable to the control group of patients undergoing PGS for advanced maternal age (32.5%)³³. Some reviews have criticised these studies for using an inappropriate control group.

5. PGS for male factor infertility

5.1 The use of PGS for patients with male factor infertility was considered by SCAG in April 2006 when it was decided to add it as a category of patients for which PGS is permitted. The group were presented with a literature review which concluded that the literature appears to show a correlation between abnormal sperm parameters and chromosomal abnormalities. It also appears that infertile men with sperm chromosomal abnormalities are less likely to achieve a pregnancy following ICSI treatment and that this could be due to the paternal chromosomal abnormalities being passed on to the resulting embryos.

5.2 The literature review stated that, although the majority of miscarriages are caused by chromosomal abnormalities of maternal origin about 8-10% of miscarriages that are due to trisomy 13, 18 and 21 are of paternal origin.³⁴

5.3 The relationship between sperm morphology and chromosomal abnormalities has been analysed³⁵. No correlation was found between sperm chromosome abnormalities

and morphology in fertile men but increased levels of aneuploidy was found in men with abnormal semen profiles such as aesthenozoospermia and oligozoospermia.

5.4 Another study demonstrated that male partners of couples with repeated reproductive failures are more likely to have aneuploid sperm. Petit and colleagues³⁶ used fluorescent *in situ* hybridisation (FISH) to analysis chromosomes 8, 9, 13, 18, 21 X and Y in 29 male patients with normal karyotypes; ten patients had ≥ 4 cycles of ICSI treatment without a pregnancy; 9 patients had a pregnancy after 1 to 3 cycles of ICSI treatment and the results were compared with the profiles of the sperm of 10 fertile men with normal sperm parameters. These researchers found that aneuploidy for each chromosome and diploidy rates were significantly higher in the infertile men.

5.5 In a preliminary study carried about by Rubio and colleagues it was shown that the male partner of couples undergoing IVF, who had had two or more miscarriages, had significantly higher chromosomal abnormalities, in particular sex chromosome disomies, in their sperm than the internal control group of men.³⁷

5.6 In a more in depth study Rubio and colleagues have shown that couples with a history of miscarriages of unknown origin or with a history of implantation failure following ICSI are more likely to have chromosomal abnormalities in the male partner's sperm³⁸. This study examined the sperm aneuploidy and diploidy rates for chromosomes 13,18, 21, X and Y in 63 patients with normal 46,XY karotypes using FISH analysis, who had an increased risk of chromosomal abnormalities based on reproductive history and compared this with the FISH analysis of sperm from nine healthy normozoospermic donors. The researchers showed that patients who had a reproductive history that indicated that they may have chromosomal abnormalities had significantly higher levels of sex chromosomal disomies compared to the control group. Furthermore patients who were oligoasthenoteratozoospermic also showed significantly higher levels of diploidy and disomies for sex chromosomes and chromosomes 18 and 21 when compared with normozoospermic patients. These researchers also reported that couples where the male partner had chromosomal abnormalities in their sperm had a higher incidence of miscarriages (80%) following ICSI when compared with the miscarriage rate (55%) in couples where the male partner had no chromosomal abnormalities in their sperm.

5.7 This group of researchers concluded that there is an increased incidence of chromosomal abnormalities in sperm of infertile men. Consequently, they studied whether these chromosomal abnormalities were passed on to the embryos created using these abnormal sperm samples. The researchers performed preimplantation genetic screening for aneuploidy on embryos created using sperm that had chromosomal abnormalities, as measured by FISH analysis, and compared then with embryos from fertile couples undergoing preimplantation genetic diagnosis for sex-linked disorders. The results showed that patients with chromosomally abnormal sperm had an increased incidence of chromosomally abnormal embryos when compared with the control group³⁹.

5.8 Another group of researchers have also shown that men with low quantity sperm have increased levels of sperm aneuploidy and that subsequently have less chances of achieving a pregnancy after ICSI treatment⁴⁰. This group used FISH analysis to study chromosomes 18, X and Y in men who had oligozoospermia or azoospermia and compared the results with the rates in fertile donors. They discovered that the frequency of sex chromosome disomy and diploidy was greater in men with severe

oligozoospermia and that the fertilisation rates were also reduced in this group when compared with the controls. However, another group of researchers showed that even though epididymal sperm of men with obstructive azoospermia have elevated sex chromosome aneuploidy rates, this had no effect on the outcome of treatment following ICSI treatment⁴¹.

5.9 A review published in 2007 concluded that advances in fluorescent in situ hybridisation (FISH) technology have facilitated the study of sperm from patients with severe spermatogenesis defects. This has demonstrated the prudence of evaluating sperm chromosome aneuploidy in men with severe male factor infertility, such as non-obstructive azoospermia or severe ultrastructure defects, especially in cases of previous repeated IVF/ICSI failure. They also recommend testing in men with chromosome translocations and unexpected recurrent pregnancy loss, and may be beneficial in patients with unexplained, repeated IVF failure⁴².

6. Safety of blastomere biopsy

6.1 The feasibility of biopsy of human embryos was first confirmed in 1990. Hardy et al⁴³ concluded that removal of one or two cells at the 8-cell stage, while reducing the cellular mass, does not adversely affect the preimplantation/development of biopsied embryos in vitro. Hardy et al suggested that this approach could be used for preimplantation diagnosis of genetic defects.

6.2 At the time the HFEA guidance regarding preimplantation tissue typing was reviewed in 2004. It was concluded the risks associated with embryo biopsy are not too great for preimplantation tissue typing to be available, subject to appropriate safeguards, in cases in which there is a genuine need for potentially life-saving tissue and a likelihood of therapeutic benefit for an affected child. It was decided that each application for such a procedure would be considered on a case-by-case basis and the policy as a whole will be kept under review as new information and evidence continue to emerge.

6.3 However, developments regarding the risks associated with the use of embryo biopsy have not been reviewed, in the context of PGD/PGS since then. Few studies have been conducted on the clinical outcomes of PGD/PGS, particularly in relation to whether embryo biopsy has a negative effect on neonatal outcome.

6.4 In a summary of the use of embryo biopsy Gianaroli (2000)⁴⁴ is of the view that the number of cells observed 24 hours after blastomere biopsy is lower than expected, implying that either the reduction in cellular mass or the trauma associated with the procedure itself may have an effect on the rate of embryo growth. Nevertheless, compaction, blastocyst formation and hatching take place normally, giving rise to viable, normally growing babies.

6.5 As the live birth rate of PGD/PGS cycles is affected by the number of embryos genetically suitable for transfer it is not useful to compare it to live birth rate figures for cycles which do not involve blastomere biopsy. Therefore live birth rates are not a useful parameter to consider whether or not blastomere biopsy negatively affects embryo development.⁴⁵

6.6 So far the limited data for follow up of children born after PGS/PGD indicates no detrimental effect of biopsy, as no differences have been reported when compared with conventional ICSI cycles.

6.7 The ESHRE PGD Consortium co-ordinates an international collaborative data collection of PGD/PGS cycles and report on the current practice on a regular basis. The latest data published by the consortium is from January to December 2004 with pregnancy follow-up to October 2005⁴⁶. Of the 456 reported deliveries following PGD, 455 ended in the birth of at least one live born baby. Analysis of the data concludes, as in previous years, that pregnancies and babies born after PGD are very similar to pregnancies and babies born after ICSI treatment e.g. complications of pregnancy, characteristics at birth and major and minor malformations. Data for the previous year⁴⁷ concluded that 4% of PGD babies were born with malformations, which is comparable to that for ICSI and parameters such as weight, length and head circumference are comparable to those of ICSI babies. The main complication (as will all IVF babies) remains multiple pregnancies leading to morbidity and mortality in PGD offspring.

6.8 Verlinky et al.⁴⁸ have also reported on the follow up of 754 babies born after 4748 PGD cycles without a significant increase on the prevalence of congenital malformations.

6.9 Tur-Kaspa et al, 2005⁴⁹ reported 4.4% minor birth defects and 1.7% major birth defects following PGD. This group concluded that preimplantation embryo development, pregnancy complications and paediatric outcome after PGD are not significantly different than regular IVF/ICSI outcome and PGD can be performed safely with a lower multiple birth rate.

7. Conclusion

7.1 In conclusion, early small scale studies showed that PGS can increase success rates in older women by excluding aneuploid embryos (which constitute 40.4%-64.0%⁵⁰ of embryos in these patient groups). However, no significant differences were found in larger randomised trials, this may be because fewer embryos are transferred following PGS. A varying definition of advanced maternal age between groups (which fluctuates between 35 and 38 years) and a variation in the number of embryos transferred may contribute to the differing results and conclusions between studies.

The BFS, in their 2007 guideline,⁵¹ recommend that:

“Patients should be informed that there is no robust evidence that PGS for advanced maternal age improves live birth rate per cycle started. Indeed from the evidence currently available the live birth rate may be significantly reduced following PGS.”

The ASRM Practice Committee²⁹ recommends that:

“Available evidence does not support the use of PGS as currently performed to improve live-birth rates in patients with advanced maternal age.”

However, these conclusions are at odds with a number of studies which conclude that satisfactory pregnancy rates are achieved in patients with advanced maternal age undergoing PGS and that PGS may be an effective treatment for AMA patients given its

diagnostic value, high ongoing pregnancy and implantation rates, and its ability to reduce the risk of multiple pregnancies.^{10 11 15 28 33 39}

7.2 In patients with recurrent implantation failure and recurrent miscarriage, there is insufficient evidence to support a beneficial effect of PGS. The BFS recommends that:

“There is an urgent need for adequately powered prospective randomised controlled studies to assess the place of PGS in patients with different indications, including recurrent miscarriage and repeated implantation failure.”

The ASRM Practice Committee recommends that:

- *“Available evidence does not support the use of PGS as currently performed to improve live-birth rates in patients with previous implantation failure.”*
- *“Because the prevalence of aneuploidy is high in the embryos of patients with recurrent implantation failure, decisions concerning future treatment should not be based on the results of PGS in one or more cycles.”*
- *“Available evidence does not support the use of PGS as currently performed to reduce miscarriage rates in patients with recurrent pregnancy loss related to aneuploidy.”*

7.3 Although groups which have analysed the use of PGS for male factor infertility conclude that more research is needed to determine if there is a beneficial effect^{29 52}, literature demonstrates that there is a link between abnormal sperm parameters, chromosome abnormalities and success rates.

7.4 Despite there being a high incidence of embryo aneuploidy in patients with advanced maternal age, recurrent pregnancy loss and recurrent implantation failure and large studies supporting the advantages of PGS, its benefits have not yet been proven in prospective, randomised controlled studies. This may be due to flaws in the studies, making them difficult to compare (e.g. small sample size, inappropriate control groups, use of different technology for chromosome analysis and biopsy of cells on different days) and mosaicism, increasing the risk of misdiagnosis. In addition, a flaw of a number of studies is that implantation rate is used as an outcome, not live birth rate.

Although most groups and guidelines conclude that PGS should not be applied to routine clinical practice (considering the risks and costs) it may be of benefit under certain circumstances, for example where the number of embryos replaced is strictly limited. In addition, it has recently been suggested that PGS could be used as a prognostic tool in assisting patients to understand the causes of their infertility, allowing them to make informed choices about potential future treatment cycles i.e. whether to continue treatment if there is at least one euploid embryo available for transfer or to undergo oocyte donation when only aneuploid embryos are encountered⁵³.

7.5 Robust randomised controlled trials with large patient populations are needed before further conclusions can be made. It is possible that advances in technology, such as microarrays to screen the entire genome, may overcome the limitations of the current methods used and prove its benefits.

8. Recommendations

8.1 It is recommended that HFEA guidance (see Annex A) should be amended to state patients should be informed that more trials are needed to assess whether PGS can significantly increase live birth rates for all indications and that centres should monitor the latest literature and professional guidance. The Code of Practice should refer to the BFS policy and practice guidelines on PGS. Following SCAG's approval these changes will be taken into account in the development of the 8th edition of the Code of Practice.

8.2 In addition it is recommended that the HFEA patient information is amended to reflect the conclusions of this literature review. These amendments could include:

- highlighting that there is a lack of robust evidence that PGS can be used to increase success rates in patients with advanced maternal age, recurrent implantation failure, recurrent pregnancy loss and male factor infertility
- stating that a number of studies support the use of this technique, particularly when its use is restricted to certain patient groups
- referring to professional body guidance and reviews

8.3 In light of the studies outlined in section 6, regarding the safety of embryo biopsy, it is recommended that the Authority's policy on preimplantation tissue typing remains unchanged as there is no evidence to suggest that embryo biopsy has a detrimental effect.

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- 17 Twisk et al *Cochrane Database Syst Rev.* 2006 Jan 25;(1):CD005291. Preimplantation genetic screening for abnormal number of chromosomes (aneuploidies) in in vitro fertilisation or intracytoplasmic sperm injection.
- 18 Pellicer A et al. In vitro fertilization plus preimplantation genetic diagnosis in patients with recurrent miscarriage: an analysis of chromosome abnormalities in human preimplantation embryos. *Fertil Steril.* 1999 Jun;71(6):1033-9.
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