ART in recurrent miscarriage: preimplantation genetic diagnosis/screening or surrogacy?

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Recently, assisted reproductive techniques have been used to prevent further miscarriages in women with recurrent miscarriage. One approach uses either screening or diagnosis of embryonic chromosomes prior to embryo replacement [preimplantation genetic screening (PGS)/preimplantation genetic diagnosis (PGD)]. The second approach involves surrogacy. However, PGS/PGD assumes that the embryo is chromosomally abnormal, and that the mother should receive a chromosomally normal embryo. Surrogacy assumes that the embryo is normal and that the maternal environment needs to be substituted. This article examines the place of both techniques in different types of recurrent miscarriage, and tries to give guidelines as to which technique is preferable depending on the likelihood of an embryonic chromosome aberration. In repeated fetal aneuploidy or in the older patient, PGS or PGD are preferable. However, with high numbers of miscarriages, or in autoimmune pregnancy loss, surrogacy is preferable. In the light of recent work, it is uncertain which treatment mode is indicated in balanced parental chromosome aberrations. In conclusion, both techniques have a place, but probably only in those patients with a poor prognosis in whom assisted reproductive techniques will be shown to improve the subsequent live birth rate above the spontaneous rate.

Key words: PGD/PGS/recurrent miscarriage/surrogacy

Introduction

Recurrent miscarriage is usually defined as three or more consecutive miscarriages prior to 20 weeks. The cause may be fetal in origin due to an anomaly which is incompatible with life, or maternal in origin due to a hostile maternal environment. There are two known embryonic causes of fetal demise, structural malformations and chromosomal aberrations. Fifty to sixty percent of sporadic miscarriages are due to chromosomal aberrations (Boue et al., 1975; Stein, 1981). Four reports have assessed chromosomal aberrations in recurrent miscarriage. Both Stern et al. (1996) and Ogasawara et al. (2000) have reported that 50–60% of abortuses are chromosomally abnormal in women with two or more miscarriages (mean number of miscarriages, 3.8 and 3.5, respectively). Carp et al. (2001) have reported an incidence of 29% in women with three or more miscarriages (mean 4.7). Ferro et al. (2003) have used hystero-embryoscopy as a means of taking directed biopsies from the chorion for karyotyping. Chromosome abnormalities were found in 37 of 55 (67.3%) samples from women with two or more miscarriages. This technique prevented contamination from maternal tissues which could lead to a false-negative result of 22% when the sample is obtained by curettage.

Although fetal karyotyping is recommended as an essential part of the investigation of recurrent miscarriage by the Royal College of Obstetricians and Gynaecologists (2003), most centres make little attempt to karyotype the fetus in order to determine whether the pregnancy loss was of maternal or fetal origin. A presumptive diagnosis is usually made after investigations for maternal causes only. Treatment is often offered for presumed maternal causes of pregnancy loss, e.g. resection of uterine septa, anticoagulants and aspirin for antiphospholipid syndrome, etc. However, the presence of a maternal cause of pregnancy loss does not guarantee that the embryo has a normal chromosome complement. Ogasawara et al. (2000) have shown, in a small series of 10 patients with antiphospholipid syndrome, that 40% of lost embryos had chromosomal aberrations. Carp et al. (2003) have found four chromosomal aberrations in the embryos of 16 patients with hereditary thrombophilia (one embryo had a balanced translocation which was not present in either parent and had arisen de novo; three other embryos had numerical chromosomal aberrations, 16 trisomy, 13 trisomy and 45XO).

There may also be structural malformations, which are not due to chromosomal aberrations. Philipp et al. (2003) have
assessed 233 missed abortions by embryo transfer; 75% had karyotypic aberrations, but 18% had a morphological defect with no chromosomal aberrations.

It is against this background that assisted reproductive technologies (ARTs) have been used to treat recurrent miscarriage. The aim of physicians working in this field is entirely laudable, to allow childless couples to have children. There are two approaches, the first involves pre-gestational preimplantation diagnosis of known chromosomal aberrations (PGD) or screening for a variety of possible chromosomal aberrations (PGS) (Rubio et al., 2003), using embryo biopsy and replacement of a chromosomally normal embryo, and the second technique involves surrogacy (Raziel et al., 2000). However, both these modalities are based on totally different and even opposing concepts. PGS/PGD assumes that the embryo is normal, and the patient should receive a normal embryo. Surrogacy assumes that the embryo is normal and that the maternal environment must be substituted. The present choice of treatment modality is entirely empiric. In order to determine appropriate treatment logically, previous miscarriages should be karyotyped. Women losing normal embryos can be advised to consider surrogacy, and those losing abnormal embryos can be advised about PGD. If PGD is used for patients with unexplained recurrent miscarriages, the results will be confounded by women who lose normal pregnancies, and vice versa. The literature contains numerous examples of treatment for maternal causes of pregnancy loss. However, randomized trials have often been unable to demonstrate evidence of efficacy, possibly due to the results being confounded by fetal chromosomal aberrations, e.g. paternal leukocyte immunization (Clark et al., 1996), progesterone and HCG supplementation, LH reduction in polycystic ovaries, etc.

It is unlikely, however, that all pregnancy losses will be karyotyped in the near future. ‘Biochemical’ or pre-clinical pregnancies cannot be karyotyped; many miscarriages are lost spontaneously, frequently in the lavatory. Abortuses which are bought in by the patient (possibly after retrieval from the lavatory) usually lead to culture failure due to bacterial overgrowth. In the future, the use of comparative genomic hybridization (CGH) (Daniely et al., 1998) may overcome some of these problems.

In the absence of karyotyping, there are few guidelines. The first question is whether ART is required at all. Cauchi et al. (1991), Cowchock et al (1990) and the Recurrent Miscarriage Immunotherapy Trialists Group (1994) have described the factors predicting a subsequent live birth if no treatment is used. These predictive factors include: the number of previous abortions, the presence of a previous live birth, the karyotype of the previous miscarriage, concurrent infertility, maternal age, and the presence of anti-paternal complement-dependent antibodies. In our experience, 50% of women who recurrently miscarry have only three miscarriages. Their prognosis for a live birth has been described to be as high as 75% (Clifford et al., 1997). Hence, they probably require no active treatment. Both Ogasawara et al. (2000) and Christiansen et al. (2002) have shown that as the number of miscarriages increases, the chance of a fetal chromosomal aberration decreases. This is in keeping with the concept that most chromosomal aberrations are chance recurrences. Additionally, the patient who loses a chromosomally abnormal fetus has a greater chance of a live birth than the patient losing a euploid embryo (Ogasawara et al., 2000; Carp et al., 2001). Hence, it might not be enough to diagnose fetal aneuploidy, it may be necessary to show repeat aneuploidy. No series has assessed the incidence of repeat aneuploidy in a large enough series of patients with recurrent miscarriage. In the series of Carp et al. (2001), 16 of the 167 patients who had their abortus karyotyped had a (second) subsequent abortion karyotyped, 11 who had had a normal initial karyotype, and five patients with an initial aberrant karyotype. All 11 patients with a normal embryonic karyotype miscarried an euploid embryo in the (second) subsequent pregnancy. Of the five patients who initially miscarried a karyotypically aberrant embryo, three had a subsequent miscarriage of an euploid embryo; only two had a repeat miscarriage with chromosomal anomalies: one a repeat trisomy (initially chromosome 7 trisomy, followed by chromosome 13 trisomy), the second a repeat unbalanced translocation. In repeat aneuploidy, PGS seems to be the treatment of choice. Rubio et al. (2003) have published the results of a trial of PGS in women with two or more miscarriages (mean 2.9). A total of 71 women were included in the trial. In 67 cycles, normal embryos were transferred, resulting in 23 pregnancies Ten of these pregnancies resulted in live births, and nine were ongoing at the time of publication. Of the other four pregnancies, one was ectopic and three terminated in miscarriages. It is still too early to determine whether this 83% live birth rate (19 of 23 pregnancies) is significantly different from the 75% live birth rate described by Clifford et al. (1997) for patients with three miscarriages. However, in the trial of Rubio et al. (2003), it is stated that most of these couples were infertile, and required IVF due to previous salpingectomy for ectopic pregnancy or failure of artificial insemination in male infertility.

The series of Rubio et al. (2003) also describes the effect of different chromosomal abnormalities in embryo development. Only 20.2% of autosomal monosomies developed into blastocysts, whereas embryos with monosomy X developed similarly to normal embryos. Trisomies also impaired embryo development; only 34.7% formed blastocysts. Most haploid embryos arrested before cavitation, and triploid and tetraploid embryos had lower rates of development to the blastocyst stage. Hence, the more severe cases of aneuploidy might be more likely to present clinically as infertility, and the less severe aneuploidies may present as recurrent miscarriage. Consequently, PGS may be more warranted in patients with recurrent miscarriage and concurrent infertility than in women with recurrent miscarriage and no concurrent infertility. Periods of infertility have been described in as many as 32% of women with recurrent miscarriage (Clifford et al., 1994). However, PGS often uses a number of DNA probes for the most common chromosomal aberrations, and could miss a chromosomal aberration for a chromosome which was not tested. If a chromosomal aberration had been diagnosed in a previous miscarriage, PGD could be used for the specific chromosome which was associated with the previous miscarriage, and PGS for the remaining chromosomes.
There are few reports of surrogacy in recurrent miscarriage. Raziel et al. (2000) reported a normal live birth in a patient with 24 prior pregnancy losses. The author has advised surrogacy in a secondary aborter with 12 consecutive miscarriages, and a primary aborter with eight previous pregnancy losses. In both cases, the surrogate delivered normal twins. The logic of surrogacy in patients with large numbers of miscarriages is due to the poor prognosis and low incidence of chromosomal aberrations. Surrogacy, however, is a limited option, as it is illegal in many countries, and there are no laws governing surrogacy in many other countries. The complicated legal situation will therefore limit strict scientific assessment of the results to countries where surrogacy is legal.

In the case of parental chromosomal rearrangements and recurrent miscarriage, PGS seems to be a logical choice. However, the live birth rate is relatively good in these patients. In the author’s series (Carp et al., 2004), the live birth rate was similar with or without parental chromosomal aberrations. Goddijn et al. (2004) reported a 70% live birth rate in 42 women with a mean of 2.9 miscarriages. Additionally, balanced chromosomal translocations are only passed on to the offspring in 40% of cases (Boue and Galleno, 1984) and usually in a balanced form. Goddijn et al. (2004) have karyotyped 26 ongoing pregnancies in women with at least two recurrent miscarriages and a parental chromosomal aberration. Fifteen pregnancies (58%) were euploid, and 11 (42%) were balanced translocations. There were no unbalanced translocations. The author has assessed the fetal karyotype in abortuses of patients with parental aberrations. Of 72 patients aborting, 39 fetuses 28 (73%) were euploid and 11 (27%) aneuploid. Hence, in the case of parental chromosomal aberrations, it is also necessary to karyotype the embryo in order to reach an accurate diagnosis. Simopoulou et al. (2003) have reported 11 PGS cycles in eight patients with various chromosomal rearrangements. Euploid embryos were replaced in all 11 cycles. Four pregnancies ensued, leading to three live births and one ‘biochemical’ pregnancy. Hence these preliminary figures are similar in terms of live births per pregnancy in the series of the author and that of Simopoulou et al. (2003).

In women above the age of 40 years, the incidence of fetal chromosomal aberrations increases [63.6% of fetuses in women aged 40–45 as opposed to 28% of fetuses in the 20–30 age group and 23% in the 30–40 age group in the series of Carp et al. (2001)]. Hence in the older patients, PGS is probably indicated.

Numerous autoimmune conditions have been associated with recurrent pregnancy loss, including the antiphospholipid syndrome (APS). The most acceptable diagnostic criteria for APS are the ‘Sapporo’ criteria (Wilson et al., 1999), which define the clinical features as one unexplained fetal death of a morphologically normal fetus over 10 weeks of pregnancy, or three or more otherwise unexplained consecutive abortions prior to 10 weeks in the presence of antiphospholipid antibodies. However, in APS, the aborted embryo may also have chromosomal aberrations, as the presence of pathological antibodies does not guarantee normal chromosomes. The incidence of fetal chromosomal aberrations has been reported to be 20 (Takakuwa et al., 1997) to 40% (Ogasawara et al., 2000). However, in the majority of cases, fetal demise is thought to be secondary to thrombosis in the small vessels of the placenta caused directly by the antiphospholipid antibodies. The most commonly used treatment is a combination of low dose aspirin and anticoagulants such as low molecular weight heparins (Tincani et al., 2003a). Using this regimen, there is a 76% live birth rate (92 of 121) if the figures in the trials of Kuteh et al. (1996), Rai et al. (1997) and Farquharson et al. (2002) are combined. In addition, when the pregnancy does develop, women with APS are at a high risk for pre-eclampsia, intrauterine growth retardation, fetal distress, stillbirth and maternal autoimmune phenomena (Tincani et al., 2003b). In APS, patients may have a clinical picture of late pregnancy losses with obstetric complications. In these cases, chromosomal aberrations are unlikely and, if the clinical picture is repeated and has not responded to anticoagulants and aspirin, surrogacy is indicated rather than PGS. However, even if there is a high preponderance of late pregnancy losses in APS (Carp et al., 1997), 60% of pregnancy losses still occur in the first trimester (Carp et al., 1997). In these patients, it is necessary to karyotype the abortus in order to reach an accurate diagnosis of cause, and, if indicated, choose PGD or surrogacy according to diagnosis.

There are patients with family or personal histories suggestive of autoimmune disease but no serological findings. In these patients, a careful history should be taken, and the decision on PGS or surrogacy may need to be based on clinical grounds alone. The author has advised surrogacy to a 40-year-old nulliparous patient. Four zygote intra-Fallopian transfer (ZIFT) cycles were followed by four pregnancies, the first with premature rupture of the membranes at 20 weeks, and two fetal deaths at 20 weeks. The last two pregnancies were accompanied by hypertension and gestational diabetes. The fourth pregnancy was a missed abortion at 14 weeks. A thorough autoimmune screen including for antiphospholipid antibodies, anti-nuclear factor (ANF) and hereditary thrombophilias was negative. There was also no other cause apparent for the pregnancy losses. Hysteroscopy and the parental karyotypes were normal. The patient underwent eight cycles of IVF before conceiving the fifth pregnancy. However, this pregnancy was terminated at 22 weeks due to severe pre-eclampsia with a blood pressure of 190/130 mmHg and ‘HELLP’ syndrome (haemolysis, elevated liver enzymes and low platelets) despite treatment with aspirin 100 mg.

At present, both of these techniques are new, and require access to high technology. As such, they capture the attention of the news media and general public. However, if these strategies are to prove their worth, prospective controlled trials are required in which the live birth rate is compared with non-treated patients. We believe that while these techniques will not solve the problems of all women with recurrent miscarriage, both techniques have a place, but the definition of specific selection criteria based on accurate and comprehensive diagnostic procedures is necessary.
References


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PGD/PGS or surrogacy for recurrent miscarriage?