Editorial Articles

Recurrent aneuploidy - fact or fiction

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Summary

Purpose: To evaluate the likelihood that some women are more prone to forming chromosomally abnormal embryos unrelated to age. *Methods:* The literature involving studies suggesting that predisposition to aneuploidy does exist was reviewed. In addition a new anecdotal unpublished report on a tendency to form trisomies is presented and a couple of case reports dealing with the possibility of predisposition to polyploidy are discussed. *Results:* The results of in vitro fertilization and pre-implantation diagnoses confirm the suspicion that some women are more prone to trisomies or polyploidy. *Conclusions:* In vitro fertilization with pre-implantation genetic diagnosis may help in preventing miscarriage from recurrent polyploidy but is not so valuable for recurrent trisomies.

Key words: Trisomies; Recurrent pregnancy loss; Polyploidy; Pre-implantation genetic diagnosis.

Introduction

The risk of chromosome abnormalities as a cause of miscarriage is approximately 50% [1, 2]. Approximately 50% of cytogenetically abnormal spontaneous abortuses are found to have autosomal trisomies [1]. The most frequent autosomal trisomy involves chromosome 16, then 22, 21, 15, 13, and 14 in descending order of frequency. However, trisomy 16 is rarely, if ever, observed in liveborns [1]. Seventy percent of trisomies involve these six trisomies [1].

The three trisomies compatible with life involve chromosomes 13, 18, and 21 [1]. Fetuses with these three chromosomes grow faster than when lethal trisomies exist, even in those who abort in the first trimester suggesting that they either live longer or have less intrauterine growth retardation [3].

When there are more than two haploid chromosomal compliments present it is termed polyploidy. Triploidy (3n = 69) has three haploid complements and tetraploidy (n = 92) has four. Polyploidy is found in approximately 10% of abortuses. Trisomies are twice as likely to be present in abortuses than polyploidy [1].

Monosomy X is about as frequent as trisomies and 80% of the time it is the paternal x that is missing [1]. There has been a suggestion that recurrent aneuploidy occurs more often than expected by chance alone. Fifty-percent of abortuses are chromosomally normal. Thus only one of eight women with three consecutive miscarriages should show chromosomal abnormalities by chance alone. Several studies found that if aneuploidy existed in the first abortus the risk of aneuploidy, especially trisomy, was more likely in the second abortus than expected by chance alone [4-6].

Some studies adjusted for age have found a correlation with a higher prevalence of aneuploidy with prenatal genetic diagnosis (PGD) in women with progressively more miscarriages [7, 8]. The exception may be those with more than four losses [9]. Since not every embryo created has aneuploidy, if the etiology is increased risk of aneuploidy then the odds are that eventually a normal fetus will be formed. When there have been ≥ 4 previous losses the etiology will favor an abnormality that will be persistent each time [9, 10]. Another study of PGD found the prevalence of trisomy to be 50% higher in women with previous trisomies vs women having PGD performed for other reasons [11]. The same conclusions were reached by Munne *et al*. in women aged ≤ 35 but no differences were found in women > 35 [6].

Even if one concedes to the argument that some women may be more prone to produce embryos with trisomies, this may have little clinical significance. Even with in vitro fertilization given the frequency of trisomic embryos even in those with a history of one or two previous miscarriages with documented trisomies, the odds are that with two or three embryos transferred that there should be at least one normal embryo. Thus it does not seem warranted to add the extra expenditure of pre-genetic diagnosis of the embryo prior to transfer for the reason of a previous loss or two of a trisomic fetus. Since a trisomic embryo occurs in about one-fourth of the embryos created one may expect one in 16 women to experience by chance alone two miscarriages related to trisomies.

The more significant question is the role of aneuploidy as a cause of recurrent miscarriages of three or more. At first glance the data from Stephenson *et al*. would suggest that a predisposition to trisomies is not an important factor in women with recurrent miscarriage because 54% of the cytogenetic diagnosis of another abortus in a group of women with recurrent miscarriage were normal euploid [12]. However to reiterate a point made above, the more miscarriages

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in a row the more likely there could be causes that could repeat in all or most pregnancies, e.g., hormonal (especially progesterone deficiency), immunological, or structural uterine defects which would favor more euploid embryos. Perhaps the 54% euploidy rate would have been higher if it had not been somewhat negated by an increased predisposition to aneuploidal embryos. In fact as previously mentioned the expected distribution between trisomy and monosomy x would be equal. However the study by Stephenson *et al*. found that 67% of the embryos were trisomies vs only 9% with monosomic x [12]. The polyploidy rate of 9% of women was consistent with the rate in abortuses of an unselected population.

These data suggest to us that the purposeful use of in vitro fertilization-embryo transfer (IVF-ET) and PGD for most women with recurrent miscarriage is not warranted based on its expense and risk of ovarian hyperstimulation. If certain genetic factors make a 32-year-old woman as prone to aneuploidy as a 42-year-old, strategies to prevent another miscarriage would not change. The knowledge might merely influence the treating physician to more strongly advise antenatal testing.

The question still exists however as to whether there still may be some women who for some reason are prone to having trisomies in the large proportion of the embryos formed. If so, that knowledge could influence the couple to change gametes if the partner causing the problem is identified or to consider donor embryos if the source of the problem is not identified. Since such cases would be rare the establishment of the existence of such problems may have to depend on anecdotal experience.

The first author of this editorial had an oral presentation at the 2008 American Society for Reproductive Medicine meeting in San Francisco entitled "The effect of the 46XX dup [8] (p23 p23) and 46XY, inv [9] (p11 913) on recurrent pregnancy loss". These chromosomal structural rearrangements are generally considered to be benign karyotypic variants. The case described was a 35-year-old primary aborter with four consecutive first trimester miscarriages. Following the first two miscarriages (in which chromosome analysis of fetal products were not performed) both male and female partners had karotyping performed.

The female partner, who did not have any phenotypic abnormalities, was found to be 46XX dup [8] (p23 p23). This karytope would be consistent with either a true 8 duplication or a euchromatic variant, i.e., variation in the number of copies of the 8p 23.1 chromosomal segment. Since the former, i.e., true duplication is associated with an increased risk of developmental delay or cardiac defects and the latter is not associated with any phenotypic defects it becomes important to distinguish these entities. Blood was sent to John Barber at Wessex Regional Genetics Laboratory in the United Kingdom and the results of molecular genetic analysis indicated that it was just a euchromatic variant and should not have any clinical significance.

The male partner was found to have a pericentric inversion of chromosome 9 which is also considered as a benign variant. Despite the fact that the chromosome abnormalities in male and female partners were considered benign there was consideration given that these chromosomal variants could possibly lead to meiosis errors leading to aneuploidy. Thus the couple elected to have this procedure performed after discussing the benefits and deficits of IVF-ET with PGD. Fluorescent in situ hybridization (FISH) was used to evaluate chromosomes 13,15,16,17,18,21,22 X and Y. Only one of five embryos with blastomere biopsy and PGD was normal and it did not survive for a day 5 transfer. A second IVF-ET PGD cycle was attempted and this time none of the three embryos evaluated were normal. The chromosome abnormalities for these seven abnormal embryos included trisomies 13, 15, 16, 18 and monosomies for chromosomes 15, 16 and 18.

Though the possibility exists that the miscarriages in this couple were related to non-genetic reasons the much higher frequency of aneuploid following PGD suggests that some women may be markedly prone to meiosis errors. In this case the question is whether the normally "benign"chromosome variations may have been responsible for this apparent predisposition to aneuploidy. This case could possibly also suggest that the problem could be related to a normally benign karyotypic variant in the chromosomes of the male partner.

As mentioned earlier, for those who think there can be some women with a predisposition to aneuploidy and that this predisposition mainly is represented by triploidy as based on evaluation of a large series of PGD, there are some anecdotal reports also suggesting a predisposition to polyploidy. Two cases have been described supporting this concept [13, 14]. One report described a woman with two previous miscarriages with chromosome analysis of fetal products revealing triploidy [13]. Subsequent IVF-ET with intracytoplasmic sperm injection (ICSI) and PGD found two embryos out of 13 with triploidy [12]. In the other case a woman had a spontaneous miscarriage at age 24. Her second pregnancy ended in a first trimester miscarriage and it was triploidy. The third pregnancy she completed the first trimester but aborted in the second trimester and again triploidy was found [14]. In vitro fertilization with ICSI and PGD were performed and 13 embryos were biopsied and six were normal. There was one tetraploidy among the seven abnormal embryos [14].

Triploidy occurs in 2% of all conceptuses [15]. Maternal origin of triploidy occurs in only 10% of the cases [1]. Thus it is estimated that one in 100 oocytes (0.2%) has a failure of maternal meiosis resulting in triploidy [15]. Tetraploidy is even less common.

These two cases strongly suggest that some women may have a predisposition for meiosis errors leading to triploidy. In these two cases there were no chromosome abnormalities in the male or female partners [13, 14]. However as illus-

trated in case 2, if it is assumed that all the abnormal fetuses had lethal chromosome abnormalities so that only the six normal embryos and the polyploidy embryo could implant was it just a coincidence that the two documented abortuses were trisomy 21 with odds of one in 50 of this happening? Another possibility is that when it comes to polyploidy for some reason the oocyte with at least one extra set of chromosomes is more likely than even the chromosomally normal oocyte in becoming the dominant follicle.

For this second case IVF with ICSI and PGD resulted in a live normal delivery. The mere development of multiple embryos may have been sufficient even without the IVF and PGD if the theory of the egg with more than one set of chromosomes becoming the dominant egg is correct. The question is whether there is some property about the polyploidy embryo that allows its dominance for implantation compared to the other embryos. If so then merely controlled ovarian hyperstimulation on IVF-ET with transfer of three or four embryos may not be sufficient and PGD could be necessary.

On the other hand, the woman with the recurrent trisomies had two IVF-ET cycles without the transfer of a single normal embryo. Thus a huge financial burden was accrued without any benefit. Thus whereas a possible role for IVF-ET and PGD exists for recurrent polyploidy it does not seem appropriate for recurrent trisomies.

For the couple with recurrent triploidy they could keep trying naturally hoping for a lucky break. The next cheapest option would be to just try donor sperm hoping the male was responsible. Donor oocytes with fertilization of half the husband's sperm and half the donor's sperm with the transfer of the embryos fertilized by the husband first is the most expensive option, but giving hope to the couple of at least carrying some of their own genetic information. Finally for this couple the use of donated embryos could be considered as it is relatively inexpensive [16, 17].

The role of fetal karytyping for repeated pregnancy loss related to structural chromosomal abnormalities, e.g., balanced or reciprocal translocation or inversion in paternal or maternal karyotyping, will be discussed in more detail in a subsequent editorial.

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