A case report supporting the concept that some women have a predisposition for maternal meiosis errors resulting in digyny

J.H. Check, B. Katsoff, D. Summers-Chase, J. Breitbart

The University of Medicine and Dentistry of New Jersey, Robert Wood Johnson Medical School at Camden, Cooper Hospital/University Medical Center, Department of Obstetrics and Gynecology, Division of Reproductive Endocrinology & Infertility, Camden, NJ (USA)

Summary

Purpose: To determine if a primary aborter with recurrent miscarriage times three with her only two fetal products that were evaluated with chromosome analysis demonstrating triploidy in both fetuses could have a predisposition for maternal meiosis errors. *Methods:* In vitro fertilization with intracytoplasmic sperm injection was performed. Embryo biopsy was performed on 3-day old embryos and a single blastomere was evaluated by fluorescent in situ hybridization (FISH). Embryo transfer would be performed on day 5 at the blastocyst stage. *Results:* There were six normal and seven abnormal embryos. One of the seven was a tetraploid embryo (92XXXX). *Conclusions:* The majority of triploidies are related to polyspermy but this factor was excluded by performing ICSI. Thus this woman showed a marked predisposition to digyny. Though the tetraploidy could be explained by fertilization of a digynic egg by a diploid sperm the probability was that in this instance the meiosis error extended back to failure to extrude the first polar body.

Key words:

Introduction

Triploidy in which there are 69 chromosomes in a given cell may be related to fertilization by two sperm (known as dispermy), or by one sperm with two sets of chromosomes, or related to problems of meiosis with the oocyte so that fertilization of a diploid oocyte occurs with a sperm with a single set of chromosomes.

Jacobs et al., found that when dealing with one set of extra chromosomes that 60% of the time the problem is related to fertilization by two sperm (dispermy), 24% due to fertilization with a diploid sperm and only 10% of the time a female factor related to fertilization of a diploid oocyte [1].

A case was reported of recurrent triploidy of maternal origin (2). She not only had two previous spontaneous miscarriages related to triploidy but when they performed in vitro fertilization (IVF) with intracytoplasmic sperm injection (ICSI), two of the 13 embryos had triploidy [2].

This case exemplifies that some women may have a predilection to meiosis errors resulting in triploidy. By performing ICSI, the embryos with triploidy evaluated by pre-implantation diagnosis had to be of maternal origin.

Triploidy occurs in 2% of all conceptuses [1]. Since maternal origin only occurs in 10% of all triploidy cases, and since triploidy comprises 2% of all conceptuses, it is estimated that one in every 500 oocytes (0.2%) has a failure of maternal meiosis resulting in triploidy [1].

In the case described there were 26.6% (4 of 15) of the embryos showing triploidy (counting the 2 miscarriages) indicating that some women may have a predisposition for recurrent triploidy related to maternal non-dysjunction during oogenesis [2].

Another case is described of maternal meiosis abnormalities leading to retention of extra sets of chromosomes.

Case Report

A 24-year-old woman had a miscarriage at nine weeks. There were no chromosome studies on the fetus performed. She came for investigation to reduce the risk as much as possible of a second miscarriage.

She had a normal hysterosalpingogram. Thyroid studies were normal as was measurement of antiphospholipid antibodies. Also chromosome analyses on both the female and male partner were normal (46XX, 46XY). The patient's dominant follicle was deemed mature (exceeding 18 mm average diameter with a minimum serum estradiol > 200 pg/ml) so she was treated in the luteal phase with 200 mg twice daily progesterone vaginal suppositories which was increased to 400 mg twice daily after she quickly conceived. When she reached six weeks of gestation there was no heart beat. Nine days later a heart beat was detected but it was only 100 per minute and the crown rump length was behind by one week. The following week it was no longer viable. A D&E was performed and chromosome analysis revealed triploidy.

A few months later she conceived again just taking progesterone in the luteal phase and the first trimester. A single viable fetus was seen at 6.5 weeks' gestation but the sac size and crown rump length was one week behind the fetus. Viability was still seen at 8.7 weeks but the crown rump length was 19 mm consistent with 8.3 weeks but the sac average was 21mm consistent with 6.95 weeks. The sac fell behind a full two weeks by 9.5 weeks of gestation. The fetus remained alive though

Revised manuscript accepted for publication May 19, 2008

through the first trimester and died shortly after the second trimester. Chromosome analysis again showed triploidy.

It was decided, based on three consecutive losses in such a young woman with triploidy in her last two (the chromosome constitution of the first miscarriage was unknown), to do in vitro fertilization-embryo transfer (IVF-ET) with preimplantation genetic diagnosis (PGD). There were 13 embryos biopsied on day 3 and they were evaluated by FISH analysis for chromosomes 13, 18, 21 X and Y. There were six "normal" embryos and five grew to blastocysts. There were two transferred and three cryopreserved. She achieved a pregnancy and successfully completed her first trimester with a completely normal rise in the serum beta-hCG level and appropriate growth of the fetus.

There were no trisomies among the seven abnormal embryos but interestingly there was one tetraploidy (92XXXX).

Discussion

One of the most common mechanisms involved in triploidy of maternal origin is non-extrusion of the second polar body [3]. This state of digynic triploidy was described by Grossman *et al.* in 1997 after performing PGD on eggs fertilized by ICSI [4].

The fact that ICSI was performed eliminates the possibility of the most common etiology for an additional set of chromosomes which is the penetration of the oocyte by two sperm [1].

One possible explanation for a tetraploid embryo was the combination of two digynic (female) pronuclei and two diandric (male) pronuclei.

Of the 42 documented cases of diandric trisomy [4]: 37 were related to dispermy and five (12%) were related to fertilization by diploid sperm.

Failure of maternal meiosis leading to an extra set of chromosomes has been estimated to occur in 1 of 500 conceptuses (0.2% [2]. Thus the chance that two consecutive miscarriages would be trisomies is 1:40,000.

Though diploid sperm are considered to occur in at least 1.9% of the sperm in an infertile population, they are rarely present in noromozoospermic males [5, 6]. The male partner in this study was considered to be normozoospermic and thus the likelihood of diploid sperm would be unlikely.

Nevertheless even if in this couple the tetraploid embryo was fertilized by a diploid sperm this would account only for an embryo with triploidy. Thus, if there was diandry present, there would also have to be a maternal meiosis error, i.e., digyny with failure to extrude the second polar body.

With the 92XXXX karyotype another possibility which seems more probable was that since the one-cell zygote is tetraploid after DNA replication, the tetraploidy may have resulted from failure to extrude even the first polar body.

With 1:500 odds of any given embryo having triploidy (or tetraploidy) related to a maternal meiosis disorder, it is highly unlikely that one of 13 embryos tested by PGD would be either a triploid or tetraploid embryo. Thus this case clearly shows that some women may have a tendency for failure to extrude the polar bodies.

Since only one in seven eggs that had the potential to result in a pregnancy was digynic, the odds of trisomy occurring in two pregnancies considering an equal chance of any egg being the one fertilized would be about one in 50. Thus this case suggests that possibly there is some property concerning a digynic egg that makes it more likely to result in attaining the status of a dominant follicle.

References

[1] Jacobs P.A., Angell R.R., Buchanan I.M., Hassold T.J., Matsuyama A.M., Manuel B.: "The origin of human triploids". *Ann. Hum. Genet.,* 1978, *42,* 49.

[2] Pergament E., confine E., Zhang J.X., Roscetti L., Chen P.X., Wellman D.: "Recurrent triploidy of maternal origin". *Prenat. Diagn.,* 2000, *20,* 561.

[3] Rosenbusch B., Schneider M.: "A brief look at the origin of tetraploidy". *Cytogenet. Genome Res.,* 2004, *107,* 128.

[4] Grossman M., Calafell J., Brandy N., Vanrell J.A., Rubio C., Pellicer A. *et al.*: "Origin of tripronucleate zygotes after intracytoplasmic sperm injection". *Hum. Reprod.*, 1997, *12,* 2762.

[5] Rosenbusch B., Schneider M., Sterzik K.: "The chromosomal constitution of multipronuclear zygotes resulting from in vitro fertilization". *Hum. Reprod.*, 1997, *12,* 2257.

[6] Zaragoza M.V., Surti U., Redline R.W., Millie E., Chakravarti A., Hassold T.J.: "Parental origin and phenotype of triploidy in spontaneous abortions: predominance of diandry and association with the partial hydatidiform mole". *Am. J. Hum. Genet.,* 2000, *66,* 1807.

Address reprint requests to:
J.H. CHECK, M.D., Ph.D.
7447 Old York Road
Melrose Park, PA 19027 (USA)
e-mail: laurie@ccivf.com