OBSTETRICS

Triploid pregnancies: genetic and clinical features of 158 cases

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OBJECTIVE: The purpose of this study was to analyze the correlation between the genetic constitution and the phenotype in triploid pregnancies.

STUDY DESIGN: One hundred fifty-eight triploid pregnancies were identified in hospitals in Western Denmark from April 1986 to April 2010. Clinical data and karyotypes were collected retrospectively, and archived samples were retrieved. The parental origin of the genome, either double paternal contribution (PPM) or double maternal contribution (MMP) was determined by an analysis of methylation levels at imprinted sites.

RESULTS: There were significantly more PPM than MMP cases ($P <$ .01). In MMP cases, the possible karyotypes had similar frequencies, whereas, in PPM cases, 43% had the karyotype 69,XXX, 51% had the karyotype 69,XXY, and 6% had the karyotype 69,XYY. Molar phenotype was seen only in PPM cases. However, PPM cases with a nonmolar phenotype were also seen. For both parental genotypes, various fetal phenotypes were seen at autopsy. Levels of human chorionic gonadotropin in maternal serum were low in MMP cases and varying in PPM cases, some being as low as in the MMP cases.

CONCLUSION: In a triploid pregnancy, suspicion of hydatidiform mole at ultrasound scanning, by macroscopic inspection of the evacuated tissue, at histology, or because of a high human chorionic gonadotropin in maternal serum level each predict the parental type PPM with a very high specificity. In contrast, the sensitivity of these observations was <100%.

Key words: diagnosis, genomic, human chorionic gonadotropin, hydatidiform mole, triploidy

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Triploidy, which is one of the most common chromosome aberrations, is estimated to occur in 1-2% of all human conceptions.[1]

Triploid pregnancies can be classified according to the genetic constitution. The genome in a triploid pregnancy is either digynic, which consists of 2 maternal and 1 paternal set of chromosomes (MMP), or diandric, which consists of 2 paternal and 1 maternal set of chromosomes (PPM).[1] Extremely varying frequencies of the 2 parental types have been reported (the frequency of PPM cases ranges from 20−73%).[1-9]

Triploid pregnancies can also be classified according to their phenotype. By the use of ultrasound scanning (US), it has been found that the placenta can appear normal, small, or enlarged and with or without vesicular changes. If a fetus is present, it can exhibit malformations but can also appear normal. Growth restriction appears to be a common, but not a consistent, phenomenon.[10] In studies that have been focused on levels of serum maternal human chorionic gonadotropin (MS-hCG), low, normal, and high levels have been reported.[11-13] In some studies that involved postmortem examinations of triploid pregnancies, 2 distinctive phenotypes have been suggested: type 1, relatively well-grown fetuses with proportionately sized body parts and large placentas with the morphologic condition of a partial hydatidiform mole; type 2, fetuses with severe growth retardation, an uneven development of various body parts that typically results in a relative macrocephaly and small, noncystic placentas.[4,14]

However, a systematic description and classification of a large cohort of triploid pregnancies has not been published. We correlate the parental origin of the genome with karyotype and phenotype of the triploid pregnancy and with the concentration of MS-hCG in a series of 158 triploid pregnancies.

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Materials and Methods

The study was approved by the Regional Committees on Health Research Ethics in Southern Denmark and the Central Region Denmark and by the Danish Data Protection Agency.

We aimed at including all triploid pregnancies in Western Denmark (Jutland) that were diagnosed from April 1986 to April 2010. In this period, triploid pregnancies were registered either in The Danish Mole Project (DMP), The Danish Cytogenetic Central Registry (DCCR), or both.

As part of the DMP, gynecologists in Jutland forward fresh placental tissue from pregnancies that are suspected to be hydatidiform moles. Triploidy is identified by karyotyping uncultured and/or cultured cells and/or by measurement of the nuclear DNA contents by flow cytometry of unfixed nuclei with the use of 2 external controls.[15]

The DCCR has held data on all karyotypes that have been made for clinical purposes in Denmark since 1960. All women in Jutland who have been registered in the DCCR with a triploid pregnancy in the study period were identified. With the use of the women's Civil Registration System number, their place of residence was found, and the laboratory that performed the genetic analysis was identified.

Frozen cell cultures and/or DNA were retrieved from the departments of clinical genetics at Aarhus University Hospital and Vejle Hospital and from the DMP.

Determination of the parental origin of the genome

DNA was purified with QIAamp DNA Mini Kit (●●●●). The triploid samples were analyzed with methylation-specific multiplex ligation–dependent probe amplification.[16] In brief, the level of methylation at 2 imprinted loci in the 11p15 region was measured with the SALSA MLPA ME030 BWS/RSS probemix (Kit ID MRCH 30808 and MRCH 36554; MRC-Holland, The Netherlands). Because imprinted loci are methylated in a parent-of-origin–specific manner, we previously have shown that the methylation level is an indicator of the proportion of maternally vs paternally inherited genomic material.[16]

TABLE 1
Karyotypes correlated to parental type

Karyotype	Total, n	Double paternal contribution/double maternal contribution, n
69,XXX	61	49/12
69,XXY	69	59/10
69,XYY	7	7/0
Total	137	115/22

Joergensen. Classification of triploid pregnancies. Am J Obstet Gynecol 2014.

Clinical data

Information regarding the first day of last menstrual period, the maternal serum concentration of the beta subunit of human chorionic gonadotropin (MS-beta hCG; if tested in the first trimester), the maternal serum concentration of total human chorionic gonadotropin (MS-total hCG; if tested later in pregnancy), and the results from histopathologic examination/autopsy of the pregnancy were retrieved from medical records. Data on the morphologic findings that were observed by US were retrieved from Astraia (a database used by the Danish Departments of Gynecology and Obstetrics).

Gestational age was calculated from last menstrual period (GA_{LMP}) by Naegele's rule.[17]

Classifications and definitions

The placenta was categorized as molar if the sonographer described the placenta with cystic spaces or molar appearance, if the placenta fulfilled the criteria for inclusion in the DMP, or if a histopathologic diagnosis of hydatidiform mole was made.

Fetal abnormalities detected by US were defined as any fetal malformation and/or oligohydramnios and/or intrauterine growth restriction (IUGR). With regards to abnormalities of the fetus that were found after termination, the morphologic condition that was described by the obstetrician after evacuation, and the autopsy findings were retrieved.

For the MS-beta hCG and MS-total hCG, the multiples of the median (MoMs) were calculated by expressing the absolute concentrations relative to the median for the relevant GA_{LMP}. For MS-beta hCG, medians were calculated by the algorithm described by Spencer.[18] For MS-total hCG, medians were calculated by the exponential regression.[19] Low levels of MS-hCG were defined as <0.5 MoM; high levels were defined as >3.0 MoM.

Categoric variables were compared with the use of the chi-square test, Fisher's exact test (Microsoft Excel 2010; Microsoft Corporation, Redmond, WA), or unpaired *t*-test (Graph Pad Prism, version 5.01; GraphPad Software, Inc, La Jolla, CA). GA_{LMP}s were compared with the use of a 2-tailed Mann-Whitney test (Graph Pad Prism software version 5.01; GraphPad Software, Inc). Significance level was set at a probability value of $< .05$.

Results

Data on each triploid pregnancy can be seen in the Appendix (Supplementary Table).

A total of 183 triploid pregnancies had been registered: 140 in the DMP, 41 in the DCCR, and 2 who were registered in both the DMP and the DCCR. We succeeded in retrieving samples from a total of 158 cases: 121 cases from the DMP, 35 from the DCCR, and the 2 cases who were registered both in the DMP and the DCCR. Clinical data were available in all 158 cases.

GA_{LMP} at termination was available in 115 cases (21 MMP and 94 PPM) and ranged from 10 + 5 to 30 + 3 weeks'

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