Received: 12 September 2019 | Revised: 2 February 2020 | Accepted: 5 February 2020

DOI: 10.1002/pd.5666

ORIGINAL ARTICLE

PRENATAL DIAGNOSIS WILEY

Prenatal sonographic features can accurately determine parental origin in triploid pregnancies

Malou A. Lugthart[1] | Judith Horenblas[1] | Emily C. Kleinrouweler[1] | Melanie Engels[2] | Alida C. Knegt[3] | Karin Huijsdens[4] | Elisabeth van Leeuwen[1] | Eva Pajkrt[1]

[1]Department of Obstetrics and Gynecology, Amsterdam UMC, University of Amsterdam, Amsterdam, The Netherlands

[2]Department of Obstetrics and Gynecology, Amsterdam UMC, VU University, Amsterdam, The Netherlands

[3]Department of Clinical Genetics and Genome Diagnostics, Amsterdam UMC, University of Amsterdam, Amsterdam, The Netherlands

[4]Department of Genome Diagnostics, UMC Utrecht, University Medical Center Utrecht, Utrecht, The Netherlands

Correspondence
Malou A. Lugthart, Department of Obstetrics and Gynecology, Amsterdam UMC, University of Amsterdam, Meibergdreef 9, Amsterdam 1105 AZ, The Netherlands
Email: m.a.lugthart@amsterdamumc.nl

Abstract

Objective: To describe the prenatal sonographic features and maternal biochemical markers in triploid pregnancies and to assess whether prenatal phenotype can determine genetic origin.

Methods: We performed a retrospective multicenter cohort study that included all triploid pregnancies diagnosed between 2000 and 2018 in two Fetal Medicine Units in Amsterdam. Fetal growth, presence of structural anomalies, extra-fetal anomalies, and maternal biochemical markers were retrieved. Asymmetrical intrauterine growth restriction was diagnosed when the head-to-abdominal circumference (HC/AC) ratio was >95th centile. Parental origin was analyzed via molecular genotyping in 46 cases (38.3%).

Results: One hundred and twenty triploid pregnancies were identified, of which 86 cases (71.6%) were detected before 18 weeks of gestation. Triploidy of maternal origin was found in 32 cases (69.6%) and was associated with asymmetrical growth restriction, a thin placenta, and low pregnancy-associated plasma protein A and free beta-human chorionic gonadotrophin (β-hCG) levels. Triploidy of paternal origin was found in 14 cases (30.4%) and was associated with an increased nuchal translucency, placental molar changes, and a high free β-hCG. Prospective prediction of the parental origin of the triploidy was made in 30 of the 46 cases based on phenotypical ultrasound presentation, and it was correct in all cases.

Conclusion: Asymmetrical growth restriction with severe HC/AC discrepancy is pathognomonic of maternal triploidy. Placental molar changes indicate a paternal triploidy. Moreover, triploidy can present with an abnormal first trimester combined test, with serum levels on the extreme end. When available results of maternal serum markers can support the diagnosis of parental origin of the triploidy, an accurate assessment of the parental origin based on prenatal sonographic features is possible, making DNA analysis redundant.

What's already known about this topic?

- Triploidy is a lethal chromosomal anomaly.
- Two distinct phenotypes are known and the extra haploid set of chromosomes can either be maternal or paternal in origin.
- Maternal complications can occur in triploid pregnancies of paternal origin when a partial hydatidiform mole is present.

What does this study add?

- A proper assessment of the parental origin of triploidy can be made, based on prenatal sonographic features and maternal biochemical markers, making DNA analysis redundant.
- As the detection of triploidy is not feasible by all cell-free DNA tests, sonographers should be aware of its sonographic features.

1 | INTRODUCTION

Triploidy is the most common type of polyploidy. It is a chromosomal anomaly characterized by an extra set of haploid chromosomes of maternal (digynic) or paternal (diandric) origin, leading to the presence of 69 chromosomes instead of 46. Triploidy is estimated to occur in 1% to 2% of all conceptions[1-4] with the majority leading to miscarriage in the first trimester, accounting for about 20% of spontaneous abortions with chromosomal anomalies.[2,4] Therefore, prevalence decreases with advancing gestation, with an estimated prevalence of 0.03% at 10 to 12 weeks[5] compared to 0.002% at 16 to 20 weeks.[6] Triploidy is a lethal condition, only 1:10.000 triploid conceptions are live born.[7]

The distinction between two phenotypes in triploid pregnancies was first described in 1991 by McFadden and Kalousek.[8] They found evidence for genomic imprinting and differentiated between two phenotypes that correlated with the parental origin of the extra haploid set.[8-10] Phenotypically, triploidy of maternal origin is characterized by a fetus with a severe asymmetrical growth restriction and a thin placenta.[9-12] Triploidy of paternal origin is characterized by a mildly growth restricted fetus with either proportionate head size or slight microcephaly, and an enlarged placenta with cystic changes.[9-12] The enlarged placenta is a partial mole in 60% to 80% of cases.[3,13,14] Triploid pregnancies of maternal origin are not associated with placental molar changes. However, the majority of triploidies are paternal in origin.[15]

The ability to distinguish between maternal- and paternal triploidy is essential because of the maternal complications that can occur in triploid pregnancies of paternal origin, due to the presence of a partial mole.[10,16-18] Complications that may occur are preeclampsia and in approximately 2% Gestational Trophoblastic Neoplasia (GTN).[10,16-19]

2 | AIM OF THE STUDY

The purpose of this study was to describe the prenatal sonographic features and biochemical results in triploid pregnancies and to assess whether prenatal phenotype can determine the parental origin in triploidy.

3 | METHODS

3.1 | Design and participants

We performed a retrospective cohort study in the greater Amsterdam region, covered by two Fetal Medicine Units: Amsterdam UMC location VUmc and location AMC. A case list of all pre- and postnatally diagnosed triploid pregnancies was obtained from the cytogenetic laboratory and merged with our prenatal database. All triploid singleton and twin pregnancies with an estimated date of delivery from January 1, 2000 until December 31, 2016 (VUmc) and from January 1, 2000 until July 31, 2018 (AMC) were included. In total, 120 triploid pregnancies were identified, of which 37 cases originated from location VUmc and 83 cases originated from location AMC. During the study period, a nuchal translucency (NT) measurement and first trimester combined test to screen for fetal aneuploidy has been available in the Amsterdam region from 2000 until 2006. Since 2007, the first trimester combined test is available for all patients in the Netherlands.

TABLE 1 Indication for referral based on gestational age at detection

<14 weeks of gestation n = 59 (49.1)		14-18 weeks of gestation n = 27 (22.5)		18-24 weeks of gestation n = 32 (26.7)		≥24 weeks of gestation n = 2 (1.7)	
Abnormal combined test	27	Fetal anomalies	9	IUGR and fetal anomalies	19	IUGR and fetal anomalies	1
Fetal anomalies	14	IUGR and fetal anomalies	9	Fetal anomalies	10	IUGR	1
Increased NT	9	Abnormal combined test	3	IUGR	1		
IUGR and fetal anomalies	6	Maternal age	3	IUFD	1		
IUGR	3	IUFD	2	History of trisomy 21	1		
		IUGR	1				

Note: Date are given as n (%).
Abbreviations: IUGR, intra-uterine growth restriction. IUFD, intra-uterine fetal death; NT, Nuchal Translucency Thickness.

3.2 | Data extraction

Data were collected retrospectively by reviewing prenatal and obstetric records. Information on demographic data, type of pregnancy (singleton/twin), gestational age at diagnosis, results of first trimester combined test, ultrasound findings including fetal biometry, structural malformations and amniotic fluid volume, prenatal suspicion of parental origin, maternal complications, pregnancy outcome and histopathologic examination of the placenta were obtained. All cases of spontaneous fetal demise were defined as intrauterine fetal death (IUFD). The results of invasive prenatal diagnostics were retrieved from our department of clinical genetics, including molecular genotyping by using microsatellites polymorphic markers to define the parental origin of the extra set of chromosomes (PowerPlex 16 System Promega). Fetal and extra-fetal anomalies detected on ultrasound were compared between parental origin of the triploidy.

3.3 | Definitions

The first trimester combined test comprised of (a) maternal age, (b) NT measurement, and (c) serum screening of free beta-human chorionic gonadotrophin (β-hCG) and pregnancy-associated plasma protein A (PAPP-A). The first trimester combined test was considered abnormal when the risk of fetal trisomy 21, 18, or 13 was increased to >1:200 for either one of the three aneuploidies. Ultrasound anomalies were divided into fetal structural anomalies and extra-fetal anomalies. Fetal structural anomalies were defined as any anatomical defect on ultrasound. Extra-fetal anomalies included amniotic fluid changes, placental changes and umbilical cord abnormalities. Placental molar changes were defined as a large or hydropic placenta and/or a placenta with multiple cysts.[16,20] Intrauterine growth restriction (IUGR) was reported separately. Early IUGR was defined as a crown rump length (CRL) below the fifth percentile, based on multiple measurements between a gestational age of 10 and 12 weeks. After 12 weeks, IUGR was defined as an abdominal circumference (AC) below the fifth percentile according to the reference curves of Verburg et al.[21] The head-to-abdominal circumference ratio (HC/AC ratio) > 95th percentile was used to define severe asymmetrical fetal IUGR.[22] Microcephaly was defined as a head circumference (HC) below the third percentile for age and sex.[23] The diagnosis of triploidy was made by fetal chromosome analysis, either pre- or postnatally. Karyotyping was used before 2011 and Quantitative Fluorescence Polymerase Chain Reaction (QF-PCR) thereafter. When QF-PCR failed for any reason, Fluorescence in situ Hybridization on interphase nuclei was performed. Parental origin of the triploidy was analyzed by molecular genotyping using microsatellite polymorphic markers.

3.4 | Statistical analysis

Ultrasound measurements were plotted against the reference curves for fetal growth using Microsoft Excel 2016 (Redmond, Washington). Binary variables were compared with use of Fisher's exact test. In cases where zeros caused computational problems, 0.5 was added to all cells.[24,25] Continuous variables were compared using the Mann-Whitney *U* test. A *P*-value <.05 was considered statistically significant. Statistical analyses were performed using IBM Corp SPSS Statistics version 23.0 released 2015 (IBM Corp, Armonk, New York).

4 | RESULTS

4.1 | Population characteristics

In total 120 triploid pregnancies were identified of which 118 were singleton pregnancies (98%) and two twin pregnancies (2%). The mean maternal age was 31.6 ± 4.9 years and 38 of the 120 cases were primigravidas (31.7%). Indication for referral to a Fetal Medicine Unit, varied with gestational age (Table 1). Before 14 weeks of gestation, an abnormal first trimester combined test was the main reason for referral, in contrast to IUGR and fetal anomalies after 14 weeks of gestation (Table 1). The rate of first trimester detection was stable during the study period. Overall, in 83 cases (69,2%) reason for invasive prenatal diagnostics were abnormalities on ultrasound (fetal anomalies with or without IUGR). In 30 cases (25%), an abnormal first trimester combined test (aneuploidy risk >1:200) was reason for prenatal invasive diagnostics. All of 30 cases with an abnormal first trimester combined test showed abnormalities on ultrasound (fetal or extra-fetal anomalies with or without IUGR). The remaining seven cases were referred for prenatal diagnostics because of advanced maternal age (n = 3; 2.5%), IUFD (n = 3; 2.5%), or a history of trisomy 21 (n = 1; 0.8%).

Table 2 shows pregnancy outcome based on gestational age at detection of the triploidy. Termination of pregnancy was the most reported outcome.

TABLE 2 Pregnancy outcome based on gestational age at detection

Outcome	<14 weeks of gestation	14-18 weeks of gestation	18-24 weeks of gestation	≥24 weeks of gestation	Total
TOP	41	18	25	1	85 (70.8)
IUFD	16	6	7	1	30 (25.0)
Unknown	2	3	NA	NA	5 (4.2)
Total	59 (49.1)	27 (22.5)	32 (26.7)	2 (1.7)	120 (100.0)

Note: Data are given as *n* (%). There were no cases of neonatal death, no live born fetuses were reported.
Abbreviations: IUFD, Intrauterine fetal death; NA, not applicable; TOP, Termination of pregnancy.

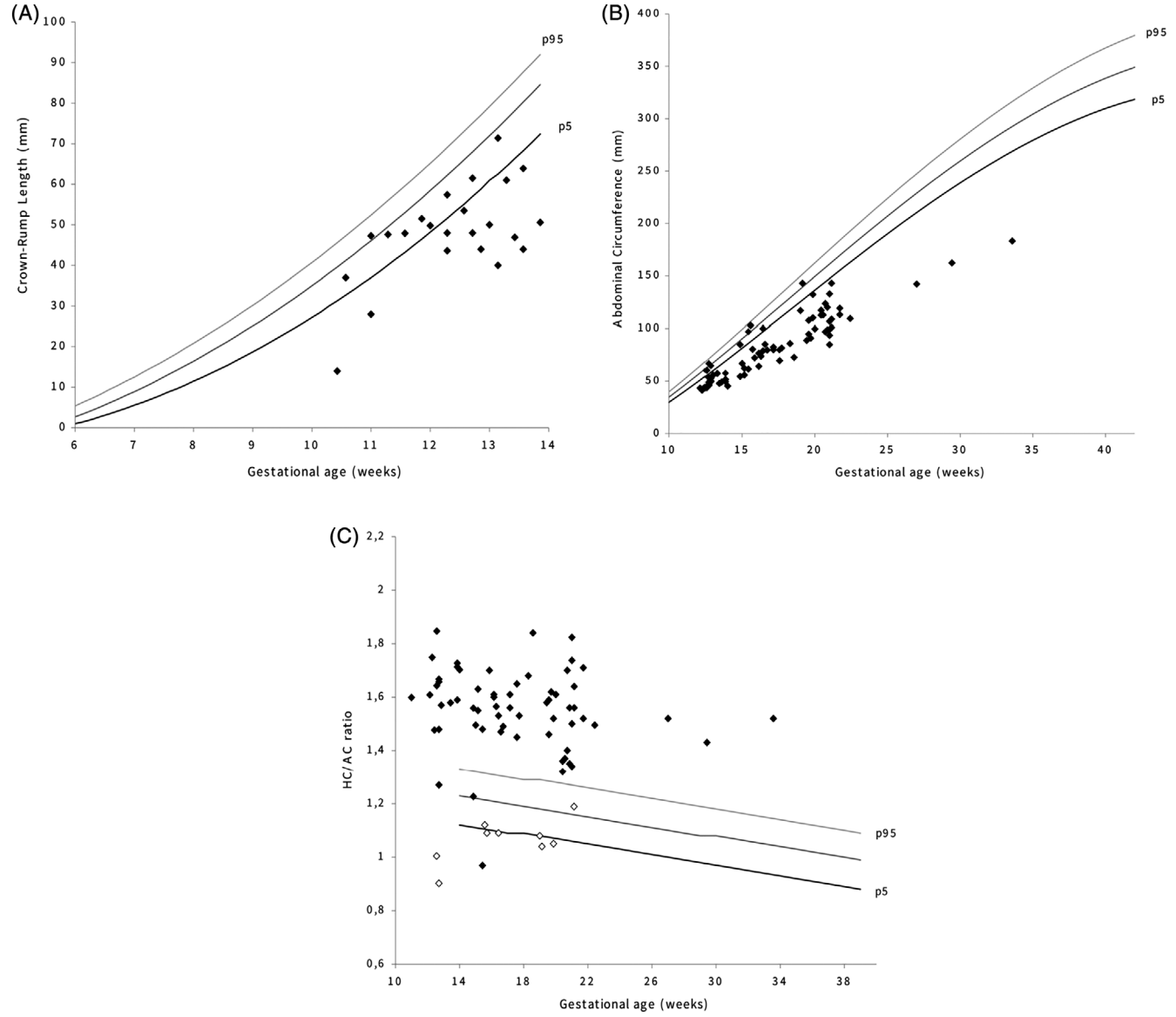

FIGURE 1 A, CRL measurements (n = 24) of triploidies plotted against a reference curve. B, Figure 1B AC measurements (n = 77) of triploidies plotted against a reference curve. **C,** Figure 1C HC/AC ratio measurements (n = 71) of triploidies plotted against a reference curve. Open dots represent the cases with placental molar changes on ultrasound

4.2 | Fetal growth

Measurements of CRL or AC were available for 101 of 120 cases. In 14 of 24 triploid fetuses (58.3%) with available CRL, early IUGR was present (Figure 1A). IUGR was seen in 69 of 77 fetuses (89.6%) with available AC measurements (Figure 1B). Overall IUGR was found in 83 of 101 cases (82.1%). In 71 of those 83 cases, a HC/AC ratio was measured, and asymmetrical fetal growth restriction was observed in 59 of those 71 cases (83.1%) (Figure 1C).

4.3 | Fetal and extra-fetal anomalies on ultrasound

Fetal structural anomalies (other than IUGR) were observed in 101 of 120 cases (84.1%), whereas in 12 cases the only observation was IUGR. Because of IUFD, three cases could not get a proper anatomy survey. In the remaining four cases, no data on ultrasound anomalies were available. Multiple fetal anomalies (ranging from 2 to 9) were detected in 74 of the triploid cases (61,6%) (Table S1). The most frequently detected anomalies were brain anomalies (41.7%), limb defects (40%), and cardiac anomalies (29.2%) (Table S1).

Placental abnormalities were the most common extra-fetal anomaly, present in 39 cases (32.5%) (Table S1). In 22 cases (18.3%), a partial mole was suspected on ultrasound (placental molar changes), with a median gestational age at detection of 13.1 weeks (Table S1). In 13 of 22 cases (59,1%), placental molar changes were evident before 14 weeks of gestation, compared to nine cases (40,9%) after 14 weeks of gestation.

In 12 out of 22 cases, the placenta was collected postpartum for histopathological evaluation. In nine of these 12 cases (75%), a partial

mole was diagnosed, in two cases (16.7%) the histopathological results were inconclusive and in one case (8.3%) the diagnosis of a partial mole could not be confirmed. In seven of these nine cases, β-hCG levels were obtained at diagnosis of the partial mole and before treatment: all levels were significantly increased with a median of 303 323 mIU/mL (IQR: 73868-576 930 mIU/mL). Maternal serum β-hCG levels were evaluated weekly until normal values were reached (<5 mIU/mL) for three consecutive weeks. Maternal serum β-hCG was normalized within 2 to 8 months in all cases. In this study, GTN did not occur.

4.4 | Maternal complications

Maternal complications occurred in 26 of 120 cases (21.6%), with vaginal bleeding as the most reported complication. Vaginal bleeding occurred in 24 of 120 cases (20%), mainly before 18 weeks of gestation. Vaginal bleeding occurred in cases with placental molar changes on ultrasound as well as in cases with a normal or thin placenta. In 16 of 24 cases (66.7%), with vaginal blood loss, the placenta had a normal aspect on ultrasound. In three cases (12.5%), the placenta showed placental molar changes and in five cases (20.8%) the placenta was described as thin. Hypertension was reported in one case (0.8%), but no placental molar changes were seen on ultrasound. The remaining case (0.8%) was complicated by pre-eclampsia, with a hydropic and cystic placenta on ultrasound and highly elevated levels of maternal serum β-hCG at 20 weeks of gestation, raising the suspicion of triploidy of paternal origin. Histopathology postpartum confirmed the presence of a partial mole.

4.5 | Biochemical markers and ultrasound anomalies in relation to parental origin

In 46 of the 120 triploid pregnancies (38.3%), the parental origin was confirmed by molecular genotyping using microsatellites polymorphic markers (Table 3). The majority, 32 cases (69.6%), were of maternal origin. The most important characteristic in those cases was the presence of severe asymmetrical IUGR with HC/AC discrepancy in 31 of 32 cases (96.9%) (Table 3). In the remaining case no fetal biometry data was available, but only severe HC/AC discrepancy was described. In 13 of 32 cases of maternal origin (40.6%) a thin placenta was described, compared to 0 of 14 cases (0%) in the paternally derived group (P = <.01).

The remaining 14 cases (30.4%) were of paternal origin at molecular genotyping: six cases (42.9%) showed symmetrical IUGR, normal growth was present in five (35.7%) and two (14.3%) only had a microcephaly with normal AC and FL. In the remaining case (7.1%), no information on fetal growth was available (7.1%). HC/AC discrepancy was never a feature in paternal triploidy (P < .001) (Table 3).

Elevated levels of free β-HCG, increased NT, and omphalocele were significantly more common in triploid pregnancies of paternal origin (Table 3). Low β-hCG and low PAPP-A levels were associated with maternal triploidy. The majority of paternal triploid cases showed placental molar changes (n = 12, 85.7%) on ultrasound compared to none of the maternal triploidy cases (P < .001) (Table 3).

TABLE 3 Comparison of biochemical markers and ultrasound anomalies in triploid cases based on parental origin***

Variables	Parental origin		p-value
	Paternal (n = 14)	Maternal (n = 32)	
Maternal biochemical markers			
Free β-hCG MoM	4.70 (2.62-6.29)[a]	0.27 (0.17-0.40)[b]	<.01
PAPP-A MoM	0.50 (0.26-2.97)[a]	0.05 (0.02-0.07)[b]	.03
Fetal biometry			
IUGR	6 (42.9)	31 (96.9)	<.001
Asymmetrical IUGR with HC > AC	0 (0.0)	31 (96.9)	<.001
Symmetrical IUGR	6 (42.6)	0 (0.0)	<.001
Fetal anomalies on US[c]			
Increased NT	8 (57.1)	1 (3.1)	<.001
Brain anomalies	7 (50.0)[c]	19 (59.4)[c]	.75
General	4 (28.6)	6 (18.8)	.47
Posterior fossa	2 (14.3)	9 (28.1)	.46
Ventricle anomalies	2 (14.3)	12 (37.5)	.17
Skull anomalies	2 (14.3)	7 (21.9)	.70
Spine anomalies	1 (7.1)	4 (12.5)	1.00
Cardiac anomalies	5 (35.7)[c]	13 (40.6)[c]	1.00
Lung or thorax anomalies	1 (7.1)	6 (18.8)	.41
Facial anomalies	3 (21.4)[c]	5 (15.6)[c]	.68
Genital anomalies	0 (0.0)	1 (3.1)	1.00
Urinary tract anomalies	2 (14.3)	3 (9.4)	.63
Abdominal wall defects	4 (28.6)	0 (0.0)	<.01
Gastrointestinal anomalies	3 (21.4)	5 (15.6)	.69
Limb anomalies	4 (28.6)[c]	15 (46.9)[c]	.33
Extra-fetal anomalies on US			
Oligohydramnios	1 (7.1)	8 (25.0)	.24
Placental molar changes	12 (85.7)	0 (0.0)	<.001
Thin placenta	0 (0.0)	13 (40.6)	<.01
Single umbilical artery	2 (14.3)	7 (21.9)	.70

Note: Data are given as median (interquartile range) or *n* (%).
[a]Data available for only 5 fetuses.
[b]Data available for only 7 fetuses.
[c]Fetuses could have multiple anomalies within a group but data is shown for the amount of triploidies with an anomaly.
Abbreviation: MoM, multiples of the median; NT, Nuchal Translucency thickness; PAPP-A, pregnancy-associated plasma protein A.

Figures 2–5, display typical ultrasound findings of a triploidy of paternal and maternal origin before and after 14 weeks of gestation.

4.6 | Prospective prediction of parental origin in tripoloidy

In 30 of 46 cases (65.2%) sonographers reported the possible parental origin of the suspected triploidy, based on phenotypical presentation. All phenotypical diagnoses were correct and corresponded with the genetic constitution (Table S2). In retrospect, after cytogenetic results were available, the correct prediction about the parental origin could have been made, based on sonographic features in the other cases (Table S2). For the assessment of the parental origin by sonographic features, a combination of one or more of the criteria had to be present and requires the absence of the criteria associated with the other origin. In case of asymmetrical growth restriction, prediction of maternal origin was made, since no cases of paternal origin showed asymmetrical growth restriction. In case of placental molar changes, paternal triploidy was predicted.

5 | DISCUSSION

The prenatal sonographic features of triploidy are well known. We demonstrate that prenatal sonographic features can also accurately predict the parental origin in triploid pregnancies. Paternal and maternal triploidy and their phenotypes have consistently been described, but have never been formally compared. We showed that sonographic features vary with parental origin, as assessed by molecular genetic analysis, and that fetal features (increased HC/AC ratio in case of IUGR) as well as extra-fetal features (placental appearance) are important for making a correct distinction. We were able to distinguish triploidy of paternal and maternal origin on ultrasound, and we could correlate the phenotypical presentation on ultrasonography in 100% of cases with the parental origin by molecular genotyping, when data on ultrasounds were available (Table S2).

Our cohort is currently the largest cohort in literature.[9] Besides its size, another strength of this study is the objective assessment of fetal growth restriction by plotting fetal biometry data in reference curves. In current literature, IUGR has been noted in 66-100% of triploid fetuses,[26-29] which is in line with our results. Our large cohort showed that fetal anomalies (without IUGR) were present in 84.1% of

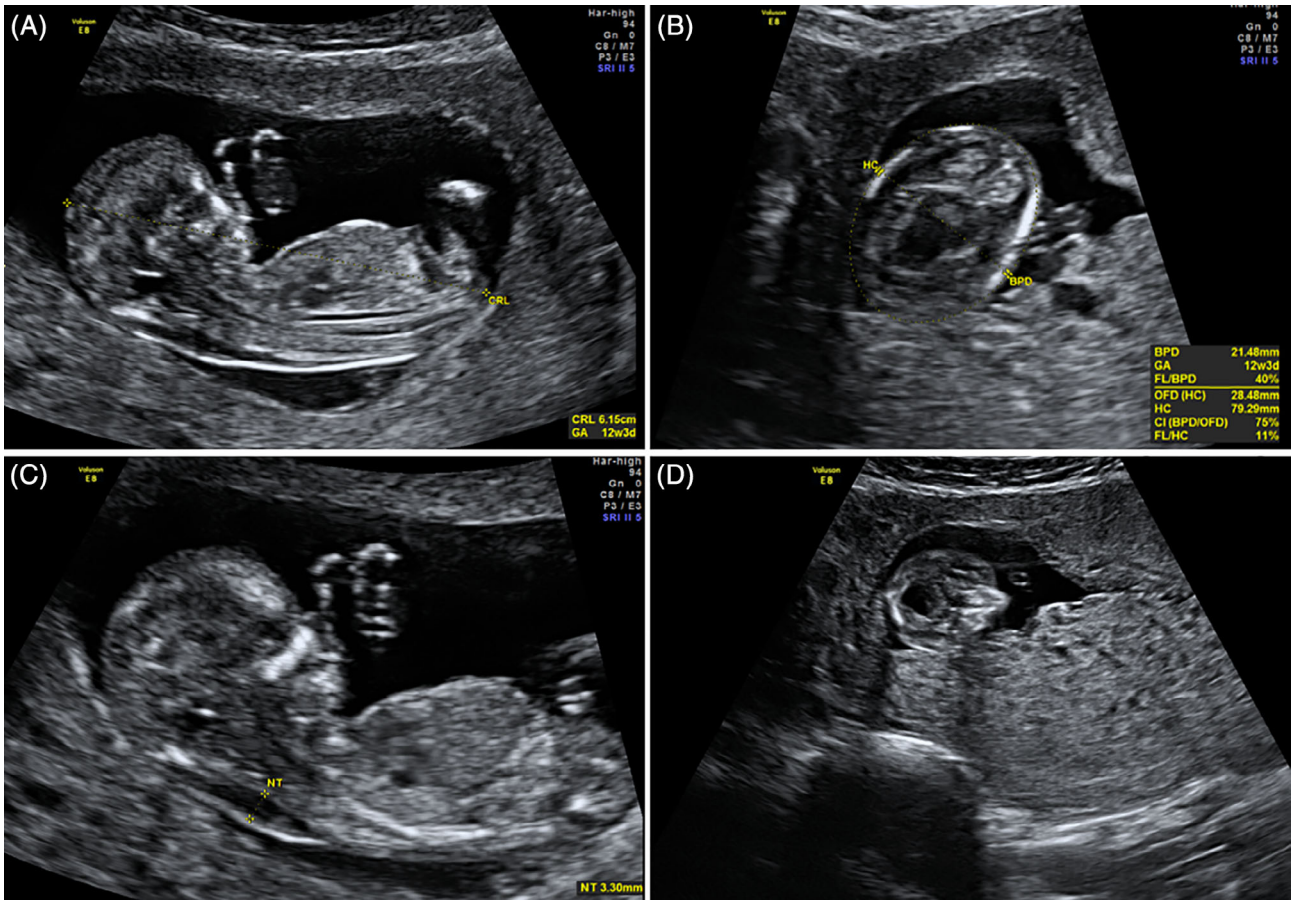

FIGURE 2 Triploidy of paternal origin at 12.5 weeks of gestation, referred because of an abnormal combined test with high levels of β-hCG *** (7.6 MoM). Normal growth (A and B), dilated fossa posterior (B), micrognathia (A and B) increased Nuchal Translucency (C) and a partial hydatidiform mole (D)

the triploid fetuses, compared with reported frequencies between 48% and 93%.[15,29] A myriad of fetal abnormalities on ultrasound have been reported,[5,13,15,26] but our study shows that types of fetal anomalies are less useful to distinguish between the parental origin of triploidy.[11,29,30] In our cohort, only one case was complicated by preeclampsia: a hydropic and cystic placenta was seen on ultrasound and elevated levels of maternal serum β-hCG were detected. This confirms an association between paternal origin of triploidy, partial moles, and high levels of maternal serum β-hCG, as described in earlier studies.[16,18]

Our study had some limitations: although the finding that parental origin can be predicted by ultrasound only, the overall number of cases undergoing molecular determination of parental origin was limited, leading to wide confidence intervals in the estimates of accuracy. Moreover, the retrospective design of the study potentially caused selection bias. The majority of cases referred to our Fetal Medicine Units were maternally derived triploidies, which are expected to be less prevalent than paternally derived triploidy. Possible reason for such selection bias is that paternally derived triploidies were miscarried more frequently. Consequently, this study may have underestimated the overall number of triploid cases, since cases resulting in early miscarriage could not be included in the study. Also, the retrospective study design led to missing data on growth measurements and ultrasound abnormalities (including fetal and extra-fetal anomalies). Not every organ system of the fetus nor the placental appearance were described in all cases, especially if major anomalies had already been found. This may have caused underestimation of the number of fetal anomalies and placental abnormalities.

Another limitation is that data on maternal serum biochemical markers were incomplete. Only for patients who opted for the first trimester combined test, results were known. In 12 of the 46 cases with known parental origin, maternal serum biochemical markers were retrieved. Since parents made this decision before the first trimester scan was performed, we expect that our findings are representative for the whole group. Our findings are consistent with those of other studies: levels of maternal serum biochemical markers are usually abnormal, with differences in these markers between triploidies of paternal and maternal origin.[31,32] In line with these results, we found that a triploidy of paternal origin, more often displays an increased NT, and high free β-hCG levels (median 4.70 MoM). In triploidy of maternal origin, the NT is rarely increased and free β-hCG and PAPP-A levels are low.

In conclusion, the first trimester combined test can be an important tool to assist in the prediction of the parental origin of the

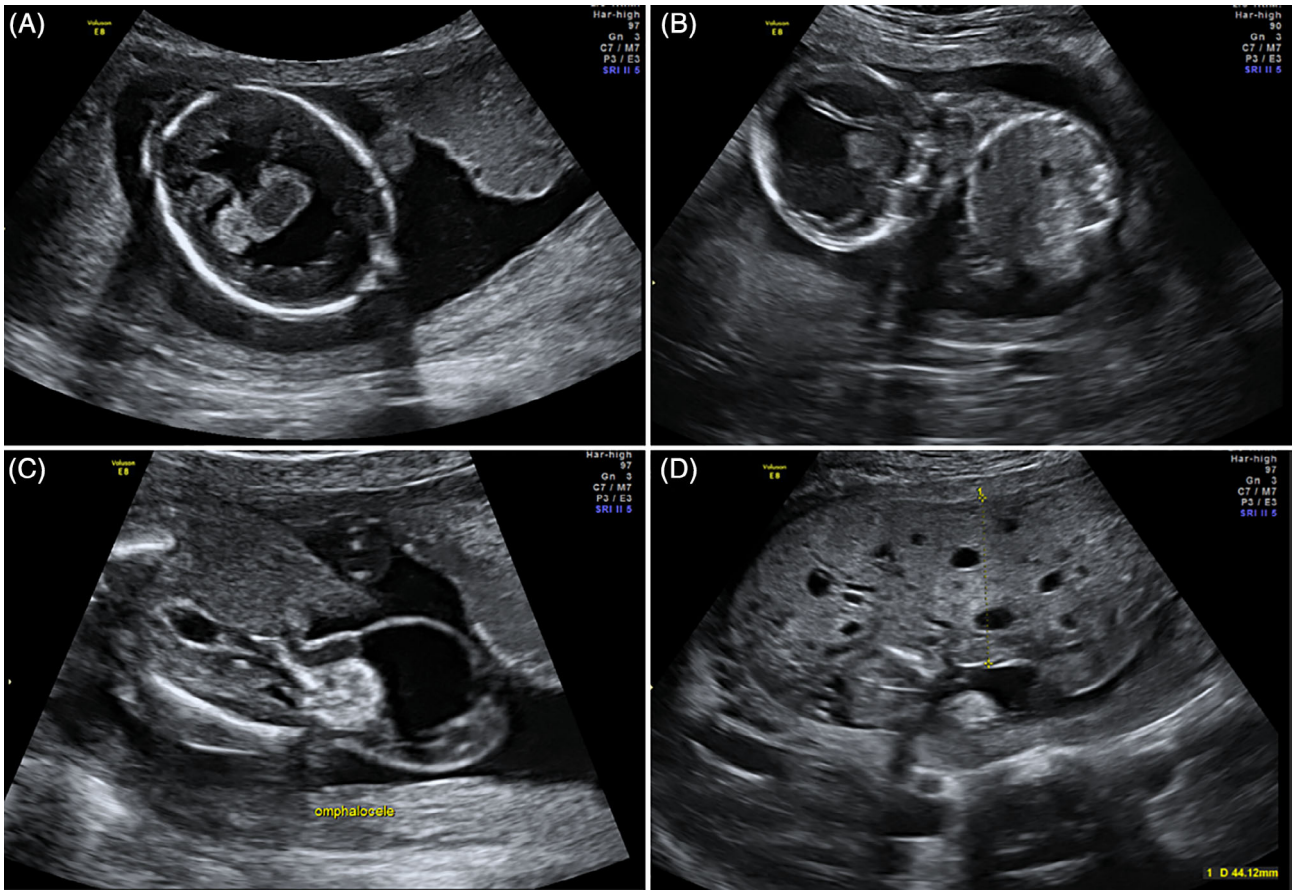

FIGURE 3 Triploidy of paternal origin at 19.6 weeks of gestation with symmetrical growth restriction, holoproscencephaly (A and B), an omphalocele (C), and a partial hydatidiform mole (D)

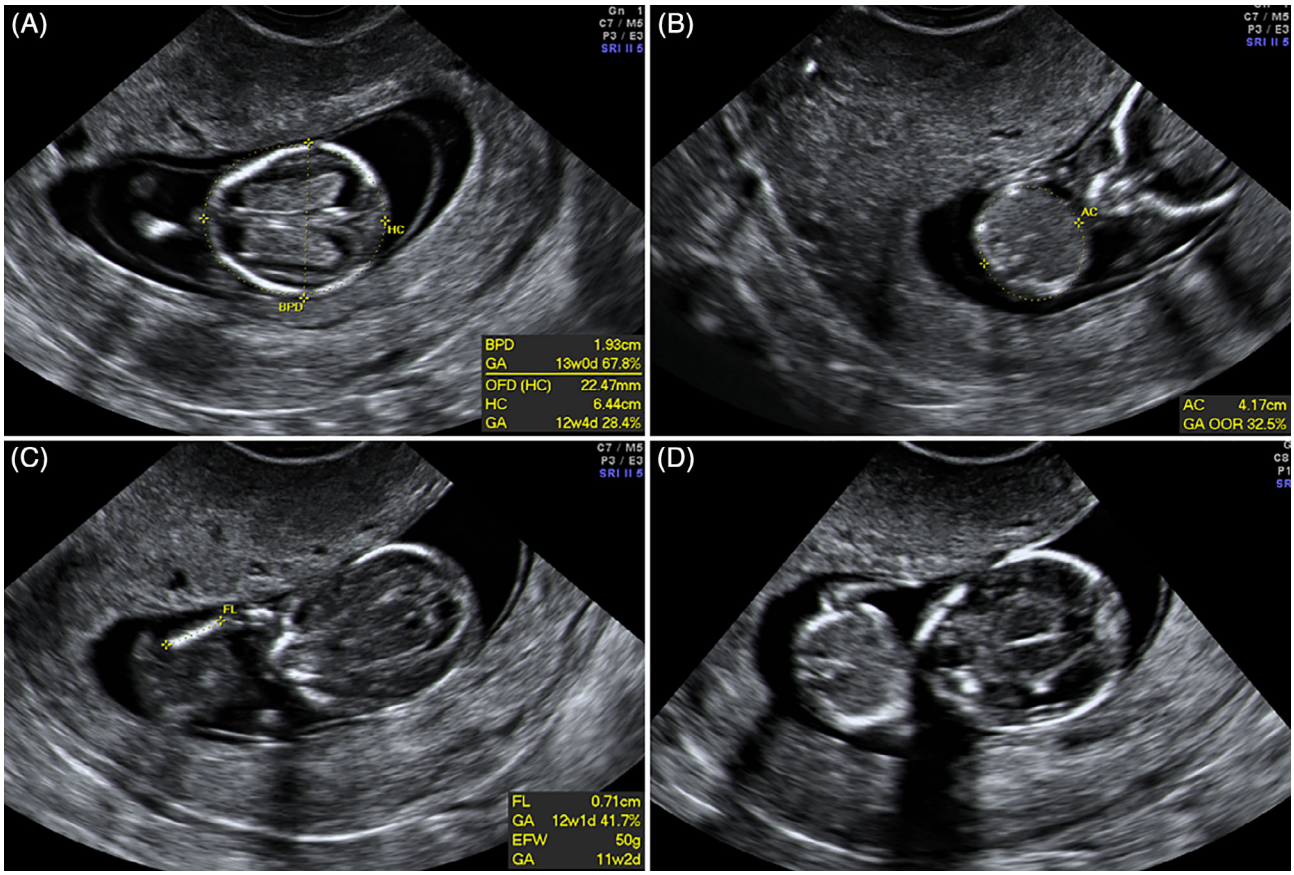

FIGURE 4 Triploidy of maternal origin at 12.2 weeks of gestation, referred because of an abnormal combined test with low pregnancy-associated plasma protein A (0.050 MoM). On ultrasound notable asymmetrical growth restriction; severe head-to-abdominal circumference discrepancy (A,B,C,D)

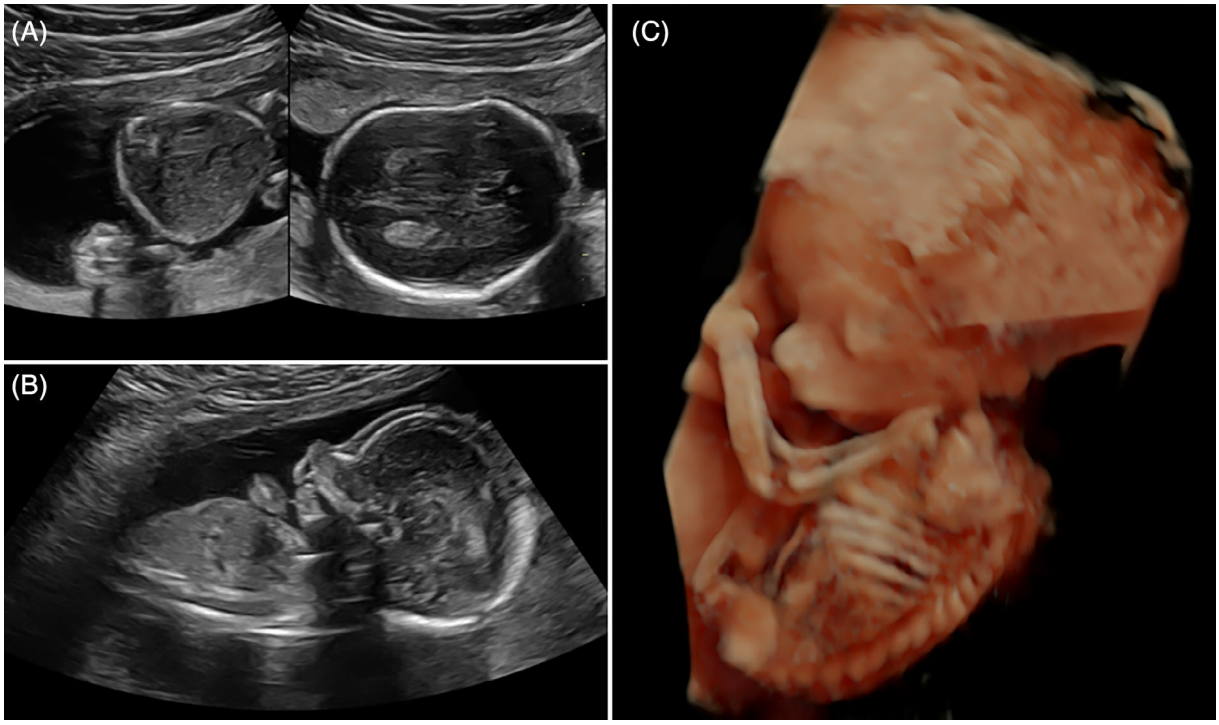

FIGURE 5 Triploidy of maternal origin at 19.2 weeks of gestation with notable asymmetrical growth restriction; severe head-to-abdominal circumference discrepancy (A,B,C), micrognathia (B,C), and a small placenta (A)

triploidy.[10,31-33] However, in the last years, the first trimester combined test has been replaced by cell-free DNA genetic screening that does not rely on free β-hCG or PAPP-A levels. Two types of cell-free DNA tests are available: the first one uses massively parallel shotgun sequencing, with quantification of the number of reads from each chromosome and a comparison among the relative number of reads from each chromosome: this type of test does not allow detection of triploidy, which affects all of the autosomes equally. The second type of cell-free DNA test utilizes SNP-based targeted sequencing and analysis of parental genotypes thus it could detect triploidy. However, the test relies on adequate representation of fetal fraction of cell-free DNA. A recent report found that the test was able to correctly identify all paternally derived triploidy cases, while all maternally derived cases tested did not yield a diagnosis owing to low fetal fraction of cell-free DNA (<4%), possibly due to the small size of the placenta in triploidy of maternal origin (placental trophoblast is the major contributor to fetal fraction of cell-free DNA).[34]

In our study, the primary indication for an ultrasound scan at 11 to 14 weeks of gestation, were abnormal results of the first trimester combined test. An advanced first trimester ultrasound at our Fetal Medicine Units showed abnormalities in all cases. A first trimester scan is recommended by all professional guidelines in cases not undergoing cell-free DNA screening: sonographers should be alerted to the fetal and placental sonographic signs of fetal triploidy in such cases. A maternal serum hCG level can be obtained and interpreted in MoM, also in the second trimester, to help integrate the sonographic findings.

A reliable assessment of the parental origin based on prenatal sonographic features implicates that molecular genotyping to determine the parental origin is redundant. This is in contrast with the findings of Massalska et al in 2017.[35] These authors report that parental origin could not be established by prenatal sonographic features in nearly 20% of cases. However, these findings were based solely on sonographic assessment without molecular genotyping. A small cohort of 67 triploid cases was described and maternal biochemical markers were unknown in these cases. Although growth measurements and NT-measurements were conducted, these findings were not included to distinguish between maternal and paternal origin.

Fisher et al stated that although molecular genotyping provides a definitive diagnosis of parental origin in cases where the histopathological review is equivocal, it is considerably more expensive than a pragmatic management approach of hCG surveillance in all such cases.[36] Alternatively, Berkowitz suggested to discuss hCG surveillance with the patient, especially when it is explained that a rapid normalization is to be expected.[19]

With increasing skills of sonographers after the introduction of prenatal screening programs, sonographic diagnosis of parental origin in triploidy may be possible without molecular genetic examination and associated health care cost can be decreased substantially. Histopathologic examination of the placenta should be reserved in cases where paternal triploidy is suspected, and only women with a triploidy of paternal origin and a partial mole would need serial monitoring of hCG levels (as nearly 2% of triploid trophoblast of a partial mole may undergo malignant transformation).[10,16-19] Women with a triploid pregnancy of maternal origin could be reassured by the sonographic features only.

6 | CONCLUSION

The present study highlights the importance of prenatal sonographic findings in the detection of triploidy. Asymmetrical fetal growth restriction is pathognomonic of maternal triploidy, whereas placental molar changes should indicate a paternal triploidy. Our data suggest that a reliable assessment of the parental origin of triploidy based on prenatal sonographic features (integrated by maternal serum biochemical markers, particularly free β-hCG) is feasible. Women with a triploid pregnancy of maternal origin can be reassured by sonographic features only. We propose that histopathological examination of the placenta is performed when ultrasound anomalies indicate a paternal triploidy or when ultrasound anomalies are inconclusive.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

ETHICS

This research does not involve human subjects and the Medical Ethics Review Committee (METc) of the AMC reviewed and approved the research protocol.

DATA AVAILABILITY STATEMENT

Data available on request from the authors.

ORCID

Malou A. Lugthart https://orcid.org/0000-0001-8385-2150

REFERENCES

1. Jacobs PA, Angell RR, Buchanan IM, et al. The origin of human triploids. *Ann Hum Genet*. 1978;42(1):49-57.
2. Boue J, Bou A, Lazar P. Retrospective and prospective epidemiological studies of 1500 karyotyped spontaneous human abortions. *Teratology*. 1975;12(1):11-26.
3. Szulman AE, Philippe E, Boue JG, et al. Human triploidy: association with partial hydatidiform moles and nonmolar conceptuses. *Hum Pathol*. 1981;12(11):1016-1021.
4. Doshi N, Surti U, Szulman AE. Morphologic anomalies in triploid liveborn fetuses. *Hum Pathol*. 1983;14(8):716-723.
5. Jauniaux E, Brown R, Snijders RJ, et al. Early prenatal diagnosis of triploidy. *Am J Obstet Gynecol*. 1997;176(3):550-554.
6. Ferguson-Smith MA, Yates JR. Maternal age specific rates for chromosome aberrations and factors influencing them: report of a collaborative european study on 52 965 amniocenteses. *Prenat Diagn*. 1984; 4 Spec No::5-44.
7. Jacobs PA, Szulman AE, Funkhouser J, et al. Human triploidy: relationship between parental origin of the additional haploid complement and development of partial hydatidiform mole. *Ann Hum Genet*. 1982; 46(3):223-231.
8. McFadden DE, Kalousek DK. Two different phenotypes of fetuses with chromosomal triploidy: correlation with parental origin of the extra haploid set. *Am J Med Genet*. 1991;38(4):535-538.

9. McFadden DE, Kwong LC, Yam IY, et al. Parental origin of triploidy in human fetuses: evidence for genomic imprinting. *Hum Genet*. 1993;92(5):465-469.
10. Engelbrechtsen L, Brondum-Nielsen K, Ekelund C, et al. Detection of triploidy at 11-14 weeks' gestation: a cohort study of 198 000 pregnant women. *Ultrasound Obstet Gynecol*. 2013;42(5):530-535.
11. Zalel Y, Shapiro I, Weissmann-Brenner A, Berkenstadt M, Leibovitz Z, Bronshtein M. Prenatal sonographic features of triploidy at 12-16 weeks. *Prenat Diagn*. 2016;36(7):650-655.
12. McFadden DE, Langlois S. Parental and meiotic origin of triploidy in the embryonic and fetal periods. *Clin Genet*. 2000;58(3):192-200.
13. Zaragoza MV, Surti U, Redline RW, Millie E, Chakravarti A, Hassold TJ. 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(6):1807-1820.
14. Wolf H, Leschot NJ, van den Kroonenberg MTA, et al. Prenatale diagnostiek van triploidie. *Ned Tijdschr Geneeskd*. 1990;134(8):394-397.
15. Joergensen MW, Niemann I, Rasmussen AA, et al. Triploid pregnancies: genetic and clinical features of 158 cases. *Am J Obstet Gynecol*. 2014;211(4):370.e1-370.e19.
16. Jauniaux E, Nicolaides KH. Early ultrasound diagnosis and follow-up of molar pregnancies. *Ultrasound Obstet Gynecol*. 1997;9(1):17-21.
17. ten Kate-Booij MJ, Lok CAR, Verheijen RHM, et al. Trofoblastziekten. *Ned Tijdschr Geneeskd*. 2008;152(22):2219-2224.
18. Rijhsinghani A, Yankowitz J, Strauss RA, Kuller JA, Patil S, Williamson RA. Risk of preeclampsia in second-trimester triploid pregnancies. *Obstet Gynecol*. 1997;90(6):884-888.
19. Berkowitz RS, Goldstein DP. Current management of gestational trophoblastic diseases. *Gynecol Oncol*. 2009;112(3):654-662.
20. Fine C, Bundy AL, Berkowitz RS, Boswell SB, Berezin AF, Doubilet PM. Sonographic diagnosis of partial hydatidiform mole. *Obstet Gynecol*. 1989;73(3 Pt 1):414-418.
21. Verburg BO, Steegers EA, De Ridder M, et al. New charts for ultrasound dating of pregnancy and assessment of fetal growth: longitudinal data from a population-based cohort study. *Ultrasound Obstet Gynecol*. 2008;31(4):388-396.
22. Snijders RJ, Nicolaides KH. Fetal biometry at 14-40 weeks' gestation. *Ultrasound Obstet Gynecol*. 1994;4(1):34-48.
23. DeSilva M, Munoz FM, Sell E, et al. Congenital microcephaly: case definition & guidelines for data collection, analysis, and presentation of safety data after maternal immunisation. *Vaccine*. 2017;35(48 Pt A):6472-6482.
24. Fleiss JL, Levin BA, Paik MC. *Statistical Methods for Rates and Proportions*. Hoboken, NJ: Wiley-Interscience; 2003.
25. Rosner B. *Fundamentals of Biostatistics*. Belmont, CA: Thomson-Brooks/Cole; 2006.
26. Mittal TK, Vujanic GM, Morrissey BM, et al. Triploidy: antenatal sonographic features with post-mortem correlation. *Prenat Diagn*. 1998;18(12):1253-1262.
27. Lockwood C, Scioscia A, Stiller R, Hobbins J. Sonographic features of the triploid fetus. *Am J Obstet Gynecol*. 1987;157(2):285-287.
28. Pircon RA, Porto M, Towers CV, Crade M, Gocke SE. Ultrasound findings in pregnancies complicated by fetal triploidy. *J Ultrasound Med*. 1989;8(9):507-511.
29. Jauniaux E, Brown R, Rodeck C, et al. Prenatal diagnosis of triploidy during the second trimester of pregnancy. *Obstet Gynecol*. 1996;88(6):983-989.
30. Toufaily MH, Roberts DJ, Westgate MN, Holmes LB. Triploidy: variation of phenotype. *Am J Clin Pathol*. 2016;145(1):86-95.
31. Yaron Y, Ochshorn Y, Tsabari S, Shira AB. First-trimester nuchal translucency and maternal serum free beta-hCG and PAPP-A can detect triploidy and determine the parental origin. *Prenat Diagn*. 2004;24(6):445-450.
32. Spencer K, Liao AW, Skentou H, et al. Screening for triploidy by fetal nuchal translucency and maternal serum free beta-hCG and PAPP-A at 10-14 weeks of gestation. *Prenat Diagn*. 2000;20(6):495-499.
33. Kagan KO, Anderson JM, Anwandter G, Neksasova K, Nicolaides KH. Screening for triploidy by the risk algorithms for trisomies 21, 18 and 13 at 11 weeks to 13 weeks and 6 days of gestation. *Prenat Diagn*. 2008;28(13):1209-1213.
34. Nicolaides KH, Syngelaki A, del Mar GM, et al. Prenatal detection of fetal triploidy from cell-free DNA testing in maternal blood. *Fetal Diagn Ther*. 2014;35(3):212-217.
35. Massalska D, Bijok J, Ilnicka A, Jakiel G, Roszkowski T. Triploidy—variability of sonographic phenotypes. *Prenat Diagn*. 2017;37(8):774-780.
36. Fisher RA, Tommasi A, Short D, Kaur B, Seckl MJ, Sebire NJ. Clinical utility of selective molecular genotyping for diagnosis of partial hydatidiform mole; a retrospective study from a regional trophoblastic disease unit. *J Clin Pathol*. 2014;67(11):980-984.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

How to cite this article: Lugthart MA, Horenblas J, Kleinrouweler EC, et al. Prenatal sonographic features can accurately determine parental origin in triploid pregnancies. *Prenatal Diagnosis*. 2020;40:705–714. https://doi.org/10.1002/pd.5666