Ultrasound Obstet. Gynecol. 9 (1997) 17–21

Early ultrasound diagnosis and follow-up of molar pregnancies

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Key words: PREGNANCY, COMPLETE MOLE, PARTIAL MOLE, ULTRASOUND, PLACENTA

ABSTRACT

The objective of this study was to investigate the role of ultrasound in the differential diagnosis and management of early pregnancies presenting with placental molar changes. Placental features were recorded over a 10-month period in women undergoing ultrasound examination at 10–14 weeks of gestation. In cases of a molar pregnancy, the fetal karyotype was obtained in utero *and, if the pregnancy continued, the maternal concentration of human chorionic gonadotropin (hCG) and uterine artery resistance to flow were measured serially. A histopathological examination of the placenta was performed in all cases after delivery. During the study period, 9425 women had an early scan and 11 molar pregnancies were identified including one classical mole, four hydatidiform moles coexisting with a normal pregnancy, three partial triploid moles and three partial moles associated in one case with a fetus presenting congenital anomalies diagnostic of Beckwith–Wiedemann syndrome. The hCG levels were high in all cases except one case of triploidy and remained high during the rest of the pregnancy in cases of hydatidiform moles coexisting with a fetus. In these cases, the uterine artery resistance was normal. The present data indicate that placental ultrasound examination can correctly identify molar changes in early pregnancy and together with hCG level and uterine Doppler measurements can establish the differential diagnosis* in utero *of the various forms of placental molar transformations.*

INTRODUCTION

Distinction between complete and partial hydatidiform moles was originally made postnatally on the basis of gross morphological, histological and cytogenetic criteria[1,2]. Complete hydatidiform moles are characterized by generalized swelling of the villous tissue and diffuse trophoblastic hyperplasia in the absence of embryonic or fetal tissue. Partial moles are characterized by focal swelling of the villous tissue and focal trophoblastic hyperplasia in the presence of embryonic or fetal tissue. Complete moles have a paternally derived diploid chromosomal constitution, resulting from the fertilization of an oocyte by a single spermatozoon which is diploid or undergoes diploidization; the maternal chromosomes are either inactivated or absent[3,4]. Partial moles are usually triploid and they mainly result from fertilization of a haploid ovum by either a single sperm that undergoes reduplication, or two sperms[4]. Development of persistent gestational trophoblastic disease can occur with both complete and partial moles[5,6].

Prenatal diagnosis of moles is based on the ultrasonographic demonstration of sonolucent areas within the placenta. In complete moles there is a characteristic 'snowstorm' appearance in the absence of a fetus. The difficulty in prenatal diagnosis arises when sonolucent areas in the placenta are found in association with a fetus. Such features may represent a triploid or diploid partial mole, a twin pregnancy combining a normal fetus with its placenta and a complete mole, or benign hydropic degeneration such as mesenchymal dysplasia[7]. Existing data on the differential diagnosis and management of these conditions are derived from case reports or small retrospective series of affected pregnancies detected during the second half of gestation. The aim of this study was to examine the role of ultrasound in the diagnosis and management of molar pregnancies detected at 11–14 weeks of gestation.

SUBJECTS AND METHODS

During a 10-month period, all cases suspected of molar changes were evaluated prospectively from 11–15 weeks of gestation. The patients were either referred to our center from other hospitals because of fetal abnormality, maternal disease or age and family or previous pregnancy history (n = 845) or were identified from an ongoing ultrasound screening study for aneuploidy (n = 8580) by measurement of fetal nuchal translucency thickness at 10–14 weeks of gestation[8]. Transabdominal and/or transvaginal

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Received 12–6–96
Revised 16–9–96
Accepted 26–9–96

sonography was used to examine the fetus and placenta. In addition, fetal karyotyping was offered to the mother, and the maternal serum concentration of β-human chorionic gonadotropin (β-hCG) was measured by an immunometric assay, as previously described[9]. In those patients who chose to continue with the pregnancy, the investigations were repeated at monthly intervals. Additionally, the pulsatility index (PI) in the uterine arteries[10] and maternal blood pressure were measured and chest X-rays were carried out. After delivery the placenta was karyotyped and a detailed histopathological examination was performed. If trophoblastic disease was confirmed by histological examination (proliferation of the cytotrophoblast and enlarged villi with absence of fetal stromal blood vessels), the mother was entered in the national registry (Charing Cross Hospital, London, UK) for molar pregnancies. The maternal and fetal charts of the study population were reviewed for the following characteristics: ultrasound findings, prenatal diagnostic procedures, pregnancy complications and cytogenetic results. Pregnancy outcome was obtained from the maternity units or the patients themselves.

RESULTS

During the period of the study, 9425 women had an early scan; 144 of these were multiple gestations (1.5%). All molar pregnancies followed a spontaneous conception. Cases 3, 4, 5, 6, 10 and 11 were referred because of unusual placental appearance (molar changes or maternal lakes) at a previous scan and 11 molar pregnancies were identified. At the initial scan, five pregnancies were classified in the complete mole subgroup and six in the partial mole subgroup (Table 1). There were no other cases diagnosed later in pregnancy or at delivery. The overall mean maternal age of the study population was 33.1 years and mean gestational age at the first ultrasound examination was 12.2 weeks. The mean maternal age in the molar pregnancy group was 33.9 years.

Table 1 Prenatal findings and outcome of 11 early pregnancies presenting with placental molar changes

		Ultrasound findings				*Outcome*	
Case	*GA* (weeks)	*Fetus*	*Placenta*	*hCG* (MoM)	*Karyotype*	*Pregnancy*	*Histopathology*
1	11	0	CM	12.2	46,XX	TOP (11 weeks)	CM
2	11	1	2 : Nl + CM	8.9	46,XX	TOP (14 weeks)	twin: Nl + CM
3[R]	11	1	2 : Nl + CM	9.2	46,XX	SVD (37 weeks)	twin: Nl + CM
4[R]	14	1	2 : Nl + CM	5.6	46,XX	IUD (28 weeks)	twin: Nl + CM
5[R]	12	2	2 : MC/DA + CM	13.2	2 × 46,XY	PIH (17 weeks)	triplet: 2Nl + 1CM
6[R]	12	1	1 PM	1.5	69,XXX	TOP (14 weeks)	triploid PM
7	13	1	1 PM	3.7	69,XXX	TOP (15 weeks)	triploid PM
8	13	1	1 PM	9.2	69,XXY	TOP (15 weeks)	triploid PM
9	11	1	1 PM	7.2	46,XX	CS (30 weeks)	MD
10[R]	14	1	1 PM	1.4	46,XX	SVD (39 weeks)	MD
11[R]	14	1	1 PM	4.5	46,XX	SVD (40 weeks)	MD

GA, gestational age; hCG, human chorionic gonadotropin; MoM, multiple of the median; [R], referred cases; CM, complete mole; MC/DA, monochorionic/diamniotic; PM, partial mole; MD, mesenchymal dysplasia; TOP, termination of pregnancy; SVD, spontaneous vaginal delivery; IUD, intrauterine death; PIH, pregnancy-induced hypertension; CS, Cesarean section; Nl, normal

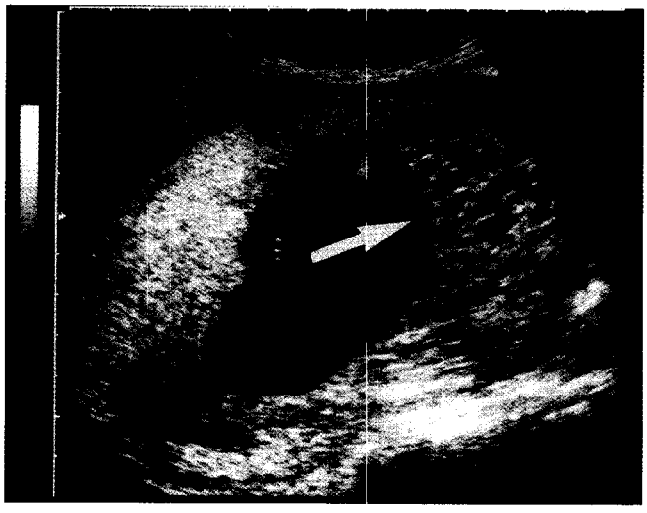

Figure 1 Ultrasonographic view of a twin pregnancy combining a complete mole (arrow) opposite to a normal fetus and placenta at 11 weeks of gestation (Case 3)

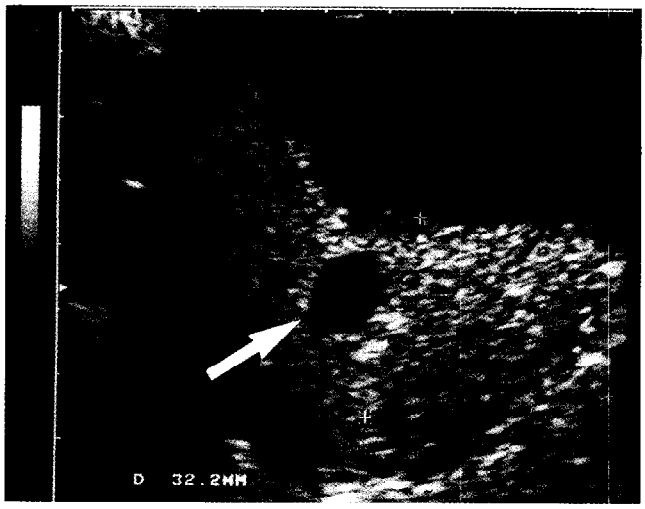

Figure 2 Ultrasound scan of the placenta at 13 weeks of gestation in a partial mole associated with triploidy (Case 8). Note the enlarged placenta with few 'cystic' molar changes (arrow)

Figure 3 Ultrasound scan of the placenta at 14 weeks of gestation in a partial mole with a euploid fetus (Case 11). The placenta contains diffuse cystic lesions

Figure 4 Macroscopic view at term of the placenta corresponding to Figure 3 (Case 11). Note the dilatation of the chorionic vessels (arrow) and a large tightly packed area made of gelatinous material (star)

In cases of complete mole coexisting with a normal singleton or twin pregnancy, the molar placenta was clearly separated from the normal placenta (Figure 1), whereas with partial moles the molar structures were dispersed inside the placental mass (Figures 2 and 3).

Maternal serum β-hCG was found to be high (> 3 MoM) in all cases of complete mole and in four of the six cases with partial mole placenta (Table 1). Bilateral multicystic ovaries were observed in all cases with hCG values > 8 MoM (cases 1, 2, 3, 5 and 8). After the initial assessment, termination of the pregnancy at the parents' request was carried out in the three cases of triploidy, in the one case of complete mole with no fetus and in one case of complete mole coexisting with a normal fetus and placenta. In the pregnancies that continued, the maternal β-hCG level remained very high (> 5 MoM) in the three cases of complete mole with a fetus, but decreased to normal values in three partial moles with a euploid fetus. From 16 weeks, uterine PI measurements in all three complete moles were below the 5th centile of normal range, whereas they were within the normal range in partial moles.

Only one case of twin pregnancy combining a complete mole resulted in the birth of a normal baby at term. Chronic vaginal bleeding was observed from 13 weeks, but the mother presented no clinical or biological evidence of pregnancy-induced hypertension and her chest X-rays were normal until delivery. The other twin pregnancy and the triplet pregnancy were respectively complicated by heavy vaginal bleeding and subsequently by intrauterine fetal death at 28 weeks, and severe pregnancy-induced hypertension at 18 weeks requiring immediate delivery. In both cases, the fetuses were anatomically normal at delivery and pathological examination of the placenta confirmed the ultrasound diagnosis of complete mole associated with a normal pregnancy. The placental karyotype obtained after delivery was identical to that obtained *in utero* by chorionic villus sampling.

The three pregnancies with euploid partial mole had an uncomplicated second trimester. Case 9 presented with polyhydramnios and premature labor at 30 weeks of gestation and the baby that was in breech position was delivered by Cesarean section. The neonate that was macrosomic (2.4 kg) with macroglossia and ear lobe creases was diagnosed as having Beckwith–Wiedemann syndrome. Cases 10 and 11 resulted in the birth of healthy babies at term. In these three cases, the placenta was large, weighing respectively 750 g, 1535 g and 1430 g, and had a karyotype identical to that of the corresponding fetus. On macroscopic examination, there was aneurysmal and varicose dilatation of chorionic vessels and tightly packed areas with clear planes of cleavage made of gelatinous material (Figure 4). Histologically, these areas were composed of enlarged stem villi with loose connective tissue, rare fetal blood vessels and cistern-like formation, whereas the rest of the placenta appeared normal. Systematic examination of the villous tissue did not reveal any abnormal trophoblastic proliferation in these cases.

DISCUSSION

The ultrasound diagnosis of complete mole is usually straightforward and accurate, whereas the diagnosis of partial mole is more complex, both *in utero* and after delivery. The presence of any form of placental molar changes and a coexistent fetus has been and is still often referred to as a partial mole[11–14]. As demonstrated by the present study at least three different categories of placental lesions must be considered when sonolucent areas are found within the placenta on ultrasound examination.

A partial mole must first be distinguished from a classical mole coexisting with a normal fetus and placenta. This complex trophoblastic disorder, resulting from molar transformation of one ovum in a dizygotic twin pregnancy, is associated with a higher risk for persistent trophoblastic disease than isolated complete mole and usually requires chemotherapy[15]. Vaginal bleeding is the most common presenting symptom in these cases and the mother is at high risk of developing severe medical complications such as

pre-eclampsia, hyperthyroidism, respiratory insufficiency and ovarian hyperstimulation with torsion or rupture of theca lutein cysts[15]. Complete hydatidiform mole with a coexisting fetus has usually been diagnosed after 20 weeks at a later gestational age than complete mole[15]. We found that as complete mole produces a characteristic vesicular sonographic pattern and low uterine artery PI measurements, their association with a normal gestational sac can be accurately determined at the end of the first trimester. As the molar placenta does not grow in proportion with the normal gestational sac, the ultrasound visualization of the tumor may be more difficult as pregnancy advances.

More than 90% of partial moles are found in triploid conceptuses[2]. Triploid fetuses almost always present on ultrasound scanning with major malformations and/or with severe asymmetrical growth retardation[7]. However, only half of the triploid placentae show hydropic and/or molar changes on the scan[7]. In early pregnancy, when the molar changes may be too small to be seen by ultrasound and the fetal anatomy too difficult to examine in detail, the antenatal screening must rely on other sonographic criteria such as increased fetal nuchal translucency[8,16] or a discrepancy between crown–rump length and menstrual age[17]. Confined placental diploid[18] or triploid mosaicism[19] can appear as triploid partial mole on ultrasound scanning, but in these cases, the fetus is anatomically normal and has a diploid karyotype. Pathological examination in some cases may be complicated by the fact that the molar placental tissue may come from a resorbed twin. Within this context, many diploid partial moles previously reported in the literature may have been complete hydatidiform moles with a coexisting normal fetus and placenta[20,21]. Further studies are needed to assess the accuracy of ultrasound in detecting triploidy during the first trimester of pregnancy.

Although the majority of partial moles are triploid, placental molar changes are not specific for gestational trophoblastic tumors, and villous hydatidiform transformations can be found in association with tetraploidy, autosomal trisomy and monosomy X[21]. Hydrops of the stem villi with placentomegaly but a normal trophoblast has also been observed in cases of Beckwith–Wiedemann syndrome[22,23], and with a phenotypically normal fetus[24,25]. This anomaly appears to be a limited malformation of the extraembryonic mesoderm involving the mesenchyme and the vessels of the stem villi of several cotyledons. Three cases were observed in the present series, one in a fetus presenting with features of Beckwith–Wiedemann syndrome. In these cases, the placental histopathological findings were comparable to those reported in other cases of mesenchymal dysplasia with or without congenital anomalies, diagnostic of Beckwith–Wiedemann syndrome[22–25]. If the fetus appears normal on ultrasound examination, the prenatal diagnosis poses a real clinical problem and will generally be made at birth or during childhood. At the time of the first ultrasound examination, the placental features were those of a typical partial mole and were associated with high maternal serum β-hCG levels, whereas from mid-pregnancy, the β-hCG level and PI values in the uterine artery were within normal ranges. These findings suggest that in early pregnancy the placental/fetal ratio is higher in these cases than in normal pregnancies, accounting for a greater trophoblastic surface area producing hCG. As pregnancy advances areas of mesenchymal dysplasia are probably limited in their development by the growing normal placental tissue, and the proportionally high hCG concentrations return to within the normal range.

The data of the present study indicate that an ultrasound scan at 11–14 weeks can correctly identify molar pregnancies and provide the basis for comprehensive risk assessment and management. The accuracy of the sonographic findings in establishing the differential diagnosis of the various forms of placental molar transformations in early pregnancy can be enhanced by consideration of the concurrent hCG levels and Doppler investigations. Cytogenetic investigation should be offered in all types of partial mole. Complete hydatidiform mole with a coexisting fetus are not at increased risk of aneuploidies compared to normal singleton or twin pregnancies. However, as this condition is more common in women over 35 years old[26], as are aneuploidies, an invasive procedure to determine the fetal karyotype may be an important factor in the mother's decision to continue the pregnancy. Ultrasound and cytogenetic findings are also valuable in alerting the attending practitioner of the need for follow-up after delivery, in orientating the histopathological examination and in counselling the patient on the risk of persistent trophoblastic disease.

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