Molar DNA in Maternal Serum in a Case of 46,XY Heterozygous
Complete Hydatidiform Mole Coexisting with a 46,XX Twin Live Fetus

To the Editor:

Cell-free fetal DNA in maternal circulation is detectable in early pregnancy, increases with gestational age, and decreases rapidly after delivery (1–3). It has been used for noninvasive prenatal diagnoses, such as fetal rhesus status and sex determination (4,5), but cell-free fetal DNA originates from villous tissue or fetal cells circulating in maternal blood has not been determined. Complete hydatidiform mole lacks a fetal component, and DNA originating from a hydatidiform mole (molar DNA) that is detected in the maternal circulation is thought to originate from villous tissue. By analyzing by real-time PCR the amount of sex-determining region Y (SRY) DNA in maternal serum before and after delivery of a 46,XY complete hydatidiform mole coexisting with a normal 46,XX fetus, we have confirmed that the DNA in maternal blood originates from villous tissue.

The patient was a 30-year-old gravida I, para 0. She was examined at our hospital at 20 weeks of gestation. Ultrasound examination showed a normally grown fetus without anomalies with a normal placenta, and a molar placenta. At 28 weeks of gestation, she spontaneously delivered vaginally a 1094-g female infant with a grossly normal placenta, and a molar placenta. Cytogenetic analyses performed on G-bands with trypsin-Giemsa-banded chromosomes showed a 46,XY complete mole and a normal 46,XX fetus.

After obtaining written consent, we sampled the woman’s peripheral blood between 20 and 28 weeks of gestation and after delivery. We centrifuged 6 mL of each maternal venous blood sample twice at 5800g and collected and stored the serum at −20°C until analysis. We measured the β-human chorionic gonadotropin (β-hCG) concentrations in the maternal serum by enzyme immunoassay (ST AIA-PACK β-hCG), and after extracting DNA from these same serum samples with a QIAamp DNA Mini Kit (Qiagen), we performed real-time quantitative PCR on an ABI PRISM 7700 Sequence Detector (Applied Biosystems) according to the method described previously by Honda et al. (5). The SRY sequence was used as a molecular marker for DNA from the 46,XY hydatidiform mole in the maternal serum.

Serum β-hCG was 367 747.8 IU/L at 20 weeks and gradually decreased as a function of gestational age. The β-hCG concentration was 147 644.2 IU/L at 1 week before delivery and rapidly decreased to 6512.4 IU/L by 1 week after delivery. The β-hCG concentration had decreased to within reference values by 13 weeks after delivery. No increase in β-hCG was observed thereafter. The highest number of SRY copies in maternal serum was observed at 20 weeks of gestation, and the number of copies decreased toward delivery. The concentration of SRY sequence was 124.43 copies/mL at 1 week before delivery and rapidly decreased to 8.24 copies/mL at 1 week post delivery. The number of SRY copies decreased further, and no SRY was detectable at 5 weeks after delivery (Fig. 1).

Hydatidiform mole is a gestational trophoblastic disease and includes complete and partial moles. The presence of Y-chromosome-specific sequences has been demonstrated in the maternal plasma from a woman with a partial hydatidiform molar pregnancy with 69,XXY karyotype (6). In the present study we have shown that the SRY sequence derived from a complete hydatidiform mole exists in maternal serum. Because our case here is a 46,XY heterozygous complete hydatidiform mole coexisting with a normal 46,XX fetus, the SRY sequence in maternal circulation originated entirely from molar placental tissue.

It was recently reported that placental DNA was released into the maternal circulation in three cases of confined placental mosaicism (7). Ohashi et al. (8) suggested that fetal
DNA in maternal circulation was from placental trophoblasts rather than from nucleated fetal cells circulating in maternal blood, based on the correlation of fetal DNA and hCG concentrations in maternal serum in the second trimester. It is therefore possible that, in a normal pregnancy, fetal DNA in maternal circulation originates at least partly from villous tissue. Our present study was performed with a molar pregnancy, however; thus, the implications of these data for a normal pregnancy are unclear.

It has been reported that fetal DNA in the maternal serum during a normal pregnancy is not detectable 1 day after delivery. In our study, molar DNA was detectable for 4 weeks after delivery. Jimbo et al. (9) reported that fetal DNA could be detected for 10 weeks after delivery in a case of placenta increta. It has also been reported that fetal DNA clearance from maternal plasma is impaired in preeclampsia (10). We therefore suggest that the clearance of fetal or molar DNA was impaired and that these forms of DNA are detectable in the maternal circulation for a longer period in abnormal vs normal pregnancies.

Jimbo et al. (9) also reported that, in the case of placenta increta, fetal DNA could be detected in maternal plasma for a longer period after delivery than β-hCG, but in our study molar DNA became undetectable earlier than β-hCG. This is probably attributable to differences between placenta increta and molar disease and between the clearance times for DNA and β-hCG in the maternal blood. The clearance time of DNA is ~16 min (11), and that of β-hCG is ~23 h (12). However, in our study, before delivery, the concentration of molar DNA showed a pattern similar to that of β-hCG, which is widely used clinically as a marker of molar diseases. It would be interesting to study whether the SRY sequence is also detectable with the recurrence of molar disease. If so, molar DNA in maternal blood could also be used as a marker for monitoring of molar diseases.

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References


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