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RESEARCH LETTER

Could ovarian choriocarcinoma be detected by maternal serum screening for Down syndrome?

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The incidence of ovarian malignancies during gestation ranges from 1 in 8000 to 1 in 20 000 deliveries. Ovarian malignancies that produce human chorionic gonadotropin (hCG) are limited to germ cell tumors, of which dysgerminoma is the most frequent (45%) malignant type encountered in pregnant patients, the others being ovarian choriocarcinoma and mixed germ cell tumors (Boulay and Podczaski, 1998). In women of childbearing age, it is hard to distinguish between metastatic choriocarcinoma on a complete mole and primary ovarian choriocarcinoma. Treatment is based on adnexectomy followed by chemotherapy. Given the extreme rarity of these tumors, the long-term prognosis is difficult to establish. Had the diagnosis for our patient been made during pregnancy, the therapeutic approach would have been discussed in terms of gestational age. In the last trimester, we could have suggested cesarean section followed by adnexectomy, and then chemotherapy. In the second-trimester, chemotherapy could have been discussed, although the fetal toxicity of cisplatin chemotherapy is not firmly defined (Ferrandina *et al*., 2005). This treatment is an alternative to termination of pregnancy. We retrospectively studied maternal serum biochemistry so as to assess the possibility of a diagnosis of ovarian choriocarcinoma at the time of maternal serum screening for Down syndrome.

KEY WORDS: prenatal diagnosis; maternal serum markers; ovarian tumor; hCG; human chorionic gonadotropin

CASE REPORT

Mrs C, a 31-year-old primipara, had her first child affected by congenital hyperplasia of the adrenal glands due to 21-hydroxylase deficiency, and so during her second pregnancy was tested for this disease by chorionic villus sampling (CVS) at 11 weeks of gestation. There was no mutation of the *CYP21B* gene, so the fetus was free of the disorder. Karyotyping could not be done because chorionic villus sample was too small. Maternal serum screening for Down syndrome was done at 16 weeks + 1 day of gestation. Total human chorionic gonadotropin (hCG) was abnormally high [6.94 multiple of median (MoM)] and alpha-fetoprotein (AFP) was normal (1.2 MoM), indicating a Down syndrome risk of 1/17. After CVS, the patient presented with genital bleeding and amniocentesis was postponed. Ultrasound findings at 22 and 34 weeks were normal and parents did not elect for amniocentesis. A girl weighing 2600 g was delivered vaginally at 36.2 weeks, and was clinically normal. Mother and child were discharged on day 5.

Three weeks after delivery, the patient consulted her gynecologist because of abdominal pain. No abnormal finding was recorded on pelvic ultrasound. Because the abdominal pain persisted, the patient returned after two weeks and pelvic ultrasound and bacteriological examination of a vaginal sample were normal. Forty eight hours later, the patient was admitted to hospital with abdominal pain plus nausea and dizziness. Computed tomography of the abdomen and pelvis, and laparoscopy, revealed a large, right, lateral uterine mass and intraperitoneal effusion containing blood. Laparotomy localized the tumoral mass of the right ovary, and right ovariectomy and right adnexectomy were performed, together with biopsy of the left ovary, which proved normal on histological examination. Histological examination of the right ovary indicated stage IV choriocarcinoma on the FIGO classification (Ngan *et al*., 2003). Staging revealed multiple metastases (brain, lung, spleen and kidneys). Four courses of chemotherapy (cisplatin, etoposide and bleomycin) were monitored by assay of maternal serum markers (total hCG, free β-hCG, ACE, AFP and CA 125). Only total hCG was abnormally high (189 389 IU/L at day one), but returned to normal (2 IU/L) after the second course of chemotherapy. The patient was in remission after the fourth course of chemotherapy, i.e. 5 months after diagnosis. Brain magnetic resonance imaging showed shrinkage of metastases, and 30 months after diagnosis the patient was in complete reemission.

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We wondered the patient's tumor could have been revealed by laboratory tests at the time of maternal serum screening for Down syndrome at 16 weeks of gestation. Table 1 shows the results of assays of five proteins in serum samples stored frozen. The sample collected at 4 weeks of gestation was uninformative. At 8 weeks, all five markers were in the normal range, but, at 16 weeks, hCG, β-hCG, hyperglycosylated hCG were abnormally high, with a discordance between total hCG and free β-hCG, which was much higher. pregnancy-associated protein-A (PAPP-A) and α-hCG were normal.

hCG is a placental glycoprotein required for the maintenance of pregnancy, and comprises an α subunit (α-hCG) and a β subunit (β-hCG), which is specific to hCG. hCG is synthesized by cytotrophoblasts and syncytiotrophoblasts. It is secreted in the maternal circulation, degraded in the liver and kidneys, then excreted in the maternal urine. Its serum concentration varies during pregnancy, with a peak around 10–12 weeks. Outside pregnancy, hCG and its subunits are undetectable, except in certain cancers, notably bladder and testicular, certain hypothalamo-pituitary tumors, and in choriocarcinoma (Bidart and Bellet, 1993; Ferrandina *et al*., 2005). During pregnancy, high hCG or β-hCG is observed in cases of hydatidiform mole, triploidy, Down syndrome, and in other fetal or placental pathologies (Liu *et al*., 1999).

In France. maternal serum screening for Down syndrome is done during the second trimester in 80% of pregnant women (Muller *et al*., 2002a). Screening is based on assay of total hCG (or free β-hCG) associated with AFP (and unconjugated estriol for triple test). When maternal serum hCG is abnormally high, it is indispensable to attempt to define the etiology. The etiologies of elevated hCG are usually the same for total hCG and free β-hCG. First, it is ensured that there is no methodological error due to storage conditions (duration and temperature) (Muller *et al*., 1999). If there is any doubt, a second sample must be collected. Severe renal insufficiency (organic, functional, or related to hypertension) must be sought (Shenhav *et al*., 2003). Once such etiologies have been discounted, further tests are needed. If the calculated risk is $>1/250$, fetal karyotyping is proposed. In fetal Down syndrome, elevated hCG (median 2.2 MoM for total hCG and 2.3 for β-hCG) is usually associated with decreased AFP (median 0.86 MoM). This increase is observed from the first trimester till the end of pregnancy (Muller *et al*., 2002b). Certain types of triploidy result in very high hCG, because of the abnormal development of placental villi (Huang *et al*., 2005). Aneuploidy confined to the placenta, usually mosaic trisomy 16, may be observed, and is generally accompanied by intrauterine growth retardation (IUGR) (Benn, 1998). Elevated hCG is also seen in IUGR of vascular origin, and in preeclampsia, in which high vascular resistance in the uterine arteries slows placental blood flow, and the resulting lack of oxygen induces trophoblastic hyperplasia and hence increased hCG production (Reis *et al*., 2002). In these nontumoral etiologies, total hCG and free β-hCG are correlated. When there is a placental tumor (mole or choriocarcinoma), hCG production increases greatly (>8 MoM), sometimes from the first trimester onwards. This increase is the result of anarchic proliferation of cytotrophoblasts and can result in an abnormal sonographic appearance of the placenta.

In our patient, at Down syndrome maternal serum screening, total hCG was high (6.94 MoM) and AFP normal. Retrospective assays showed that this anomaly was not present at 8 weeks of gestation. At 16 weeks, there was a major disagreement in assay findings between total hCG and free β-hCG (31 MoM), which suggested placental choriocarcinoma. The predominant rise in free β-hCG is considered as indicative of tumor aggressiveness. The great rise in hyperglycosylated hCG (140 MoM) showed that total hCG was very largely hyperglycosylated. Hyperglycosylated hCG is produced physiologically in the weeks following implantation of the immature cytotrophoblast (Kovalevskaya *et al*., 1999). Its increase in placental choriocarcinoma reflects the immature and invasive character of the cytotrophoblast (Elliott *et al*., 1997), and its assay has been used to assess the invasive nature of placental tumors (Cole *et al*., 2006). The normal levels of α-hCG and PAPP-A (which reflect the placental syncytial mass) contrast with the very high concentrations of hyperglycosylated hCG and free β-hCG. The discordance between the concentrations of β-hCG and hyperglycosylated hCG on the one hand, and the concentrations of α-hCG and PAPP-A on the other, may reflect dysregulation of placental development, with persistence of a population immature and invasive cytotrophoblasts constituting the choriocarcinoma. Nowak-Markwitz *et al*. (2004) demonstrated that the β-hCG gene was active in ovarian carcinoma cells, thus explaining the very high maternal serum β-hCG value.

In our patient with ovarian choriocarcinoma, the serum marker values determined during Down syndrome screening were characterized by a discrepancy between moderately increased total hCG and greatly increased

Table 1—Maternal serum markers at different gestational ages

	Total hCG (mIU/mL)	Free β-hCG (ng/mL)	Free α-hCG (mIU/mL)	ITA (ng/mL)	PAPP-A (mIU/mL)
4 weeks of gestation	2193	3.8	35	56	5.4
8 weeks of gestation	149 200 (2 MoM)	131 (2 MoM)	199 (ND)	1045 (2.1 MoM)	1187 (2.3 MoM)
16 weeks of gestation	163 900 (6.94 MoM)	423 (31 MoM)	416 (1.75 MoM)	4057 (140 MoM)	9126 (1 MoM)
16 weeks post-partum*	505	4.1	41	16	42
24 weeks post-partum**	27	0.5	39	0.8	11.6

hCG: human chorionic gonadotropin; ITA: invasive trophoblast antigen; PAPP-A: pregnancy-associated protein A; MoM: multiple of the median. * end of first course of chemotherapy. ** end of second course of chemotherapy

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free β-hCG. Once other causes have been ruled out, these two markers may serve as a warning of possible choriocarcinoma. Magnetic resonance imaging could then be used to screen for suspicious ovarian lesions, which would be biopsied. Given the rarity of this serious tumor pathology, a large-scale study should be set up to study cases where high total hCG is associated with very high free β-hCG.

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