Hydatidiform mole coexistent with a twin live fetus: a national collaborative study in Japan

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A national collaborative study was conducted in Japan to evaluate the clinical course and the sequelae of patients with hydatidiform mole coexistent with twin live fetus (HMTF). Seventy-two cases of HMTF were diagnosed based on gross appearance and histopathological criteria. In 18 cases, the molar parts were cytogenetically confirmed to be of androgenetic origin (complete mole). The overall incidence of persistent trophoblastic tumour (PTT) in patients with HMTF was 30.6%, and it increased to 50.0% in the 18 patients with proven androgenetic complete mole coexistent with twin live fetus (CHMTF). Among these patients, the mean gestational age at termination of pregnancy or delivery in those who developed PTT (n = 9) and those who did not (n = 9) were 20.6 and 19.4 weeks respectively. The incidence of severe maternal complications was significantly higher in patients who subsequently developed PTT (P < 0.05). The rate of subsequent development of PTT in patients with CHMTF was found to be considerably higher than in a previous study of patients with single complete mole (50 and 12.5% respectively). However, since the risk of malignancy is unchanged with advancement of gestational age, continued pregnancy may be allowed in patients with HMTF provided that severe maternal complications are controlled and fetal karyotype and development are normal.

Key words: coexistent fetus/hydaditiform mole/persistent trophoblastic disease/twin pregnancy

Introduction

Hydatidiform mole coexistent with a twin live fetus (HMTF) is a rare entity, occurring in 0.005–0.01% of all pregnancies (Beischer, 1961; Jones and Lausen, 1975). Two different mechanisms of the formation of HMTF are possible: a complete mole (46 chromosomes; all paternal in origin) coexistent with twin live fetus(es) (46 chromosomes; 23 maternal and 23 paternal), and a partial mole with an abnormal triploid fetus(es) (both having 69 chromosomes of maternal and paternal origin). The abnormal triploid fetus coexisting with a partial mole tends to die in the first trimester (Jauniaux et al., 1997), while the fetus coexisting with a complete mole in the dizygotic twin pregnancy has a chance to survive.

Several case reports and reviews describe the diagnosis of HMTF by morphological criteria, DNA polyploidy or karyotype analyses (Jones et al., 1975; Block and Merrill, 1982; Thomas et al., 1987; Lage et al., 1992; Steller et al., 1994; Fishman et al., 1998). In these reports, the risk of developing maternal complications, such as pre-eclampsia and persistent trophoblastic tumour (PTT), seems to be higher in cases of HMTF than in cases of single complete mole. However, since complete cytogenetic information on both the mole and the fetus is available in only a small number of cases, it is difficult to distinguish androgenetic complete hydatidiform mole coexistent with twin live fetus (CHMTF) from triploid partial moles, especially at the early stages of gestation (Ohama et al., 1985; Miller et al., 1993). Moreover, it is uncertain whether management of this rare pregnancy has a greater risk of developing severe maternal complications than immediate termination.

We have reported that the incidence of PTT seems to be high in patients with CHMTF, although the number of cases was small (Matsui et al., 1999).

In this report, we survey patients with HMTF in Japan and describe the prenatal and postpartum management of this rare gestational condition.

Materials and methods

In 1997, questionnaires were mailed to the Department of Obstetrics and Gynaecology of 87 university hospitals in Japan to assess the clinical course of HMTF. The eligibility criteria were based on perinatal ultrasound and postpartum morphological findings. Eighty-two questionnaires were returned and 72 patients with HMTF were analysed in this study. The questionnaires contained the following parameters: maternal age, gestational week at diagnosis and delivery or termination of pregnancy, fetal karyotype, fetal anomalies, birth weight, fetal sex, DNA analyses of molar parts, ovulation induction, maternal complications during and after pregnancy with HMTF, and whether the physicians and parents intended to continue the pregnancy.

Statistical analyses were performed by Welch’s t-test, analysis of variance followed by Scheffe’s F-test, and the χ² test.

Results

All HMTF cases

The clinical characteristics of 72 patients with HMTF are shown in Table I. Gestational age was calculated from the last
menstrual period and corrected by ultrasound measurements of the fetuses. Twenty-six patients had intended to continue the pregnancy with or without knowledge of the accompanying mole, but pregnancy was terminated in nine of the 26 in the second trimester because of maternal complications.

Pregnancy was terminated in the first trimester in 24 of 72 patients; because of intrauterine fetal deaths in 10 and at the parents’ request in 14. Pregnancy was terminated in 31 patients in the second trimester; due to intrauterine fetal deaths in five, maternal complications in nine, and at the parents’ request in 17 (including two fetuses with chromosomal abnormalities).

Seventeen patients delivered at 34.8 ± 3.5 weeks gestation (ranged between 29 and 40 weeks). The mean (±SD) birth weight was 2059 ± 557 g (range 1280–3019 g). One neonate was stillborn and 16 were alive and well, with no gross anomalies.

The mean (±SD) maternal age of 72 patients with HMTF was 29.2 ± 5.0 years. The karyotypes of 27 fetuses were analysed during pregnancy or postpartum, and 25 had normal diploid karyotype while the remaining two were triploidy and trisomy. Ovulation induction had been performed in 16 patients (22.2%). Maternal complications, such as pre-eclampsia and massive bleeding, were observed in 14 patients (19.4%). PTT developed in 22 patients (30.6%).

### CHMTF cases

Of the 72 cases of HMTF, 18 moles were confirmed to be of androgenetic origin by restriction fragment length polymorphism or DNA fingerprinting after delivery or termination of pregnancy (Table II). Zygosity was also examined in 12 molar parts. There were 10 homozygous androgenetic moles and two heterozygous androgenetic moles. Seven of these cases have been reported elsewhere (Harada et al., 1997; Ishii et al., 1998). The fetal karyotype was analysed in 14 cases and all were normal. In this group, the mean (±SD) maternal age at delivery or termination of pregnancy was 29.0 ± 4.7 years, and the gestational age was 20.0 ± 9.0 weeks. Pregnancy was terminated before the 15th gestational week in three patients. Thirteen patients intended to continue the pregnancy, but pregnancy was terminated in 10 patients because of deterioration of maternal complications or intrauterine fetal death. The overall rate of PTT in patients with these CHMTF was 50%. Lung metastases were found in six cases (cases 5, 6, 11, 14, 15 and 17). All nine patients achieved primary remission with chemotherapy alone.

Among the 18 patients with CHMTF, the mean (±SD) gestational ages at delivery or termination of pregnancy in patients with PTT and without PTT were 20.6 ± 7.5 and 19.4 ± 10.7 weeks respectively. Development of PTT was not associated with a difference in the period of gestation (Table III). The incidence of maternal complications, such as pre-eclampsia and massive genital bleeding, was significantly higher \( (P < 0.05) \) in patients with PTT than in patients without PTT.

### Discussion

Clinicians and parents with HMTF cases are presented with a clinical dilemma having to decide between continuation or immediate termination of the pregnancy (Steller et al., 1994; Garbin et al., 1995; Bristow et al., 1996). Recent advances in ultrasonography have enabled early diagnosis of HMTF (Jauniaux, 1998) and provided a host of information regarding the fetus. Moreover, prenatal analyses of the karyotype of the coexistent fetus using chorionic villous sampling, amniocentesis or fetal blood sample are now available. In addition, recent widespread use of ovulation induction may increase the incidence of HMTF (Altaras et al., 1992; Nwosu et al., 1995).

The problems in the management of HMTF involve the risks of fetal abnormality, malignant trophoblastic change, and severe maternal complications. Since complete cytogenetic information on both the mole and the fetus is available only in a small number of reports, an optimal management protocol is controversial (Vejerslev, 1991; Steller et al., 1994; Garbin et al., 1995; Bristow et al., 1996).

An association of fetal abnormalities with triploid partial mole pregnancy has been reported (Beischer, 1961; Block et al., 1982; Vejerslev, 1991). Triploid fetuses tend to die before the end of the first trimester and surviving fetuses after midpregnancy are rarely encountered (Jauniaux et al., 1997). In our patient population, there were no gross anomalies in 17 fetuses that survived to the third trimester. The karyotype of 27 fetuses was analysed during pregnancy or postpartum, and 25 were demonstrated to have normal diploid karyotype, while the remaining two fetuses were triploidy and trisomy. In cases of diploid fetus, dizygotic twin pregnancy with a complete mole is the most probable mechanism. However, the inclusion of triploid partial mole cannot be ruled out if the diagnosis is based only on ultrasound and postpartum morphological findings (Miller et al., 1993).

Immediate termination has been recommended (Jones and Laursen, 1975; Block and Merrill, 1982) after the diagnosis

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### Table I. Demographic and clinical data of hydatidiform mole coexistent with fetus

<table>
<thead>
<tr>
<th>Gestational age at delivery/termination of pregnancy</th>
<th>Age (years)</th>
<th>Cytogenetic analyses of fetus</th>
<th>Ovulation induction (n)</th>
<th>Maternal complications (n (%))</th>
<th>PTT (n (%))</th>
</tr>
</thead>
<tbody>
<tr>
<td>First trimester (&lt;15 weeks) ( (n = 24) )</td>
<td>30.0 ± 6.2</td>
<td>2</td>
<td>4</td>
<td>3 (12.5)</td>
<td>5 (20.8)</td>
</tr>
<tr>
<td>Second trimester (≥15 &lt;28 weeks) ( (n = 31) )</td>
<td>29.1 ± 4.0</td>
<td>14</td>
<td>9</td>
<td>10 (32.3)</td>
<td>14 (45.2)</td>
</tr>
<tr>
<td>Third trimester (≥28 weeks) ( (n = 17) )</td>
<td>29.3 ± 4.8</td>
<td>11</td>
<td>3</td>
<td>1 (5.9)</td>
<td>3 (17.6)</td>
</tr>
<tr>
<td>Total ( (n = 72) )</td>
<td>29.2 ± 5.0</td>
<td>27</td>
<td>16</td>
<td>14 (19.4)</td>
<td>22 (30.6)</td>
</tr>
</tbody>
</table>

PTT = persistent trophoblastic tumour.
Table II. Clinical course and sequelae of 18 patients with complete hydatidiform mole coexistent with fetus(es) in a Japanese national survey

<table>
<thead>
<tr>
<th>Case no.</th>
<th>Age (years)</th>
<th>Gestational age at delivery/termination of pregnancy (weeks)</th>
<th>Cytogenetical analyses</th>
<th>Pregnancy outcome (birth weight)</th>
<th>PTT*</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>28</td>
<td>10</td>
<td>46XY</td>
<td>Termination for vaginal bleeding</td>
<td>No</td>
</tr>
<tr>
<td>2</td>
<td>33</td>
<td>12</td>
<td>ND</td>
<td>Induced abortion</td>
<td>No</td>
</tr>
<tr>
<td>3</td>
<td>23</td>
<td>13</td>
<td>ND</td>
<td>Induced abortion</td>
<td>No</td>
</tr>
<tr>
<td>4</td>
<td>36</td>
<td>15</td>
<td>46XX</td>
<td>Termination for pre-eclampsia</td>
<td>Yes</td>
</tr>
<tr>
<td>5</td>
<td>25</td>
<td>15</td>
<td>46XX</td>
<td>Termination for pre-eclampsia</td>
<td>Yes</td>
</tr>
<tr>
<td>6</td>
<td>21</td>
<td>15</td>
<td>46XX</td>
<td>Termination for vaginal bleeding</td>
<td>Yes</td>
</tr>
<tr>
<td>7</td>
<td>29</td>
<td>15</td>
<td>46XY</td>
<td>Hetero*</td>
<td>No</td>
</tr>
<tr>
<td>8</td>
<td>27</td>
<td>15</td>
<td>46XY</td>
<td>Hetero*</td>
<td>No</td>
</tr>
<tr>
<td>9</td>
<td>31</td>
<td>15</td>
<td>46XY</td>
<td>Hetero*</td>
<td>No</td>
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<tr>
<td>10</td>
<td>26</td>
<td>16</td>
<td>ND</td>
<td>Termination for pre-eclampsia</td>
<td>Yes</td>
</tr>
<tr>
<td>11</td>
<td>33</td>
<td>18</td>
<td>46XX</td>
<td>Termination for vaginal bleeding</td>
<td>Yes</td>
</tr>
<tr>
<td>12</td>
<td>30</td>
<td>20</td>
<td>ND</td>
<td>Homo</td>
<td>Yes</td>
</tr>
<tr>
<td>13</td>
<td>29</td>
<td>20</td>
<td>46XX</td>
<td>Homo</td>
<td>Yes</td>
</tr>
<tr>
<td>14</td>
<td>35</td>
<td>23</td>
<td>46XX</td>
<td>Homo</td>
<td>Yes</td>
</tr>
<tr>
<td>15</td>
<td>30</td>
<td>25</td>
<td>46XX</td>
<td>Homo</td>
<td>Yes</td>
</tr>
<tr>
<td>16</td>
<td>27</td>
<td>35</td>
<td>46XX</td>
<td>Homo</td>
<td>Yes</td>
</tr>
<tr>
<td>17</td>
<td>37</td>
<td>38</td>
<td>46XX</td>
<td>Homo</td>
<td>Yes</td>
</tr>
<tr>
<td>18</td>
<td>22</td>
<td>40</td>
<td>46XX</td>
<td>Homo</td>
<td>Yes</td>
</tr>
</tbody>
</table>

*Intrauterine fetal death.
**Not determined.
**Homozygous androgenetic mole.
**Heterozygous androgenetic mole.
**Persistent trophoblastic tumour.

PTT = persistent trophoblastic tumour.

Table III. Gestational age, maternal complications and the persistent trophoblastic tumour in patients with CHMTF

<table>
<thead>
<tr>
<th>Patients</th>
<th>Gestational age (weeks)</th>
<th>Maternal complications (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>With PTT (n = 9)</td>
<td>206 ± 7.5*</td>
<td>7 (77.8)**</td>
</tr>
<tr>
<td>Without PTT (n = 9)</td>
<td>19.4 ± 10.7</td>
<td>1 (11.1)</td>
</tr>
</tbody>
</table>

CHMTF = complete hydatidiform mole coexistent with twin live fetus; PTT = persistent trophoblastic tumour.

*Not significant.
**P < 0.05.

of HMTF because of the risks of developing PTT and maternal medical complications. In contrast, other authors (Vejerslev, 1991; Garbin et al., 1995; Bristow et al., 1996) suggested that in the absence of fetal anomaly or pre-eclampsia, the pregnancy can be allowed to continue irrespective of the development of PTT. However, cytogenetic information on both the mole and the fetus seems to be insufficient to decide whether to continue or to terminate the pregnancy (Fisher et al., 1982; Ohama et al., 1985; Ohmichi et al., 1986; Vejerslev et al., 1986; Azuma et al., 1992; Miller et al., 1993; Soysal et al., 1996; Hurteau et al., 1997). In our previous report of a limited series (Matsui et al., 1999), the potential of malignancy in patients with CHMTF was significantly higher than that of single complete mole, while advanced gestational age was not an independent risk factor for the development of PTT.

PTT rates in simple complete mole were reported to be 12.5% (141/1130) in a previous study at our university (Matsui et al., 1999). In the present patient population, the risk of developing PTT was considerably higher than this in patients with HMTF. The overall incidence of PTT in patients with HMTF was 30.6% and the rate increased to 50% in 18 patients with CHMTF. At present, it is uncertain whether the increased risk of PTT in patients with HMTF is due to the prolonged gestation or to the more aggressive biological behaviour of abnormal trophoblasts coexisting with a fetus in twin gestation. In our patients with CHMTF, the incidence of developing PTT was unchanged with advancement of gestational age, but maternal prenatal complications were reported to be significantly associated with PTT, as previously reported (Miller et al., 1993). Despite no increased risk of PTT with continuation of pregnancy, only about one-third had a live outcome (excluding those women who opted to terminate), and pre-eclampsia, intrauterine fetal death and bleeding remain important problems.

In conclusion, our results suggest that patients with HMTF may be allowed to continue the pregnancy, provided that the fetal karyotype is normal and maternal complications can be controlled. However, further clinical assessment of the risks of continuation of pregnancy awaits collection of a larger series of patients with complete cytogenetic data.

Acknowledgements
We are grateful to all the colleagues who provided cases for this study.

References
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Received on August 20, 1999; accepted on November 19, 1999