Are fertility drugs a risk factor for persistent trophoblastic tumour?

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BACKGROUND: The introduction of ovulation-inducing drugs has raised concern that women exposed to these therapies may be at increased risk of cancer. We assessed the potential association between exposure to fertility drugs and the risk of developing persistent trophoblastic tumour (PTT). METHODS: We conducted a systematic review of the English and non-English language literature using the National Library of Medicine’s Medline to identify all observations of patients with hydatidiform mole (HM) after treatment with ovulation-inducers. RESULTS: Fifty-two cases were considered including 26 singleton molar pregnancies and 26 multiple molar pregnancies consisting of an HM and one or more co-existent fetus(es) (HM-and-CF). PTT occurred in 15% of patients with singleton HM and in 42% of patients with HM-and-CF, 15% of whom had a metastatic disease. Of those patients with HM-and-CF, 16 patients delivered at <24 weeks gestation, mostly because of vaginal haemorrhage. Ten patients delivered at ≥24 weeks of gestation, six of whom (25%) had a normal live child. These results are similar to spontaneously conceived pregnancies. CONCLUSIONS: Although women having an HM after therapy with ovulation-inducing drugs seem to have no added risk of PTT, multiple pregnancies are more likely to occur, and the overall risk may be increased.

Key words: hydatidiform mole/metastasis/ovulation induction/persistent trophoblastic tumour
Materials and methods

All cases of HM pregnancies following the use of assisted reproductive technologies published in the literature from January 1966 through July 2001 were retrieved by a key word search of the National Library of Medicine’s Medline and reviewed. Key words used were: molar pregnancy or hydatidiform mole accompanied by any of the following: ovulation induction or clomiphene citrate or gonadotrophin or HMG or HCG or FSH or IVF or ICSI. The citation lists of retrieved articles were then reviewed to source other potential publications.

All reports were reviewed with regards to (i) pre-evacuation clinical features: type of fertility therapy used, maternal age at diagnosis, estimated gestational age at diagnosis, gravidity, parity, presenting symptoms, ultrasound findings, pre-evacuation HCG; and (ii) post-evacuation clinical features: type of HM, molar karyotype, PTT, and presence of metastasis. For pregnancies combining an HM and coexistent fetus(es) (HM-and-CF), the additional following features were extracted: presence before the transfer of two pronuclei, estimated gestational age at termination, indication for termination/delivery, fetal karyotype, and fetal outcome.

Patients with HM-and-CF were divided into two groups: (i) pregnancy with a delivery <24 weeks gestation; and (ii) pregnancy with a delivery at ≥24 weeks gestation. The percentage of patients was calculated only for those with available data. Missing or incomplete clinical data of reported patients were considered as a not-available (NA) category. We have considered that patients with a mention of one negative β-HCG or other mention attesting an absence of PTT, as having no PTT. Differences in continuous variables were evaluated using the Mann-Whitney U-test and differences in proportion by the two-tailed Fisher’s exact test. Statistical significance was defined as a P-value < 0.05.

Results

Identified reports and exclusions

A total of 58 observations were retrieved. Six cases were further excluded for the following reasons: (i) no follow-up information provided concerning remission or persistence (n = 3); (ii) patients with choriocarcinoma (n = 2); (iii) patients with no histological examination (n = 1). The present study comprises 52 patients presenting an HM after ovulation induction. They were divided into two groups: (i) patients with a singleton HM (n = 26), and (ii) patients with HM-and-CF (n = 26). The first group included 11 CHM, one PHM and 14 cases of HM of unknown type (corresponding to reports of more than one ovum, the question can be raised as to whether the increase in the production of immature or anucleated ova or other cytogenetic examinations were reported in only one case). In the remaining cases, it was only made at the second trimester. Chromosomal analysis or other cytogenetic examinations were reported in only one instance for patients with singleton HM, and in 16/25 of those with HM-and-CF. In other cases, the specific diagnosis was confirmed only upon the histological examination. For those cases where the genetic origin had been demonstrated, namely, androgenetic for molar tissue and biparental for the fetus, the information was available in six instances. In this group, the risk of PTT was 50%. The assessment of the early fertilization process was mentioned in six cases, and in five cases the 2PN stage was observed before the embryo transfer.

Discussion

The use of ovulation-inducing drugs such as clomiphene citrate or gonadotrophin (HMG or FSH) is very popular in therapy for anovulation, but the introduction of these new technologies has raised concern that these women may be at increased risk of cancer. Several studies have investigated this topic and shown that fertility drugs were not associated with an increased maternal risk of breast, ovarian or uterine cancer (Gluds et al., 1998; Venn et al., 1999). As ovulation-inducers cause ovulation of more than one ovum, the question can be raised as to whether the increase in the production of immature or anucleated ova (an underlying mechanism of HM) by these drugs may be a contributing factor to the development of HM or invasive HM.

CHM may be considered as a precancerous condition which can transform into an invasive tumour. The aim of our study was to identify potential carcinogenic effects of ovulation-inducers and to analyse the clinical outcome of singleton HM and HM-and-CF pregnancies occurring after fertility therapy.
This information could provide a basis for decision-making and the counselling of patients when an HM is diagnosed in early or late pregnancy. The present series is comprised exclusively of patients with an HM after having undergone fertility treatment and, to the best of our knowledge, no previous study has evaluated this issue, apart from isolated case reports.

Patients with singleton HM have an incidence of PTT after evacuation of the mole of 14%. This rate is similar to those with pregnancy occurring naturally. Compared with HM-and-CF, singleton HM are diagnosed earlier in the pregnancy (11.5 versus 16 weeks gestation; P < 0.05) probably because the presence of fetal heartbeat falsely reassured the clinician and is responsible for the delayed diagnosis. A statistically significant difference in age between the two groups was observed (31 versus 27.5 years; P < 0.05), but we have no immediate explanation for this finding.

Patients with an HM-and-CF have a pregnancy composed of two different conceptus; one is a normal fetus and placenta and the other is a molar pregnancy. This type of pregnancy has a more aggressive post-evacuation behaviour with a risk of PTT significantly higher than a singleton HM. Steller et al. reported 12/22 (55%) PTT in patients with HM-and-CF compared with only 10/71 (14%) in patients with single HM (Steller et al., 1994). Other reports have confirmed this observation with a risk of PTT which has been estimated as between 40–57% (Vejerslev, 1991; Miller et al., 1993; Bristow et al., 1996; Fishman et al., 1998; Bruchim et al., 2000; Matsui et al., 2000). We found similar results in our series with a risk of PTT occurring of 42%, suggesting that the course of CHM-and-CF after ovulation induction has a similar evolution to a natural one. It is still unclear if the greater risk of PTT is associated with a more aggressive behaviour of the molar tissue or because of delayed delivery. However, recent reports have observed that an advancement of the gestational age does not appear to increase the risk of developing a PTT (Bristow et al., 1996; Matsui et al., 2000). Our report concurs with the existing literature in that the rate of PTT in pregnancy of <24 weeks and ≥24 weeks gestation is similar.

At present, it is possible to distinguish between a prenatal diagnosis of a triploid non-viable fetus and a chromosomally-normal and viable infant. The latter condition presents the patient and the physician with a critical dilemma between a therapeutic abortion or an expectant management until fetal viability. The conservative approach is supported by the fact that there have now been several reported cases of HM-and-CF after natural conception that have been carried to viability. The conservative approach is supported by the fact that there have now been several reported cases of HM-and-CF after natural conception that have been carried to viability.

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### Table III. Hydatidiform mole after fertility therapy: clinical features of patients with complete hydatidiform mole co-existing with fetus(es) of ≥24 weeks gestation.

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>First authors</th>
<th>Patient age (yrs)</th>
<th>EGA term (week)</th>
<th>Indication for termination/delivery</th>
<th>Evacuation procedure</th>
<th>Type of pregnancy molar and fetal karyotype ( )</th>
<th>Fetal outcome (sex and birth weight)</th>
<th>PTT (meta)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Van de Geijn et al. (1992)</td>
<td>31</td>
<td>24</td>
<td>Chorioamnionitis + tocolysis failed</td>
<td>Spontaneous vaginal delivery</td>
<td>Triplet: CHM (46,XX) + 2 normal fetuses (46,XY) + (46,XY) + 1 normal fetus (NA)</td>
<td>Neonatal death (males 595g and 525g)</td>
<td>No</td>
</tr>
<tr>
<td>2</td>
<td>Adachi et al. (1992)</td>
<td>27</td>
<td>24</td>
<td>NA</td>
<td>Vaginal delivery</td>
<td>Twin: CHM (NA) + 1 normal fetus (NA)</td>
<td>NA (female)</td>
<td>Yes (lung)</td>
</tr>
<tr>
<td>3</td>
<td>Jinno et al. (1994)</td>
<td>35</td>
<td>31</td>
<td>NA</td>
<td>Spontaneous vaginal delivery</td>
<td>Twin: CHM (46,XX) + 1 normal fetus (46,XY)</td>
<td>Neonatal death (male 1729g)</td>
<td>Yes (lung)</td>
</tr>
<tr>
<td>4</td>
<td>Steller et al. (1994)</td>
<td>23</td>
<td>31</td>
<td>Fetal distress</td>
<td>Caesarean section</td>
<td>Twin: CHM (diploid) + 1 normal fetus (diploid)</td>
<td>Alive (male)</td>
<td>No</td>
</tr>
<tr>
<td>5</td>
<td>Cheng et al. (1995)</td>
<td>29</td>
<td>29</td>
<td>Tocolysis failed + placenta praevia</td>
<td>Caesarean section</td>
<td>Twin: CHM (46,XX) + 1 normal fetus (dizygotic)</td>
<td>Alive (female 986g)</td>
<td>No</td>
</tr>
<tr>
<td>6</td>
<td>Shahabi et al. (1997)</td>
<td>28</td>
<td>38</td>
<td>None</td>
<td>Caesarean section (breech)</td>
<td>Twin: CHM (46,XX) and 1 normal fetus (46,XX)</td>
<td>Alive (female 2775 g)</td>
<td>No</td>
</tr>
<tr>
<td>7</td>
<td>Montes de-Oca-Valero et al. (1999)</td>
<td>41</td>
<td>28</td>
<td>PE + vaginal bleeding</td>
<td>Caesarean section</td>
<td>Twin: CHM (46,XX) + 1 normal fetus (NA)</td>
<td>Alive (female 980 g)</td>
<td>No</td>
</tr>
<tr>
<td>8</td>
<td>Chao et al. (1999)</td>
<td>28</td>
<td>25</td>
<td>PROM + tocolysis failed</td>
<td>Caesarean section</td>
<td>Quadruplet: CHM (NA) + 3 normal fetuses (diploid)</td>
<td>Neonatal death</td>
<td>Yes</td>
</tr>
<tr>
<td>9</td>
<td>Bruchim et al. (2000)</td>
<td>28</td>
<td>41</td>
<td>None</td>
<td>Vaginal delivery</td>
<td>Twin: CHM (46,XY) + 1 normal fetus (46,XY)</td>
<td>Alive (female, 3240g)</td>
<td>No</td>
</tr>
<tr>
<td>10</td>
<td>Bruchim et al. (2000)</td>
<td>25</td>
<td>26</td>
<td>PROM + tocolysis</td>
<td>Caesarean section</td>
<td>Twin: CHM (46,XX) + 1 normal fetus (46,XY)</td>
<td>Alive (male, 870g)</td>
<td>Yes (lung)</td>
</tr>
</tbody>
</table>

Patient age = patient age at diagnosis; NA = not available; EGA term = estimated gestational age at termination; CHM = complete hydatidiform mole; PE = pre-eclampsia; PROM = premature rupture of membranes; PTT = persistent trophoblastic tumour, meta = presence of metastasis and localization.
Once a diagnosis of gestation consisting of an HM and co-existing chromosomally-normal fetus(es) has been made, and if the clinical course is stable, the decision to allow such a pregnancy to continue should be taken with the couple. The women should be aware of the increased risk of pregnancy complications such as severe antepartum haemorrhage, pre-eclampsia or hyperemesis gravidarum that may require prompt uterine evacuation. As previously mentioned, if the gestation shows a benign clinical course, an expectant observation until infant viability must be considered. Such a management may be encouraged in those patients having undergone fertility therapy, sometimes at an advanced age and after many attempts of assisted conception, which implies a profound desire to continue the pregnancy until viability of the fetus. According to our series and that of Brustow et al., ~25% of patients will have the possibility of having a viable live birth (Bristow et al., 1996).

Results from the present study must be interpreted within the context and limitations of our data as they include reports from the literature only and, with meta-analyses, are subject to reporting bias. It is well known that cases with complications are documented more frequently than uneventful observations. Another limitation is that some observations have been included despite the fact that no cytogenetic analysis was carried out. However, at present, the only way to have some insight into the course of HM after ovulation-inducers, and to acquire knowledge about the optimal management of this type of pregnancy, is to retrieve from the literature all the well-documented cases.

In conclusion, our study suggests that women having a singleton or multiple pregnancy after exposure to ovulation-inducers seem to have no additional risk of PTT than those who conceive naturally. However, as this therapy is more likely to result in multiple pregnancy than spontaneously conceived singleton pregnancy, patients are at greater risk of developing PTT. In clinical practice, the overall rate of PTT after ovulation-inducing drug treatment is probably increased.

Table IV. Hydatidiform mole after fertility therapy: comparison of clinical and biological features between pregnancies of <24 weeks and ≥24 weeks gestation

<table>
<thead>
<tr>
<th>Features</th>
<th>&lt;24 weeks&lt;sup&gt;a&lt;/sup&gt; (n = 16)</th>
<th>≥24 weeks&lt;sup&gt;b&lt;/sup&gt; (n = 10)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>median (range) or n (%)</td>
<td>median (range) or n (%)</td>
<td></td>
</tr>
<tr>
<td>Maternal age (years)</td>
<td>26 (23–40)</td>
<td>28 (22–41)</td>
<td>NS</td>
</tr>
<tr>
<td>Gravidity</td>
<td>1 (0–4)</td>
<td>1 (0–3)</td>
<td>NS</td>
</tr>
<tr>
<td>Parity</td>
<td>0 (0–2)</td>
<td>0 (0–2)</td>
<td>NS</td>
</tr>
<tr>
<td>EGA at diagnosis (week)</td>
<td>15.5 (7–26)</td>
<td>16.5 (9–41)</td>
<td>NS</td>
</tr>
<tr>
<td>EGA at termination/delivery (week)</td>
<td>17.5 (7–26)</td>
<td>28.5 (13–41)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Pre-evacuation urinary HCG (IU/l)</td>
<td>868 340</td>
<td>327 150</td>
<td>NS</td>
</tr>
<tr>
<td>Pre-eclampsia</td>
<td>4/16 (25%)</td>
<td>2/10 (20%)</td>
<td>NS</td>
</tr>
<tr>
<td>Persistent trophoblastic tumour</td>
<td>6/16 (37%)</td>
<td>5/10 (50%)</td>
<td>NS</td>
</tr>
<tr>
<td>Metastasis</td>
<td>1/16 (6%)</td>
<td>3/10 (30%)</td>
<td>NS</td>
</tr>
</tbody>
</table>

<sup>a</sup>Singleton molar pregnancy.
<sup>b</sup>Multiple pregnancy combining a molar pregnancy with one or more normal fetus(es).
EGA = estimated gestational age.

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References


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