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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 metastasic 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

Introduction

Hydatidiform moles (HM) are tumours originating from placental tissues and currently two main types are recognized: the complete hydatidiform mole (CHM) and the partial hydatidiform mole (PHM) (Vassilakos *et al.*, 1977; Szulman and Surti, 1978a,b). In most patients, HM regresses spontaneously after uterine evacuation. Nevertheless, 18–29% of those with CHM and ~4% with PHM have persistently elevated β-HCG values, corresponding to residual trophoblastic tissue or persistent trophoblastic tumour (PTT) in pelvic or extrapelvic sites (Berkowitz and Goldstein, 1996). PTT corresponds to an invasive HM with neoplasic behaviour because the molar tissue invades deeply into the myometrium, penetrates into the uterine vessels, and may be transported haematogeneously to distant sites such as the lung, brain, or liver to form metastases.

HM after fertility therapy seems to be a rare complication despite the widespread use of these treatments. The true incidence is however not known due to the lack of sufficient information regarding the number of treatments performed and the number of HMs avoided by current policies in reproductive medicine. These policies imply that only embryos derived from normally fertilized oocytes are selected for replacement. The normal fertilization process is usually considered to have occurred when two pronuclei (2PN) and two polar bodies are observed. If the number of pronuclei is different, as for monopronuclear (1PN) or tripronuclear (3PN), the embryos are generally not transferred as it is presumed that some of them could be an origin for HM. An incidence of 1/659 pregnancies has been disclosed by Merril-National Labs., Cincinnati, Ohio, USA, and reported by Schneidermann and Waxman in a group of 2 369 clomiphene-induced pregnancies (natural incidence estimated as 0.5–1.1/1000 in USA) (Schneiderman and Waxman, 1972). In another report Kurachi reported a rate of 1/1034 pregnancies in Japan (natural incidence estimated as 1.9–2.8/1000 in Japan) (Kurachi, 1982; Bracken, 1987).

New treatments in assisted reproductive medicine represent a major step forward but a careful evaluation is necessary to identify potential harmful effects on the mother. Molar pregnancy after exposure to fertility drugs is a rare condition that precludes an appropriate prospective study. Currently, the only available information is on the basis of case reports. These data do not permit an assessment of the real rate of PTT due to reporting bias but only allow the discussion of the potential association between the exposure to this treatment and the subsequent development of PTT.

Our study aim was to identify all published reports of molar pregnancies after ovulation induction and to evaluate if there could be an association between this therapy and the development of PTT or metastatic disease.

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 $\geqslant$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 mostly published pre-1980 without classification into CHM or PHM). The second group included 25 CHM with normal fetus(es), and one PHM with a normal fetus.

Comparison between singleton HM and HM-and-CF

Table I summarizes the clinical and laboratory parameters of the reported cases and compares patients with singleton HM and those with an HM and CF. A total of 15% of patients with singleton HM developed a PTT but none had metastasis. In patients with HM-and-CF, 42% developed a PTT with 15% developing metastasis. All patients with metastatic disease had lung metastasis and all achieved a complete remission after chemotherapy. Among the cases of HM-and-CF, 17 were twin, and there were eight triplet or quadruplet pregnancies. In these two groups, PTT was 41% (7/17) and 50% (4/8) respectively.

Type of fertility therapy used and risk of PTT

Table II shows the type of fertility drugs used and the risk of PTT for singleton HM and HM-and-CF.

CHM-and-CF: Comparison between deliveries <24 and ≥24 weeks gestation

Data on features of pregnancy with a gestational age of $\geqslant$24 weeks are summarized in Tables III and IV. Among these women ($n = 10$), six women delivered live infants without any anomalies (five Caesarean section and one vaginal delivery). One subsequently developed PTT with lung metastasis. In patients who delivered $<$24 weeks, the information about delivery was available in 12/16 cases. This included: uterine evacuation before fetal viability due to spontaneous vaginal abortion ($n = 4$), vaginal bleeding ($n = 4$), pre-eclampsia ($n = 3$), and hyperemesis gravidarum with abdominal pain ($n = 1$). None of the patients with a triplet ($n = 6$) or quadruplet ($n = 2$) pregnancy delivered a live infant.

Other features

Since 1985, the results of ultrasonographic examinations were available in all cases of singleton HM and in 24/25 CHM-and-CF. The diagnosis was correctly made in 7/13 (53%) and 14/24 (58%) cases respectively. In the remaining cases, it was either a misinterpretation or simply the diagnosis of HM was not recognized. The diagnosis of HM was made earlier for singleton HM than HM-and-CF ($P < 0.05$) where frequently 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.

Table I. Hydatidiform mole after fertility therapy: comparison of clinical and biological features between singleton and multiple pregnancies combining a hydatidiform mole with coexistent fetus(es)

Features	Singleton[a] ($n = 26$) median (range) or n (%)	Multiple[b] ($n = 26$) median (range) or n (%)	P-value
Maternal age (years)	31 (23–40)	27.5 (22–41)	< 0.05
Gravidity	0 (0–4)	1 (0–3)	NS
Parity	0 (0–2)	0 (0–2)	NS
EGA at diagnosis (week)	11.5 (7–26)	16 (9–41)	< 0.05
EGA at termination/delivery (week)	11.5 (7–26)	20.5 (13–41)	< 0.05
Pre-evacuation urinary HCG (IU/l)	300 000 (23 500–3 000 000)	561 808 (10 000–6 400 000)	NS
Pre-eclampsia	1/26 (3.8)	6/26 (25)	NS
Persistent trophoblastic tumour	4/26 (15)	11/26 (42)	NS
Metastasis	0/26 (0)	4/26 (15)	NS

[a]Singleton molar pregnancy.
[b]Multiple pregnancy combining a molar pregnancy with one or more normal fetus(es).
EGA = estimated gestational age.

Table II. Hydatidiform mole after fertility therapy: type of ovarian stimulation and development of persistent trophoblastic tumour and metastasis

Drug usage	Singleton[a] ($n = 26$)		Multiple[b] ($n = 26$)		
	n	PTT	n	PTT	Metastasis
Clomiphene	17	3 (18)	10	3 (30)	2 (20)
Clomiphene + gonadotrophin	2	–	1	1	–
Gonadotrophin	7	1 (14)	15	7 (46)	2 (13)
Total	26	4 (15)	26	11 (42)	4 (15)

[a]Singleton molar pregnancy.
[b]Multiple pregnancy combining a molar pregnancy with one or more normal fetus(es).
PTT = persistent trophoblastic tumour.

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 $\geqslant 24$ 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 and delivery of a live infant. In a review of the literature, Bristow *et al.* have found 26 cases of HM-and-CF with seven cases of surviving infants (Bristow *et al.*, 1996).

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

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

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.

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

Features	<24 weeks[a] (n = 16) median (range) or n (%)	⩾24 weeks[b] (n = 10) median (range) or n (%)	P-value
Maternal age (years)	26 (23–40)	28 (22–41)	NS
Gravidity	1 (0–4)	1 (0–3)	NS
Parity	0 (0–2)	0 (0–2)	NS
EGA at diagnosis (week)	15.5 (7–26)	16.5 (9–41)	NS
EGA at termination/delivery (week)	17.5 (7–26)	28.5 (13–41)	< 0.05
Pre-evacuation urinary HCG (IU/l)	868 340 (10 500–6 400 000)	327 150 (256 000–1 224 680)	NS
Pre-eclampsia	4/16 (25%)	2/10 (20%)	NS
Persistent trophoblastic tumour	6/16 (37%)	5/10 (50%)	NS
Metastasis	1/16 (6%)	3/10 (30%)	NS

[a]Singleton molar pregnancy.
[b]Multiple pregnancy combining a molar pregnancy with one or more normal fetus(es).
EGA = estimated gestational age.

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 Bristow *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.

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