GESTATIONAL TROPHOBLASTIC NEOPLASIA—CERTAIN INTERESTING OBSERVATIONS

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SUMMARY

Vesicular mole is essentially a pregnancy disorder of young women in whom there is an urgent need for preservation of fertility. While vaginal bleeding is a very prominant symptom in 91.67% of subjects, waiting for this symptom delays the diagnosis in 58.33% of occasions. Hence, routine sonography after 8 completed weeks appears optimal for early diagnosis of vesicular mole. Sonography imaging of vesicular mole resembled missed abortion in 33.33% of subjects, and 25% of sonographic diagnosis of missed abortions proved to be vesicular mole at evacuation.

Sonographic monitoring of postmolar cases should replace check curettage. Sonographic surveillance also enables diagnosis of invasive mole in 16.67% of patients undergoing regular postmolar monitoring.

A minimum of 3 ß-hCG samples studies within the first 8 weeks of molar evacuation is good enough for identifying postmolar trophoblastic disease in majority of occasions. If regression has occurred, as seen in all subjects who had no trophoblastic activity, further monitoring will be by employing clinical examination, menstrual calender and BBT. Pregnancy can be safely undertaken with regular ovulatory menstrual cycles, 6 months after ß-hCG regression.

Failure of ß-hCG regression or abnormal regression pattern observed in the 3 samples studied over a period of 8 weeks is a strong indication for Methotrexate therapy. In majority of cases one course of the drug for 5 days in the standard dose is sufficient to regress the post-molar disease. If titre is regressed, next pregnancy should be allowed one year after the last dose of the drug.

Surprisingly, among the 381 subjects achieving conception following treatment for various infertility problems none had gestational trophoblastic disease.

Introduction

Three conditions are usually considered under 'gestational Trophoblastic neoplasia': Hydatidiform mole, Invasive mole and Choriocarcinoma (Driscoll, 1984). Our ability to diagnose hydatidiform mole with confidence has dramatically changed with the advent of

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utlrasonography (Kohorn, 1984). Postmolar close surveillance and early diagnosis of postmolar trophoblastic disease (PMTD) are best obtained by serial estimation of ß-hCG by serum radioimmunoassay (Morrow, 1984). Fortunately, trophoplastic malignancies are uniquely sensitive to chemotherapy, namely, methotrexate and actinomycin D, and thus complete remission can be attained and fertility preserved (Goldstein and Berkowitz, 1984).

Since March 1985 we have been employing ultrasonography for diagnosis of vesicular mole (Rajan and Rajan, 1987), and serial estimation of ß-hCG for postmolar surveillance. Over this period of 2 years and 2 months (ending with April 1987), 12 cases with vesicular mole were diagnosed by ultrasonography from 300 subjects scanned during early pregnancy. This high incidence of vesicular mole, namely 4.00%, is partly due to referals from the peripheral centres for sonographic diagnosis. These subjects had post-molar surveillance employing ß-hCG and sonography, and further management decided accordingly.

In addition, there were 6 subjects who were referred for surveillance following molar evacuation. They were similarly managed. This study of 18 cases reveals certain contradictory but interesting observations which will be discussed.

Study design

We advocate routine sonography during early pregnancy or in the midtrimester, particularly where there are clinical grounds (Rajan and Rajan, 1987). By this approach vesicular mole was diagnosed in 12 subjects, in some as eary as 9th week of gestation. Suction evacuation of the mole was done. Earnest attempt was made at emptying the uterus completely, and a second curettage (check curettage) was totally avoided. Instead, a sonographic monitoring was advocated within 7 days of evacuation, to reveal (i) normal uterine cavity indicating complete evacuation of moles; (ii) measurements of the uterus, to ascertain further reduction in size; (iii) nodules in the myometrium indicating the presence of invasive mole; and (iv) lutein cysts, which could not be located at the first scan due to uterine enlargement. Sonography was repeated at 2 to 4 weeks interval.

A preevacuation ß-hCG titer was not obtained for technical reasons. However, following evacuation ß-hCG assay was performed within 7 days and at interval of 1 to 2 weeks for atleast 3 studies. Once the ß-hCG titer falls to below 10 mIU further monitoring was based on clinical and if needed sonographic parameters.

Chest X-ray was routinely obtained before evacuation of the mole to indicate lung infiltration if any and serve as control for future review. Patients were advised to avoid a pregnancy, and majority had preferred natural methods of contraception. From the time menstrual cycles were initiated the patients were encouraged to maintain a menstrual calender and also a basal body temperature recording. The purpose was to find out the establishment of atleast 6 consecutive regular ovulatory cycles which practically evidenced a complete regression of trophoblastic activity.

If the patient desired another pregnancy she was advised to undertake it provided: (i) she had atleast 6 regular ovulatory cycles after the ß-hCG titer had fallen below 10 mIU/ml; (ii) Lutein cysts had completely regressed; (iii) uterine size had regressed to normal; and (iv) uterine nodules or other evidences of

metastasis were absent. Evidently, when the first criterion was satisfied all the other criteria were met.

We did not come across any multiparous elderly subjects in this series who could have had hysterectomy with moles insitu to avoid development of postmolar trophoblastic disease.

Following molar evacuation, if the ß-hCG regression pattern (Morrow, 1984) was abnormal or normal regression did not result within 4 to 6 weeks, chemotherapy with methotrexate was advocated. Presence of metastasis was the other indication for methotrexate therapy. High risk subjects with repeated molar gestation, disproportionately increased uterine size and lutein cysts were considered candidates for chemotherapy particularly when they could not be regularly followed.

Methotrexate was administered in a dose of 0.40 mg per Kg body weight per day, intravenously, for 5 days. The regimen is repeated at 1 to 2 weeks interval depending on ß-hCG regression pattern and also on her blood parameters. Usually these subjects needed 1 to 2 courses of treatment for achieving remission. Future pregnancy was advocated one year after the last chemotherapy dose.

Observations and Discussion

Epidemiology: Contrary to the accepted reports (Buckley, 1984) that molar gestation is common in elderly age group, and hence probably in multiparous subjects, in our study of 18 subjects, 10 (55.56%) were below 25 years of age, and only 1 was above 30 years of age (5.56%). Moreover, except for 1 subject (5.56%) all were either nulliparous or second gravidae (94.44%). Thus in our series vesicular mole was more frequently encountered in young subjects who were nulliparous, necessitating careful surevillance not only to detect and treat post molar trophoblastic disease, but also to ensure restoration of future fertility.

In our Christian dominated population the distribution of trophoblastic disease was: Christians—55.56%, Hindus—27.78% and Muslims—16.67%.

Clinical Symptoms: It is universally held that vaginal bleeding is present in 94 to 97% of patients (Curry *et al*, 1975 and Goldstein and Berkowitz, 1983), and complete moles usually become symptomatic by 6 to 8 weeks (Kohorn, 1984). Our findings are in agreement with the former observation, and vaginal bleeding was recorded in 91.67%. However, there were only 5 subjects (41.67%) among the 12 cases of molar gestation who had bleeding before 8 completed weeks of amenorrhoea. Vaginal bleeding was recorded late in the first trimester in 4 subjects (33.33%), by 15-19 weeks in 2 (16.67%) and not at all in 1. Hyperemesis gravidarum was the presenting symptom of molar pregnancy in only 1 of the 12 subjects (8.33%).

Altogether, more than 50% of the subjects with molar gestation (58.33%) remained asymptomatic till the 8 completed weeks of amenorrhoea, and hence a diagnosis based on vaginal bleeding appears to be a less optimal method of early diagnosis of molar gestation. It is also evident from the number of molar gestations diagnosed at different weeks of gestation. Only 4 of the 12 subjects (33.33%) had reported in the first trimester (before 12 weeks), and the rest 66.67% had reported between 13 and 24 weeks. Waiting for the symptom of vaginal bleeding for performing ultrasound scanning has delayed the diagnosis of molar gestation to mid-trimester in 2/3rds of the subjects. Diagnosis of vesicular mole in the first trimes-

ter has got lot of advantages including a safe termination, minimal blood loss, absence of medical complications and early diagnosis of the disease. For all these reasons it is strongly felt that routine ultrasound scanning in the late first trimester (after 8 completed weeks) should be the preferred method of diagnosis than waiting for symptoms like vaginal bleeding to develop.

Ultrasound diagnosis: In this study diagnosis of vesicular mole was possible from the 9th week onwards. The typical snow-storm pattern which is diagnostic of vesicular mole was encountered only in 8 of the 12 subjects (66.67%). The remaining 4 subjects (33.33%) showed a sonographic pattern resembling missed abortion. Missed abortion may be difficult to distinguish from a regressing mole or a mole associated with early fetal demise (Kohorn, 1984). Hence the clinician should always be alert to a sonographic diagnosis of missed abortion, and carefully look for vesicular mole at the time of evacuation. The physician will stumble on a vesicular mole atleast in 25% of such situations, because among the 16 sonographic diagnosis of missed abortion 4 subjects proved to have vesicular mole.

In the early first trimester molar sac is indistinguishable from that of blighted ovum (Romero *et al*, 1984), since the vesicles are not well developed. We have not encountered such a situation since all 12 cases were diagnosed only after 9 weeks.

Lutein cysts associated with molar pregnancy are easily identified by ultrasonography, particularly after evacuation of the mole. Among the 12 subjects who had regular postmolar surveillance lutein cysts were diagnosed at sonography in 4 subjects (33.33%).

More than identifying lutein cysts, sonography had a distinctive significant role in post-molar surveillance. In 2 of the 12 subjects, (16.67%) having regular sonography and ß-hCG surveillance, solitary myometrial nodules measuring 4 to 6 cm in diameter were imaged, proving a diagnosis of invasive mole. The diagnosis was confirmed atleast in one subject (36 years old parous patient) undergoing hysterectomy, in whom a well encapsulated mass containing molar tissue, and another haemorrhagic nodule were identified in the myometrium of posterior uterine wall. The other subject, a nulliparous patient, with persistant hCG titer and not responding to chemotherapy was referred to the trophoblastic centre. In both subjects invasive mole was diagnosed within 4 to 8 weeks of molar evacuation. Hence, regular sonographic examination at 2 to 4 weeks interval must be an integral part of post-molar surveillance. Sonographic diagnosis of invasive mole has been documented by Driscoll (1984).

ß-hCG Estimation: Serial hCG titer analysis, which is the tumour marker, is the basis of medical care subsequent to molar pregnancy (Morrow, 1984). The present study describes ß-hCG follow-up immediately after molar evacuation and repeated at 1 to 2 weeks interval for a minimum of 3 sample reports. It is observed that the titer falls to less than 10 mIU (normal regression) over a period of 4 to 8 weeks, and these subjects do not develop trophoblastic malignancies and return to normal ovulatory menstrual cycles with normal reproductive capability.

Hence it may be prudent to perform atleast 3 ß-hCG estimations between 4 to 8 weeks of molar evacuation, and if found to regress normally they can be further monitored by sonography, menstrual

calender and BBT recording. Six months of regular ovulatory cycles from the time of hCG regression should permit the patient to attempt a pregnancy safely. If the ß-hCG titer is abnormal in the first 3 samples studied it will be safer to start methotrexate, and also make a meticulous search for evidence of trophoblastic tumour in the uterus or for metastasis. Repeat X-ray chest, sonography and pelvic examination should be helpful at this stage. However, if sonography reveals an empty uterine cavity there is no place for a curettage even if there is vaginal bleeding. Trophoblastic malignancy is better diagnosed by abnormal ß-hCG regression pattern and sonography rather than by curettage. Hysterectomy is in order in multiparous subjects, but the aim should be to achieve total regression of the tumour by chemotherapy in young subjects who need their reproductive function to be safeguarded. In the 3 subjects treated with methotrexate, ß-hCG regression was normal in 2 subjects after a single course of therapy (66.67%). The third subject had invasive mole diagnosed by ultrasound and was referred to the trophoblastic centre. Thus, it is felt that even subjects needing chemotherapy are mostly cured by 1 to 2 courses of the drug and hence drug toxicity should not be a serious problem.

Pregnancies of Infertile Couple: From September, 1983 to April, 1987 we have followed 381 pregnancies resulting following treatment of various forms of fertility disorders which included endocrine disorders, pelvic factors and male factors. While all types of pregnancy complications such as abortions, ectopic gestation, multiple gestation and fetal anomalies were recorded, surprisingly there was not a single case of molar pregnancy in this series. We find no explanation forthcoming.

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