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Diagnostic approaches to hydatidiform mole

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DIAGNOSTIC APPROACHES TO HYDATIDIFORM MOLE

by

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For Presentation to the Thesis Committee
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TABLE OF CONTENTS

	Page
LIST OF TABLES	iii
LIST OF ILLUSTRATIONS	iv
INTRODUCTION	v
THE CLINICAL DIAGNOSIS OF HYDATIDIFORM MOLE	2
Epidemiology	2
Etiology	3
Pathogenesis	4
Pathology	4
Clinical Symptoms and Signs	6
THE USE OF HUMAN CHORIONIC GONADOTROPIN IN THE DIAGNOSIS OF HYDATIDIFORM MOLE	9
THE ULTRASOUND DIAGNOSIS OF HYDATIDIFORM MOLE	20
THE RADIOLOGIC DIAGNOSIS OF HYDATIDIFORM MOLE	26
Roentgenograms of the Pelvis for Fetal Age and Death	26
Pelvic Angiography	27
The Use of Radioactive Photoscanning in the Diagnosis of Hydatidiform Mole	31
Amniography	32
MINOR TESTS FOR THE DIAGNOSIS OF HYDATID MOLE	36
Fetal Heart Beat and Electrocardiogram	36
Passage of the Uterine Sound	36
Amnioscopy	37
CONCLUSION	38
LIST OF REFERENCES	41

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LIST OF TABLES

	Page
TABLE 1 Frequency with which Hydatidiform Mole has been Described in Relation to Pregnancy in Different Countries	2
TABLE 2 Incidence of Mole by Age Group.	3
TABLE 3 Bioassay Methods for Quantitative Determination of Human Chorionic Gonadotropin (HCG).	10
TABLE 4 Immunological Methods for the Quantitative Determination of Human Chorionic Gonadotropin	11
TABLE 5 The Variable Range of HCG Excretion in Molar Pregnancy. .	16
TABLE 6 HCG Titers for Various Factors in Cases of Hydatidiform Mole.	17
TABLE 7 Comparison of Angiographic Features of the Normal Placenta and of Hydatidiform Mole.	30
TABLE 8 Comparison of the Accuracy of the Transabdominal and Endocervical Hystogram in 44 Suspected Cases of Hydatidiform Mole	34

LIST OF ILLUSTRATIONS

	Page
FIGURE 1	
HCG Excretion in Normal Pregnancy	12
FIGURE 2	
Comparison of the Excretory Levels of HCG in Normal Pregnancy with Those of a Molar Pregnancy	14
FIGURE 3	
Somagrams of a Normal Pregnancy	21
FIGURE 4	
Somagrams of a Molar Pregnancy	22
FIGURE 5	
Somagrams of Lutein Cysts of Ovaries in Conjunction with Hydatid Mole	23
FIGURE 6	
Arteriogram of a Normal Intrauterine Pregnancy	28
FIGURE 7	
Hydatidiform Mole Showing Good Opacification of Intervillous Spaces	29
FIGURE 8	
Hydatidiform Mole Showing Poor Opacification of Intervillous Spaces	30
FIGURE 9	
Radioactive Photoscan of a Hydatidiform Mole	31
FIGURE 10	
Hystogram by Cervical and Abdominal Routes	33

INTRODUCTION

Hydatidiform mole is the most common trophoblastic disease of early pregnancy. It is best defined as a benign neoplasm of the chorion. Although molar pregnancy occurs once in 2,500 pregnancies, its varied clinical pattern, complications and malignant potential necessitates an early, rapid and accurate diagnosis.

In the first and early part of the second trimester, hydatidiform mole may present as a normal pregnancy, an incomplete or spontaneous abortion, toxemia of pregnancy, multiple fecundity or as hyperemesis gravidarum. The disease itself is complicated by severe hemorrhage, anemia, endometritis, pulmonary embolism and uterine perforation. Figures vary, but approximately two to eight percent of hydatid moles will be transformed into choriocarcinoma. One-third of the cases of metastatic choriocarcinoma and three-fourths of persistent nonmetastatic trophoblastic disease originate from molar pregnancy.

It is apparent that early and accurate diagnosis is essential for a good maternal outcome. Therefore, the purpose of this paper is to review and discuss the current methods and procedures which are available to the clinician for the diagnosis of hydatid mole. To accomplish this, the thesis will be divided into five sections. The first section will discuss the clinical

presentation of the mole; the second will discuss the use of human chorionic gonadotropin in the evaluation of a potential mole; the ultrasonic diagnosis of hydatid mole will be discussed in the third section; the fourth section will present the radiological procedures which are available to diagnose hydatid mole; and the fifth section will discuss several minor procedures which may be helpful in the diagnosis of molar pregnancy.

DIAGNOSTIC APPROACHES TO HYDATIDIFORM MOLE

THE CLINICAL DIAGNOSIS OF HYDATIDIFORM MOLE

Epidemiology

Each year there are approximately 3,000 cases of hydatidiform mole in the United States. The incidence is approximately one per every 2,500 cases of pregnancy. However, the incidence varies in different parts of the world as shown by Table 1.

TABLE 1

Frequency with which Hydatidiform Mole has been
Described in Relation to Pregnancy in
Different Countries

<u>Author</u>	<u>Country</u>	<u>Incidence</u>	<u>Percentage</u>
Novak	United States	1:2,500	0.04
Hertig and Sheldon	United States	1:2,062	0.05
de Snoo	Holland	1:1,200	0.08
Fernandes	Brazil	1:1,071	0.09
Caberea	Chile	1: 829	0.12
Aramburu	Guatemala	1: 670	0.14
King	China	1: 530	0.18
Brindean, et al	France	1: 500	0.20
Karzavina	Russia	1: 333	0.30
Hasegawa	Japan	1: 232	0.43
Acosta-Sison	Philippines	1: 173	0.59
Fernandez-Dublado	Mexico	1: 400	0.25
Marquez-Monter, et al	Mexico	1: 200	0.50

(From Marquez-Monter, 1965)

This wide variation in incidence, however, does not imply an ethnic or racial factor. Marquez-Monter reported in 1965, that

hydatidiform mole has a higher incidence among the lower socio-economic groups rather than the entire Mexican population. His work is supported by Fox and Tow (1967) who have also found a greater incidence among the lower socioeconomic groups of the Oriental race.

Hydatidiform mole has been reported in a 12-year-old girl and in a 52-year-old woman. The young adult woman, however, is most commonly affected. Also, the older women from ages 40 to 45 will show a higher incidence. These trends are reflected in Table 2.

TABLE 2

Incidence of Mole by Age Group

<u>Age group</u>	<u>Cases</u>		<u>Mole cases/No. of deliveries (approx.)</u>
	<u>No.</u>	<u>%</u>	
15-19	3	5.9	1/950
20-24	18	35.4	1/500
25-29	13	25.5	1/679
30-34	7	12.7	1/1000
35-39	3	5.9	1/1151
40-45	5	9.7	1/268
45 and over	2	3.9	1/90

(From Fox and Tow, 1967)

As reported by Marquez-Monter, multiparity does not influence the incidence of molar pregnancy. The reoccurrence of hydatidiform mole is less than two percent of all cases. Subsequent pregnancies and further child bearing are usually normal.

Etiology

Undernourishment, advanced maternal age, tuberculosis and viral infections have been suggested as etiological factors in

molar pregnancy. Currently, malnourishment is the only factor which is considered to have any etiological significance. Fox and Tow feel that the low protein diets which are prevalent among the lower socioeconomic groups of Oriental women leads to their higher incidence. This is further supported by the epidemiology studies in the lower socioeconomic groups of Mexican women who also have protein deficient diets.

Pathogenesis

There are essentially two theories as to the origin and development of hydatidiform mole. In 1940, Hertig and Edmonds suggested that the mole develops following an early death of the embryo. The trophoblast soon undergoes tissue atrophy while the chorionic villi undergoes hydropic degeneration and swelling. The remaining trophoblastic tissue then becomes hyperplastic and anaplastic.

Park (1959), on the other hand, supports the theory of an abnormal trophoblast from conception. This would lead to the hydropic swelling of the chorionic villi and to early death of the fetus. Since fetuses of varying gestational ages have been removed with molar tissue, the latter theory seems the most tenable.

Pathology

On gross examination, a hydatidiform mole specimen will either be completely or incompletely vesicular. In most instances, it is complete and the vilus structure replaces the fetus and placenta. In a smaller percentage of cases, a limited number of villi are affected and a normal fetus and placenta make up the majority of the specimen. Rarely will hydropic villi be found in

a mature placenta of a normal full term infant.

If the mole has advanced to a late stage, the vesicular tissue may be found in the endocervical canal and in some rare instances may even protrude from the external os. In other instances, the molar tissue will have undergone such degenerative changes that its gross pathology will present as an incomplete or missed abortion. The hydropic villi are of various sizes and range from 0.1 to 0.4 cm in diameter. Physically, the appearance of the mole mimics a bunch of vesicular "grapes" which are held together by "stems" of connective tissue. Usually, the vesicles are attached to the uterine wall but on rare occasions will lie deep within the myometrium.

Microscopically, the molar trophoblast is characterized by several pathological changes. The most important diagnostic change is seen in the marked proliferation of the Langhans and syncytial layers of the trophoblast. These line the hydropic villi and show variable degrees of hyperplasia and anaplasia. Other important differences are congestion, myxomatous degeneration of the struma, scanty Hofbauer cells and few blood vessels.

For all practical purposes, the degree of anaplasia is not diagnostic nor prognostic of the malignant potential of the mole. However, as a means of classifying the hydatidiform moles, three groups have been formulated:

- Group I Slight hyperplasia, "benign"
- Group II Frank hyperplasia but no anaplasia,
 "probably benign"
- Group III Marked hyperplasia and anaplasia,
 "more malignant"

(From Novak, 1967)

It is also important to note that the villi which are formed near the uterine wall tend to be more "malignant" than those formed in the central portion of the cavity.

Clinical Symptoms and Signs

The early development of a mole is clinically indistinguishable from a normal pregnancy. Thus, one cannot make a clinical diagnosis of hydatidiform mole in the early weeks of pregnancy. As the pregnancy progresses, however, certain clinical symptoms and signs will become evident.

In most cases, the first and earliest sign of molar pregnancy is uterine bleeding. Usually the first episode is slight, similar in appearance to prune juice and may occur as early as the sixth week of pregnancy. However, in some cases, it may not occur until the eighteenth week. The amount of blood loss will vary from mild spotting with the onset of bleeding to profuse hemorrhage when the mole is expelled. An anemia may develop from the chronic blood loss or shock may be associated with the profuse hemorrhage. Occasionally, the bleeding may be associated with expulsion of necrotic tissue and vessicles. If the characteristic grape-like vessicles are found, they would unquestionably establish the diagnosis of a mole and rule out that of spontaneous or threatened abortion.

If the mole is not aborted, the uterus will usually grow out of proportion to its normal gestational size. The size at two to three months will be that of a normal pregnancy with a gestational age of five to six months. Marquez-Monter (1965) reports this to be true in approximately fifty to sixty percent

of the patients with a mole. Twenty-five percent will have a normal size uterus for gestational age and fifteen percent will have a smaller one.

Another symptom of hydatidiform mole is toxemia which becomes prevalent before the twenty-fourth week of pregnancy. Preeclampsia is more prevalent in a mole which grows rapidly. Marquez-Monter (1966) reports several cases of eclampsia in patients with unusually large amounts of molar tissue. Hyperemesis associated with the toxemia and mole has been reported to be more severe than the normal "morning sickness." Protracted vomiting occurs in about fifteen percent of all molar patients. Moderate hypertension is present in fifteen percent and albuminuria is present in seven percent (Marquez-Monter, 1966).

A persistent, dull, aching pain over the hypogastrium, not unlike that of a full bladder, is often associated with a hydatidiform mole. The pain results from the rapid growth of the uterus. Its quality should be differentiated from the cramping pains associated with abortions and the sharp shooting pains which occur with cystitis. Endometritis will often accompany a mole. This is thought to be due to the long period of threatened abortion, the patulous cervix, bleeding, and the large mass of poorly vascularized tissue in the uterus.

On physical examination, palpation of the uterus for ballottable or irregular masses that might be fetal parts is negative in sixty-two percent of the patients. As mentioned earlier, the presence of a fetus does not rule out hydatidiform mole. Bilateral luteal cysts are palpable in the adnexyl areas of ten percent of patients with hydatidiform mole. Unilateral

cysts are present in approximately forty percent of patients. These cysts may reach 10 cm in size and usually have high content of HCG. The cysts usually disappear after the expulsion of the mole.

It is evident from the foregoing discussion that there is paucity of accurate clinical signs which would lead the clinician to a definite diagnosis. Uterine bleeding, an enlarged uterus for gestational age, early toxemia, protracted vomiting, endometritis, and absence of fetal parts on palpation are all presumptive symptoms and signs of molar pregnancy. They may be apparent as early as the sixth week but in most instances, are not present until the second trimester. The only definite sign, the protrusion or passage of molar vesicles, is a rare occurrence and is not usually present until the second trimester. It is concluded that the clinical symptoms and signs should encourage the clinician to further investigate the possibility of a molar pregnancy.

THE USE OF HUMAN CHORIONIC GONADOTROPIN IN THE
DIAGNOSIS OF HYDATIDIFORM MOLE

A presumptive diagnosis of hydatidiform mole has often been made by demonstrating an elevated level of human chorionic gonadotropin in serum or urine. This level would be out of proportion to what would normally be expected for that period of gestation. The HCG produced by a mole is chemically and immunologically indistinguishable from the protein that is produced by a normal trophoblast. The site of production is the same as in normal pregnancy. Wynn and Davis (Eastman, 1966) have demonstrated special organelles in the syncytial layer of the trophoblast for the production of HCG. Therefore, the methods which are used to quantitate the amount of HCG in normal pregnancy can also be applied to those of a molar pregnancy.

Assays for HCG are useful in diagnosing hydatid mole if the following criteria are met: a reliable, accurate and reproducible quantitative method should be used; a positive correlation should exist between the clinical symptoms and titer; and the elevated titer must correlate with the normal HCG excretory pattern for a normal pregnancy. For methods of comparison, all assays must be standardized against the international unit of HCG: one international unit of chorionic gonadotropin is the amount of hormone equivalent in activity to that of

one tenth of a milligram (0.1 mgm) of the international standard powder of chorionic gonadotropin deposited in the National Institute of Health, London, England (Eastman, 1966).

HCG has been quantitatively determined by either biological or immunological methods. Table 3 summarizes some of the biological methods that have been used in the past and some which are still being used today because of their sensitivity.

TABLE 3

Bioassay Methods for Quantitative Determination
of Human Chorionic Gonadotropin (HCG)

<u>Name</u>	<u>Animal</u>	<u>Technique</u>
Uterine weight (Klinefelter, 1940)	Mice	Serial dilution
Ovarian or uterine weight (Delfs, 1940)	Mice or rats	Dilution technique against standard curve
Ventral prostate (Lorraine, 1950)	Hypox. rats	4 point assay against International Standard
Toad (Hon and Morris, 1956)	-----	Serial dilution or concentration- quantal assay

(From Taymor, 1967)

Of the above tests, the ventral prostate method in hypophysectomized rats is probably the best because of its greater accuracy and specificity. By using hypophysectomized rats, the assay eliminates the animal's own source of gonadotropin. The uterine weight and ovarian weight assays are performed on immature animals where the animal's own pituitary production may effect the accuracy of the assay. The toad test of Hon and Morris utilizes

a dilution technique for high levels and a concentration one for lower levels. The test is sensitive for levels greater than 750 IU and thus is used only to follow patients with high levels of HCG.

There are several methods for immunoassay and these are presented in the following table.

TABLE 4

Immunological Methods for the Quantitative Determination
of Human Chorionic Gonadotropin

<u>Test</u>	<u>Medium</u>	<u>Sensitivity IU/ML</u>	<u>Specificity</u>
Precipitation	Serum or urine	16	Fair
Complement fixation	Serum or urine	.1-0.5	Better
Agglutination inhibition	Serum or urine	.1-20	Good
Radioimmunoassay	Serum or urine	.003	Excellent

It is somewhat difficult to objectively compare the above tests since each has its limitations and advantages. Of course, the best would be the radioimmunoassay with its high sensitivity and high specificity. Because of its specificity, radioimmunoassay may be carried out in different tissue fluids without the interference of contaminating agglutinins which plague the other methods. Radioimmunoassay is limited by its complexity and expense.

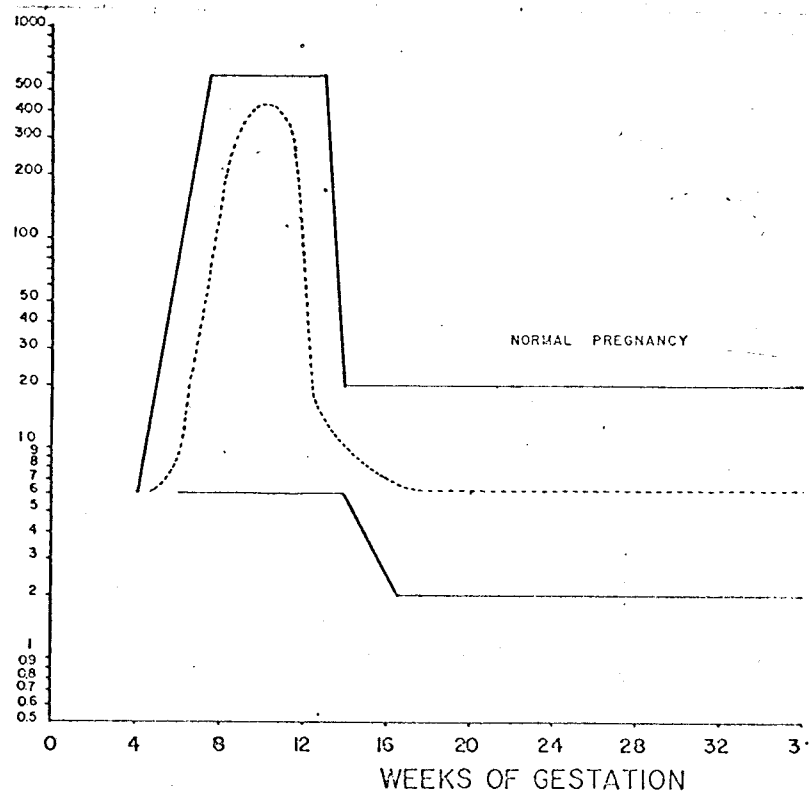
Because of its simplicity, the agglutination inhibition test is used in most laboratories for the quantitative determination of HCG. Its accuracy, however, is limited by the presence of similar antigens which contaminate the sample and gives a false

high reading. If accuracy is to be obtained, these must be removed from the sample, a task which often is not achieved.

In Figure 1, the HCG excretion pattern for a normal pregnancy is shown. The dotted line is a typical curve while the solid lines are the maximum and minimum limits.

FIGURE 1

HCG Excretion in Normal Pregnancy



(From Taymor, 1967)

During a normal pregnancy, HCG appears in the urine as early as the twenty-sixth day of pregnancy and will increase until it reaches a peak between the eighth and sixteenth week. From here it falls and reaches a low level between the eighteenth and twentieth week of gestation. It then remains essentially unchanged until the termination of pregnancy. Serum levels precede those of urine and are detectable as early as the first missed period. The

serum levels will parallel those of urine and will show similar excretory patterns. It is important to note that the total excretion of HCG in a twenty-four hour period can vary from 7,000 to 500,000 IU/L of urine. Also, levels as high as 600,000 to 700,000 IU/L have been reported in a few cases of normal pregnancy.

In normal pregnancy, the biological and immunological activity has been reported by Wide and Hobson (1966) to be somewhat less than unity when the two methods of assay are compared by the B/I ratio. This ratio is not constant throughout pregnancy and is the highest during the first trimester and lowest in the last two. The B/I ratio of serum is significantly higher than urine. The significance of this is not known at the present time but it is clear that the two methods must measure different portions of HCG proteins.

Since two animals of the same species will respond differently to the same stimulus, Fox and Tow (1967) feel that all biological tests have an element of uncertainty in them. Fox and Tow also favor the immunological methods of assay because they are less time consuming in obtaining a result as they do not require maintenance of large animal colonies. For these reasons, the majority of current assays utilize the immunological method of assay.

As early as 1929, Professor Bernard Zondek reported that patients with hydatidiform mole excreted two to three times more chorionic gonadotropin as would be expected if they were having a normal pregnancy. Figure 2, on the following page, was taken from a study by Delfs and compares the normal HCG excretory pattern with that of a molar pregnancy. *

FIGURE 2

Comparison of the Excretory Levels of HCG in Normal Pregnancy with those of a Molar Pregnancy

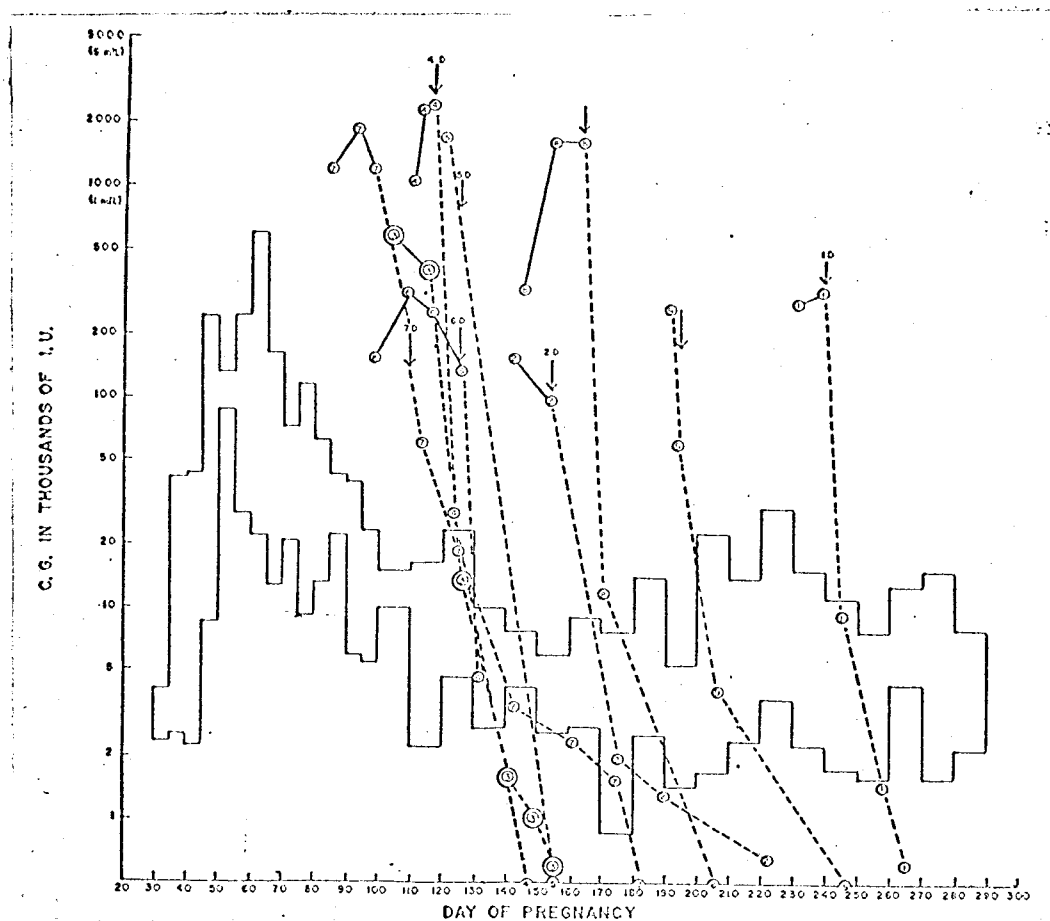


Fig. 2. Diagnosis of mole. The block background shows the range of gonadotrophin observed in normal pregnancies. Chorionic gonadotrophin in thousands of International Units per liter of serum is plotted on a semilog scale for the day of pregnancy, counting from Day 1 of the last menstrual period. The arrow in each case indicates delivery of the mole with subsequent rapid decrease in gonadotrophin.

(From Delfs, 1957)

The block background represents the normal range for serum gonadotropin in repeated assays on twenty-four pregnant women. Nine suspected cases of hydatid mole are represented by the curved lines. These show an elevated level of HCG - 21,000 to 2,050,000 IU - which is far above the expected range of a normal pregnancy for that gestational age.

As mentioned earlier, the biological and immunological

activities reported as the B/I ratio are less than unity in early pregnancy. In urine from women with hydatid mole, Wide reports the B/I ratio is higher than urine from women with normal pregnancies. This also could be used to distinguish between normal and molar pregnancies. However, there is still much work to be done to determine the significance of these ratios.

HCG titers will often help to differentiate molar pregnancies from multiple ones and from threatened abortions. Delfs (1957) has assayed four cases of twins and reported the excretion curves to follow those of a normal pregnancy except for a slight shift to the right on the descending side. When repeated assays are made during the subsequent weeks, twin pregnancies show titers in the 5000 IU range. Hobson (1961), however, reported one case of a woman with a normal twin pregnancy that excreted between 1,200,000 and 1,500,000 IU/L at the fourteenth week of pregnancy.

With threatened abortions, HCG levels will be within normal limits as reported by Delfs (1957). Hyperemesis which often accompanies hydatid mole can also be differentiated from hyperemesis gravidarum as the latter has no elevated level of HCG (Lorraine, 1966).

It is evident from Figure 2, that a reliable titer cannot be obtained until after the one hundredth day of pregnancy. If a titer was made during the first trimester, its significance would be invalidated by corresponding values of a normal pregnancy. Since it is necessary to have a pattern of excretion for comparison with the normal pregnancy, several assays must be taken over a period of three to four weeks. This would tentatively put the

date for the most accurate diagnosis at between the fourteenth to twentieth week of pregnancy.

If the above pattern is followed, a reasonably accurate diagnosis of hydatid mole can be made. After evaluating 100 patients with clinically suspected hydatid mole, Delfs (1958) reports the following results: There were 18 positive cases and 82 negative ones. The latter were either normal pregnancies or abortions. There were no false positive or false negatives.

Even though Delfs was able to make an accurate diagnosis of hydatid mole, most authors report that only a presumptive diagnosis may be made with elevated levels of HCG (Taymor, 1967). There are several reasons for this and they are discussed below.

One of the most pressing problems is to determine the level of HCG which would be considered to be pathologically high. Many authors have reported a variable range of HCG production in their patients with hydatid mole. Some of these are shown in Table 5.

TABLE 5

The Variable Range of HCG Excretion
in Molar Pregnancy

<u>Investigator</u>	<u>Year</u>	<u>Specimen</u>	<u>Method of Assay</u>	<u>Range</u>	<u>Mean</u>
Hamburger	1944	Urine	Immature rat uterus	6,000 - 20,000,000	300,000
Delfs	1957	Serum	Immature rat uterus	19,600 - 2,130,000	186,500
Hobson	1958	Urine	Female xenopus laevis	3,000 - 300,000	200,000
Fox and Tow	1967	Urine	Hemagglutination inhibition	5,000 - 980,000	139,000

As indicated in the preceding table, there is a significant discrepancy between the mean values of Hobson and Delfs with those of Fox and Tow. Fox and Tow explain this by noting that a normal pregnant Asian woman excretes a titer which is much lower than the normal range for Caucasian women. With Asian women, the normal range is 20,000 to 40,000. Fox and Tow also mention that the majority of the patients in their study were threatening to abort or aborting at the time of the initial titer. This would also help to explain the lower titer.

When the normal range of pregnancy is compared with Table 5, a diagnosis would certainly be impractical before the one hundredth day of pregnancy. Of course, this problem is overcome if the titers are put off until after the normal HCG titers would be expected to fall. But what if the patient has irregular menstrual cycles or has simply miscalculated her dates? Certainly different investigators, different methods of testing and laboratory errors would also contribute to these variations. However, if they are standardized against the international standard, they should be error free.

Several factors which influence the level of HCG excretion have been investigated by Fox and Tow (1967). These include uterine size, type of mole and method of delivery. Table 6 on the following page compares these various factors with the HCG excretion.

Fox and Tow (1967) found a positive correlation between the pre-evacuation size of the uterus and the titer of HCG. They also report a strong positive association between the amount of HCG excreted and the amount of molar tissue and whether the mole

is completely intact or partially aborted. On the other hand, as the mole progresses in age, Hobson (1958) reports a decline in the excretion of HCG. The amount of HCG in moles is highest between the third and fourth months of gestation and from this point declines.

TABLE 6

HCG Titers for Various Factors in
Cases of Hydatidiform Mole

<u>Factor</u>	<u>Cases</u> <u>No. %</u>	<u>Average</u> <u>pre-evacuation</u> <u>titer (IU/L)</u>
Uterine size vs. period since LMP		
Larger	26 51	173,000
Equal	12 23	109,000
Smaller	13 26	42,000
Type of mole		
Actively growing	44 86	139,000
Minimal tissue	5 10	22,000
Degenerating	2 4	2,500
Aborted vs. intact moles		
Intact (prior to surgery)	14 25	225,000
Spontaneous abortion	29 67	89,000

(Fox and Tow, 1967)

Fox and Tow report two cases of degenerating hydatidiform mole with HCG titers of 5,000 and 0 IU/L. Delfs also reports two cases of degenerating moles. These had initial titers of 300,000 IU/L and 200,000 IU/L which declined to approximately 20,000 IU/L before evacuation. In both studies, the delivered moles were largely necrotic tissue surrounded by a fibrous capsule. Delfs feels these cases were probably strongly positive during their early development. Degenerating moles are uncommon and they do not seriously invalidate the utility of HCG as a diagnostic tool

as dying moles are not as potentially hazardous as growing ones.

It is quite evident from the above material that many factors contribute to the level of HCG that is excreted at any particular time. Most European and American investigators have set the 600,000 IU/L as the pathonemonic level for differentiating between normal and abnormal pregnancy as very few normal pregnancies exceed this level (Taymor, 1967). Both studies by Delfs and Hobson confirm this level as being diagnostic. This diagnostic criteria cannot be applied to Asian women since their normal titers are much lower than Caucasians. In their study, Fox and Tow found that a woman with a titer greater than 220,000 IU had either a mole or a choriocarcinoma. The level, however, does not really help to separate abnormal from normal pregnancies. When applying this criteria to their study, Fox and Tow concludes that a definite pathonemonic level is impractical if the clinician is trying to accurately diagnose all cases of hydatid mole.

It may be concluded from the foregoing that HCG titers are helpful in establishing a presumptive diagnosis of hydatid mole. If repeated titers remain elevated during the second trimester, then a presumptive diagnosis can be made. If the level of HCG should exceed 600,000 units in Caucasian women, then a definite diagnosis can usually be made. The same applies for a level of above 220,000 units for Asian women. However, the majority of cases must be followed with repeated assays which are compared to the normal excretory pattern as well as the respective stage of gestation and population.

THE ULTRASOUND DIAGNOSIS OF HYDATIDIFORM MOLE

In the last two decades, ultrasound has been used as a diagnostic tool in many phases of medical investigations. In 1958, Donald introduced it into obstetrics and gynecology. Since that time, ultrasound has been used to determine fetal age, growth and development, position, number and abnormalities. It has also been used to localize placental implantation and to diagnose uterine, ovarian and other pelvic tumors. Also, a characteristic sonogram is produced by the vesicular tissue of a hydatidiform mole.

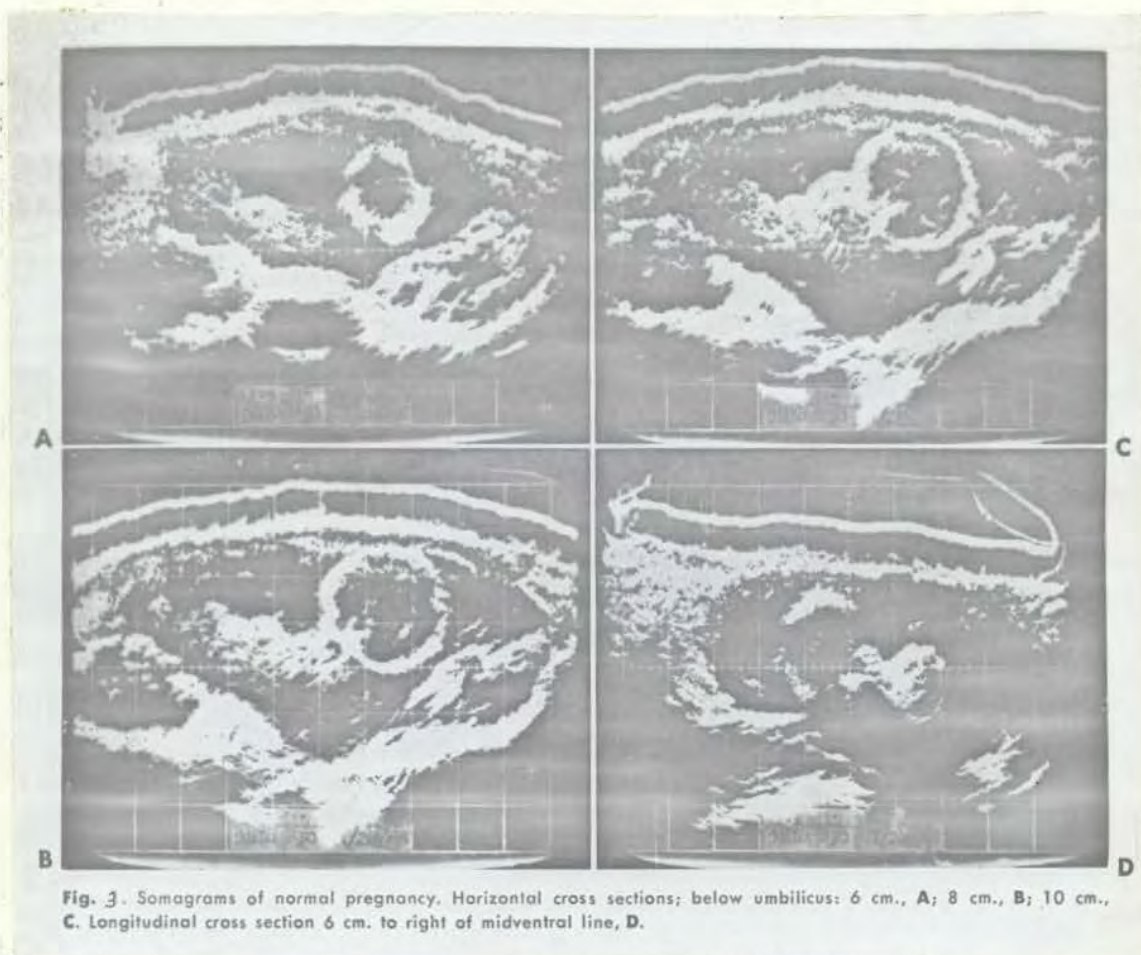
The principle of ultrasound is based on a pulse ranging technique which gives a two dimensional pattern on a photosensitive screen. A beam of sound is transmitted in a known direction and an echo is received from a tissue interface at a time proportional to the distance from the echo's source. The impulses of sound are then picked up by a receiver and converted by a transducer into electrical energy and are then displayed on an oscilloscope.

Using this technique, a two dimensional scan may be taken of any gravid uterus. For diagnostic purposes, scans are taken at two cm intervals in both coronal and sagittal planes. Coronal sections are begun at the fundus and end at the symphysis pubis. Sagittal ones are usually started on the lateral side of the abdominal wall, proceed across the midline and then end on the opposite side.

A somagram of normal pregnancy of approximately eight weeks gestation is shown in Figure 3.

FIGURE 3

Somagrams of Normal Pregnancy



(From Gottesfeld, 1967)

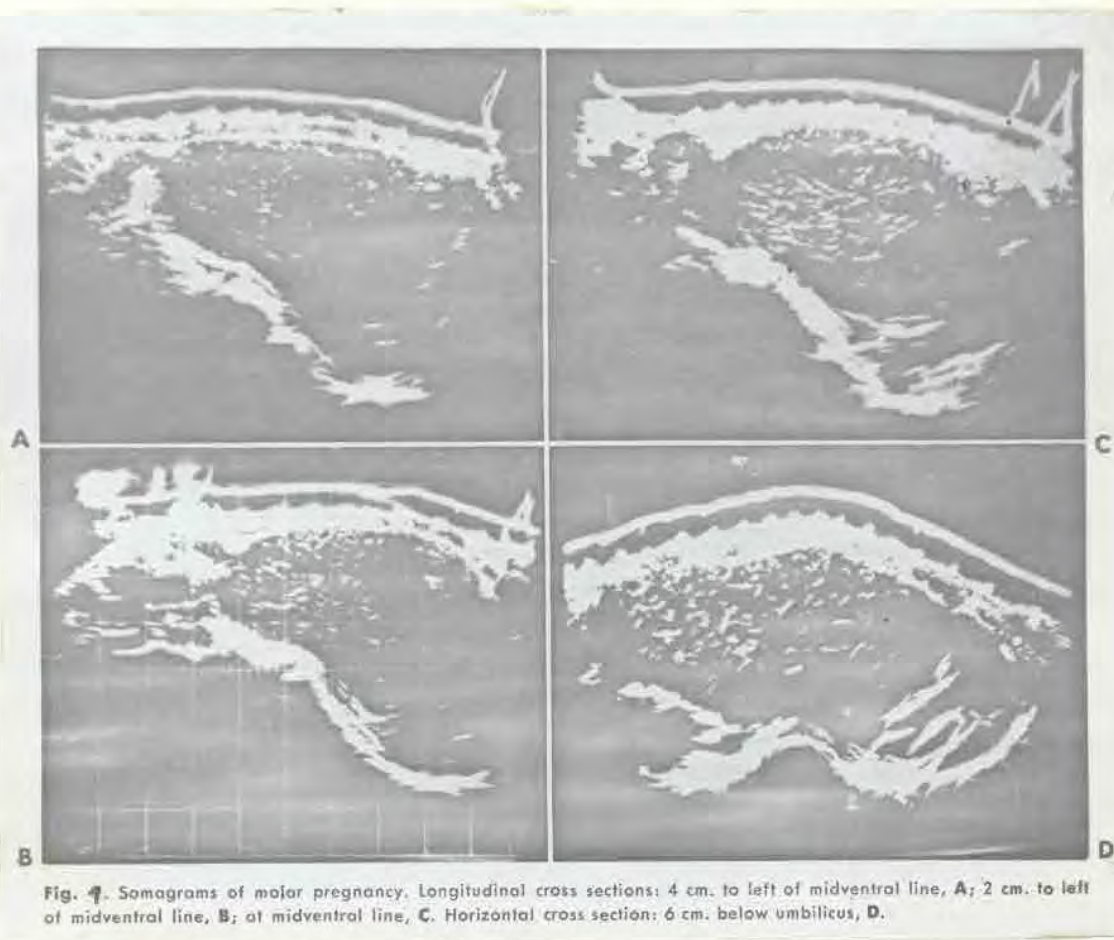
In Figure 3-A, the uppermost portion of the abdominal wall is represented by a thick white line. Below and parallel to this is a curved white line which is the ventral wall of the uterus. The small spiculed area beneath the wall is the placenta. Enclosed within the large dark cavity is a circular structure which is the fetal thorax. Then, in order of succession is the dorsal uterine wall, hollow vertebral canal with the psoas musculature bilaterally.

In Figure 3-B, the fetal thorax and the placenta show an increase in size. The thorax is still larger in Figure 3-C. In the longitudinal cross section, the fetal thorax is again represented by the white circle and the head is visualized in the fundal region of the uterus. (Left side of picture.)

In a molar pregnancy, a specific echo pattern is formed by the vesicular tissue. In the following group of somagrams, Figure 4, the mole is represented by a series of white dashes and dots or what is described as a "radiating spicule-like pattern." (Gottesfeld, 1967.)

FIGURE 4

Somagrams of a Molar Pregnancy



(From Gottesfeld, 1967)

The somagrams of Figure 4 are read in the same manner as Figure 3 but the fetus has been replaced by the spicule pattern.

The lutein cysts which are common in a molar pregnancy may be identified by their typical echo pattern. These are shown in Figure 5.

FIGURE 5

Somagrams of Lutein Cysts of Ovaries
in Conjunction with Hydatid Mole

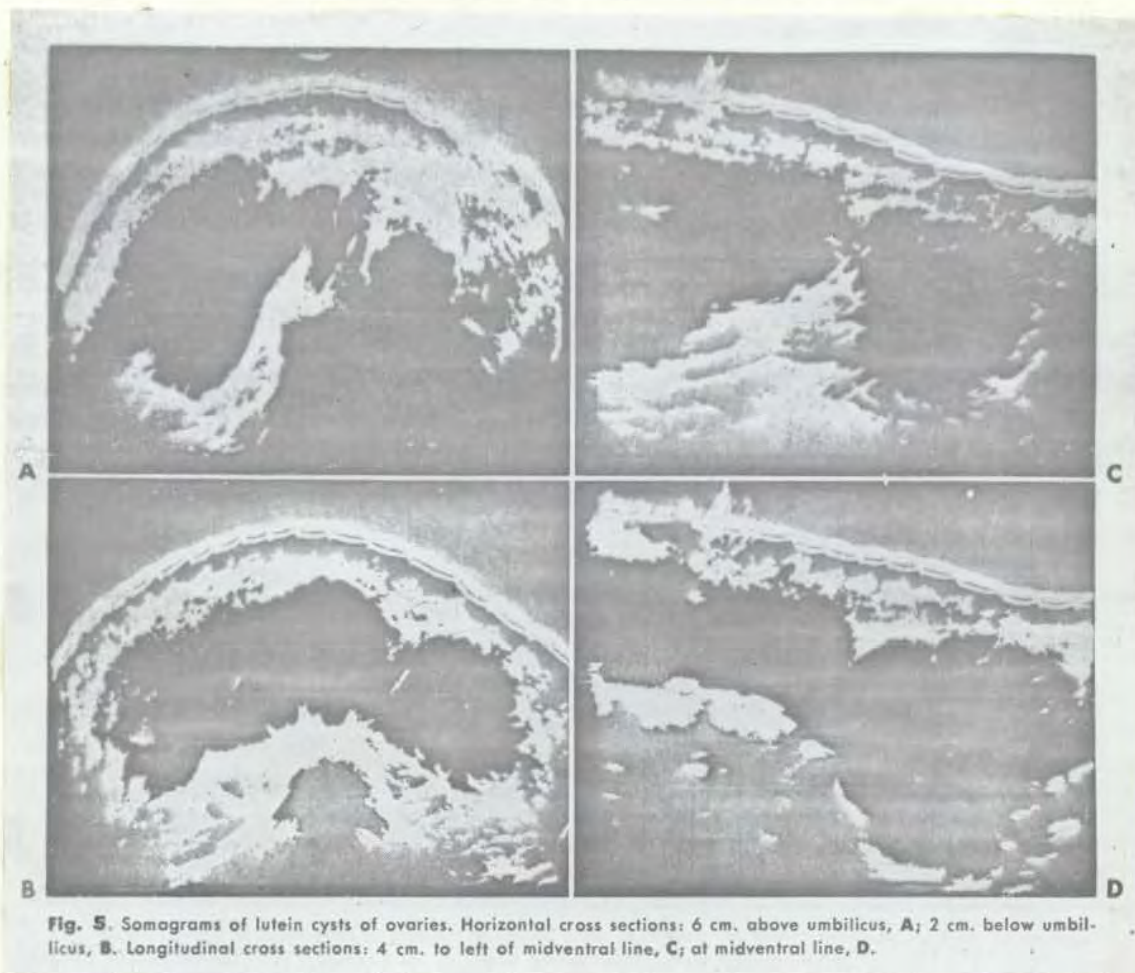


Fig. 5. Somagrams of lutein cysts of ovaries. Horizontal cross sections: 6 cm. above umbilicus, A; 2 cm. below umbilicus, B. Longitudinal cross sections: 4 cm. to left of midventral line, C; at midventral line, D.

(From Gottesfeld, 1967)

In Figure 5-A, the top white line is the abdominal wall and the large dark area on the left side of the picture is a large cyst. In Figure 5-B, a cystic structure is seen on both the left and right. In Figure 5-C, a longitudinal cross section 4 cm to

the left of the mid ventral line shows an elongated cystic structure at the left and a second smaller one on the right. The cyst on the left of Figure 5-D, has decreased while the one in the pelvis has increased. Thus, there is a large right ovarian cyst in the pelvis and another large left ovarian cyst in the abdominal cavity.

Fetal parts can be recognized as early as eight weeks of gestation when the type B scanner is used. (Thompson, 1968.) After the second month of gestation, molar tissue can be differentiated from a fetus by varying the sensitivity of the transducer. Because of their respective densities, molar vesicular tissue will be lost with a minimal decrease in sensitivity while the image of the fetal parts will be retained on the oscilloscope screen.

Differentiating the mole from the placenta is not as easy. In early pregnancy, the placenta's appearance mimics that of a mole. When sensitivity is varied, the placental tissue will disappear as does the vesicular mole. To differentiate the normal pregnancy and placenta from a mole, the entire uterus must be scanned to find fetal parts. However, this will not be infallible in every case as a mole may present with a fetus intact.

Ultrasonic examination may also be used to differentiate hydatid mole from twin or multiple pregnancies. Thompson (1968) reports that it is possible to diagnose multiple pregnancy as early as the tenth week. However, it is often necessary to do subsequent examinations to confirm the diagnosis. In most cases, hydatidiform mole may be differentiated from a multiple pregnancy by the sixteenth week.

Ultrasound examination is safe, simple, involves no

patient discomfort and may be repeated as often as required. Suden (1963) has observed no harmful effects or patient discomfort from ultrasonic scan. When using a type B scanner, the entire procedure takes fifteen to twenty minutes.

Ultrasonic evaluation of a gravid uterus gives both an early and accurate diagnosis of a mole. In a study of twelve cases of clinically suspected moles, Suden (1963) made a definite diagnosis of hydatidiform mole as early as twelve weeks from the last menstrual period. This was reduplicated by Gottesfeld (1967) who also made the diagnosis at ten weeks. In the Suden study, there were no false positive or false negative results; three of the twelve cases were diagnosed as having moles and proved later by curettement. In Gottesfeld's study, 61 cases were referred to him for evaluation. On the initial scan, seventeen patients were accurately diagnosed as having the disease. He had one false positive and only one false negative. The latter case was originally felt to have a missed abortion but delivered a molar tumor. When the original scan was reviewed and with his new knowledge of fetal death on sonograms, Gottesfeld was able to differentiate the missed abortion from a molar pregnancy. He concludes, "the diagnosis should be 100 percent accurate."

Thus, a well qualified examiner could be expected to differentiate molar tissue from pelvic tumors, multiple pregnancies, missed abortions or a normal placenta.

THE RADIOLOGIC DIAGNOSIS OF HYDATIDIFORM MOLE

The radiologist has many techniques at his disposal to aid the obstetrician as he attempts to establish the diagnosis of hydatid mole. These include pelvic films for fetal age and death, angiography, amniography and radio active scanning of the gravid uterus. Inherent in all of these procedures is the potential hazard of radiation to a developing fetus and mother. The teratogenic and lethal factors of radiation cannot be over emphasized and must not be forgotten when the clinician is zealously seeking a correct diagnosis.

Roentgenograms of the Pelvis for Fetal Age and Death

In most cases of hydatidiform mole, the embryo never develops and roentgenograms of the pelvis would be an easy method to rule out a normal pregnancy when the fetal skeleton could not be demonstrated. This method of diagnosis, however, is not really applicable to the evaluation of a mole as the fetal skeleton is seldom demonstrated radiographically until the fourth month of gestation. It has been demonstrated as early as the thirteenth week by Edwards and Blain (Eastman, 1966). In most cases, as shown by Bartholomew, the fetal skeleton is present in about one-third of their patients at twenty weeks and in one-half at twenty-four weeks (Eastman, 1966). Therefore, it must be concluded that the fetal skeleton is not a very helpful aid in the diagnosis

of a molar pregnancy.

In those cases in which the fetus coexists with a molar pregnancy, the signs of fetal death can be very helpful when the clinician wants to evacuate the uterus. These include Spalding's sign — overlapping of the fetal skull bones; exaggerated curvature of the spine, and the presence of gas within the fetus. (Eastman, 1966)

Pelvic Angiography

Pelvic arteriography was first used by Borell in 1955 for the diagnosis of hydatidiform mole. Since then, its diagnostic value has been widely recognized. This method, when used with the elevated HCG and hystography, is probably the most widely used method to evaluate a suspected mole pregnancy.

The current method of angiography is essentially unchanged from that described by Borell (1955). A polyethylene catheter is passed percutaneously to the femoral artery and then introduced into the abdominal aorta. Thirty milliliters of contrast media, urograffin 76%, are injected within two seconds and both femoral arteries are externally compressed. Serial anteroposterior films of the abdomen are obtained at one second intervals for seven seconds.

For descriptive purposes, angiographic findings may be divided into three phases: an arterial phase, a sinus or intervillous phase and a venous phase. In a normal pregnancy, the main uterine arteries are enlarged. The distance between them and their ascending branches shows the size and position of the uterus. In the first months of pregnancy, the spiral myometrial arteries are enlarged and tortuous. When the intervillous spaces are opacified, they appear as multiple, regular, nonconfluent, rounded groups or as

"cotton fluffs." The venous filling phase does not usually occur in normal pregnancy. A normal intrauterine pregnancy of twenty weeks is shown in Figure 6.

FIGURE 6

Arteriogram of a Normal Intrauterine Pregnancy

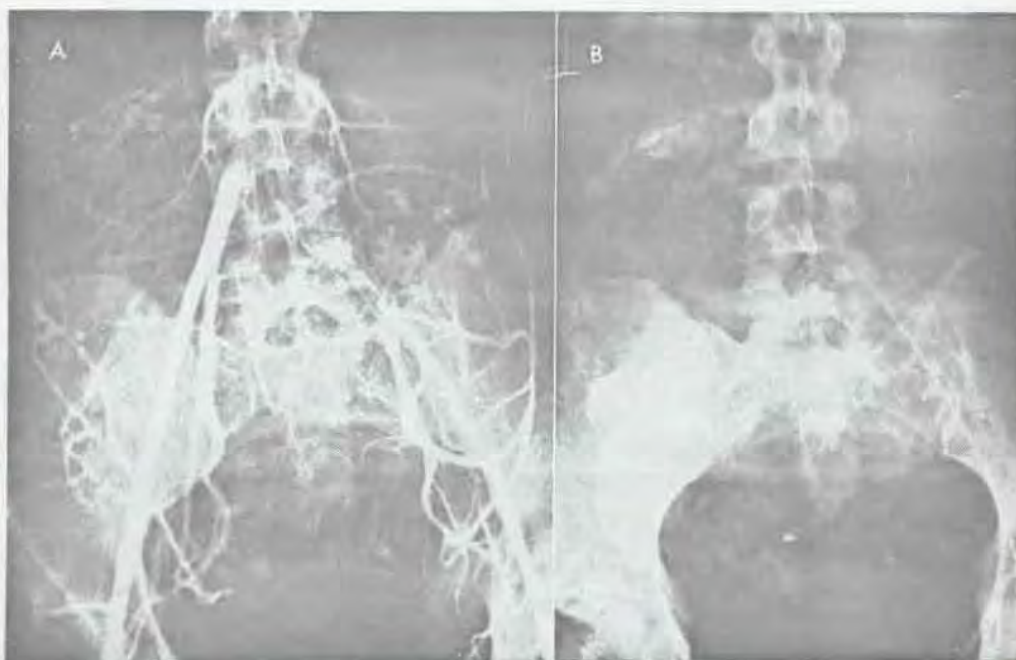


Fig. 5. Normal intrauterine pregnancy at fifth month. A. Arterial phase: size and position of uterus well outlined by stretched branches of uterine arteries. B. Villous phase: uniform opacification of large intervillous spaces with indistinct edges.

(From Hirsch and Ben-Aderet, 1967)

In contrast to a normal pregnancy, the arterial phase of a molar one shows only moderate enlargement of the uterine arteries. A characteristic radiologic sign of a molar pregnancy is seen in the straight fundal arteries.

During the sinus or intervillous phase, there are two angiographic patterns which characterize the hydatid mole. Both Hirsch (1967) and Borell (1955, 1961) report a pattern that shows multiple small intervillous spaces with polypoid filling deficits and curvilinear borders. Figure 7 shows this characteristic pattern.

in a patient with a mole at the ninth week of pregnancy.

FIGURE 7

Hydatidiform Mole Showing Good Opacification
of Intervillous Spaces



(From Hirsch and Ben-Aderet, 1967)

Figure 8 on the following page, shows the other characteristic pattern during the intervillous phase. In these two cases (see Figure 8, page 30), the intervillous spaces are small, few in number, widely scattered and do not show the filling deficits which are present in Figure 7. Hirsch, (1967) reports that the second pattern is a better indication of benignity.

The normal placenta and hydatidiform mole angiographic features are summarized in Table 7. (See Table 7 on page 30.)

Pelvic arteriography is a rapid and accurate procedure for the diagnosis of hydatidiform mole. Most authors feel that arteriography is a safe procedure but offer little information on the effects of radiation on a normal fetus. Arteriography is one of the earliest methods available to diagnose a mole pregnancy.

FIGURE 8

Hydatidiform Moles Showing Poor Opacification
of Intervillous Spaces

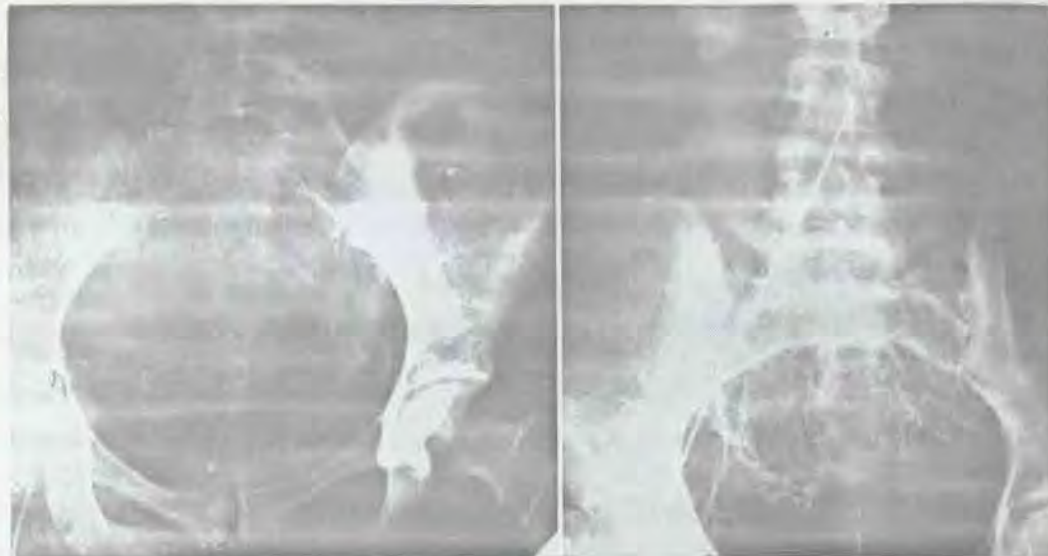


Fig. 5 (left). Case 4. Hydatidiform mole at tenth week of pregnancy. In the villous phase only a few tiny and scattered intervillous spaces are demonstrated. Fig. 6 (right). Case 5. Hydatidiform mole at nine weeks of pregnancy. Only few and tiny intervillous spaces are seen. In center of pelvis opacified vessels are in sigmoid wall.

(From Hirsch and Ben-Aderet, 1967)

TABLE 7

Comparison of Angiographic Features of the Normal
Placenta and of Hydatidiform Mole

<u>Phase</u>	<u>Normal Placenta</u>	<u>Hydatidiform Mole</u>
Arterial Phase	<ol style="list-style-type: none"> 1. Hypervascularity 2. Numerous coiled myometrial branches 	<ol style="list-style-type: none"> 1. Relative avascularity 2. Scant myometrial branches with less fundal branches
Sinus Phase	<ol style="list-style-type: none"> 1. Uniform opacification of placental intervillous spaces giving "cotton fluff" effect 2. Retains contrast 	<ol style="list-style-type: none"> 1. Fewer intervillous spaces, small and less distribution 2. Absence of "cotton fluff" effect 3. Filling defect due to cysts.
Venous Phase	<ol style="list-style-type: none"> 1. No venous filling 	<ol style="list-style-type: none"> 1. Occasional venous pooling

(From Sanders, 1965)

Since the molar tissue is present from early gestation, arteriography can be used as early as the mole is expected.

The Use of Radioactive Photoscanning in the Diagnosis of Hydatidiform Mole

In the last several years, radioiodine (I^{131}) has been used to localize the placenta. Masterson and White in 1966 reported a case in which a photscan was performed on a patient with the clinical signs of a molar pregnancy. These included rapid uterine enlargement, greater than four million units of HCG/L of urine and hyperemesis. A photscan of her uterus is shown in Figure 9.

FIGURE 9

Radioactive Photoscan of a Hydatid Mole



Fig. 9. Photscan of uterus and blood pooling within the intervillous space (AP projection). Black markings indicate position of xiphoid and pubic symphysis. Increase in vascular activity is seen in the superior left lateral portion of the uterus extending to the lower aspect of the uterus, the pattern of which simulates a fully developed placenta in respect to observed size of the uterus.

(From Masterson and White, 1966)

The preceding scan was interpreted as being a normal placenta and on the basis of this, evacuation was delayed. In subsequent days, however, the patient developed an interuterine infection and hypertension. A hysterectomy was performed and one liter of molar tissue was removed. Masterson concludes, "avoid delay in evacuation of the uterus on finding what appears to be normal appearing placental circulation on an isotope photoscan." It may be concluded from the foregoing that radioactive photo-scanning is currently little help in evaluating a molar pregnancy.

Amniography

In 1957, Apelo and Brazan reported the intrauterine injection of a radiopaque dye which lead to the diagnosis of hydatidiform mole. Amniography either alone or combined with arteriography seemed to be one of the best methods for diagnosis of a molar pregnancy.

Presently, there are two routes by which the dye may be injected into the uterus; transabdominally or endocervically. The transabdominal route may be used only if the uterine size is equal to or greater than eighteen weeks. Under local anesthesia, an eighteen gauge needle is passed into the uterine cavity one inch below and to the right of the umbilicus. Aspiration is carried out and if neither blood nor amniotic fluid is returned, twenty cc's of hypaque is injected. This is followed by a one and five minute film.

When the endocervical route is used, the vagina and cervix are prepared and a size eighteen French catheter is inserted as far as the internal os. The cervix is then closed with a tenaculum and the hypaque is injected. Again, a one and five minute film is obtained.

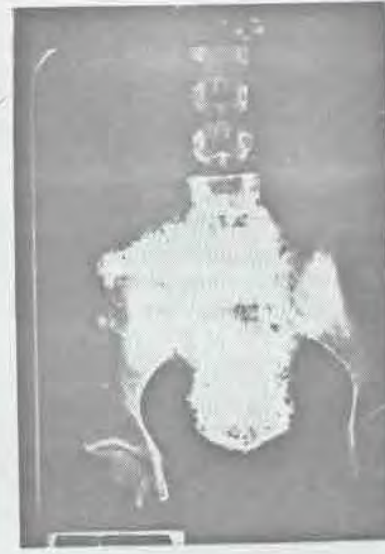
A characteristic hystogram of a molar pregnancy is depicted by a moth eaten or honey combed pattern that fills the uterine cavity. A hystogram of a mole by the endocervical and transabdominal route is shown in Figure 10.

FIGURE 10

Hystogram of Cervical and Abdominal Routes



HYSTEROGRAM THRU THE CERVICAL ROUTE



HYSTEROGRAM THRU THE ABDOMINAL ROUTE

(From Apelo and Cunanan, 1966)

Apelo and Cunanan in 1966 reported a study in which they compared the accuracy of the two procedures. The results of this study are presented in Table 8.

TABLE 8

Comparison of the Accuracy of the Transabdominal and Endocervical Hystogram of 44 Suspected Cases of Hydatid Mole

<u>Technique</u>	<u>Cases</u>	<u>Pos.</u>	<u>Neg.</u>	<u>False +</u>	<u>False -</u>	<u>No Follow-up</u>	<u>Error in Procedure</u>
Transabdominal	20	18	1	0	1	1	0
Endocervical	22	16	2	0	1	1	3

From the above table, it can be concluded that either method will give accurate results. There were more errors in procedure with the endocervical method. These would probably be eliminated with more practice and refinement of technique.

All authors reviewed felt that amniography was a safe procedure for either the mother or for a viable fetus. Apelo reports no radiological evidence of metastatic trophoblastic tissue in the lungs following a hystogram. Apparently the hypaque does not wash trophoblastic tissue into venous sinuses. Both Gladstein (1967) and Torres (1966) report a case in which hypaque dye was injected into an amniotic sac containing a normal fetus. Each case was carried to full term, had normal delivery and produced a normal infant.

As with arteriography, amniography may be used as early as the mole is suspected. The characteristic pattern will be present in early pregnancy.

It may be concluded that plain roentgenograms of the pelvis and photoscanning will offer little help in the early

diagnosis of hydatid mole. Both arteriography and amniography appear to be early, rapid, safe methods for the diagnosis of molar pregnancy. Wilson (1964) compared pelvic angiography with amniography and concluded that either method would usually confirm the diagnosis. If either is questionable, the other would verify the diagnosis.

MINOR TESTS FOR THE DIAGNOSIS OF HYDATID MOLE

Fetal Heart Beat and Electrocardiogram

There are several minor procedures which the physician has at his disposal for the diagnosis of hydatid mole. The first is the use of the fetal ECG or the doptone for early detection of the fetal heart beat. The earliest that the doptone can pick up the heart beat is twelve weeks. The fetal ECG will pick up the heart rate at twelve to fourteen weeks. If a heart beat is detected, this does not rule out hydatid mole as there have been a few cases in which a molar pregnancy has coexisted with a normal fetus.

Passage of the Uterine Sound

Acosta-Sison in 1958 was the first to use a uterine sound to diagnose a molar pregnancy. He carefully selected patients who presented with a disproportionately enlarged uterus and absence of a fetus. Then, he would try to pass a uterine sound into the fundus. If the sound passed the internal os, Acosta-Sison felt this was pathognomonic of hydatid mole. He also reported that the sound would pass the canal in case of abruptio placenta and missed abortions. Recently, 1966, he reported several moles in which the sound did not go past the internal os. This was due to the decidua cupularis which had not yet been infiltrated by the trophoblastic tissue.

Amnioscopy

As an outgrowth of the passage of the uterine sound, Mashiach (1967) has reported one case of direct visual observation of molar tissue with the use of Saling's amnioscope. The procedure entails the introduction of a catheter with a light source into the uterine canal. If molar tissue is noted on entry into the fundus, a dilation and curettage can be carried out. If the uterus has a viable fetus, the amniotic membrane will be visualized and the catheter can be withdrawn. Masiach describes this method as being both rapid and accurate as well as being safe. The latter is questionable

CONCLUSION

As indicated in the introduction, the purpose of this thesis was to review and discuss the current methods for diagnosing hydatidiform mole. Each method was reviewed and discussed with emphasis on the safety to the mother and fetus and on an early, rapid and accurate diagnosis. Also, an effort was made to distinguish molar pregnancy from ones that may mimic it. Each of the five methods are summarized by the following conclusions.

(1) At best, the clinical symptoms and signs can only make a clinician suspicious of a hydatid mole. Certainly symptoms of uterine bleeding during the first trimester, toxemia before the twenty-fourth week, hyperemesis, anemia and abdominal pain would necessitate further investigation. A uterus with a gestational size greater than would be expected for a normal pregnancy, the absence of ballottable fetal parts, or the presence of bilateral ovarian cysts would help to confirm his suspicion. However, the only physical sign which would be pathonemonic of a mole would be the passage of vessicles. The latter, of course, is extremely rare and seldom occurs until late in the course of the disease. Therefore, only a suspicion of molar pregnancy may be entertained with the clinical signs and symptoms.

(2) Increased levels of human chorionic gonadotropin which are out of proportion to what would be normally expected for

the respective gestational age should be considered as presumptive evidence of a molar pregnancy. These levels are only significant if repeated titers remain elevated during the second trimester. In Caucasian women, titers of 600,000 units or greater are considered to be diagnostic, however, the mean titer of most studies reviewed was less than 200,000 units. In some cases of degenerating moles, the HCG level was below that of a normal pregnancy.

(3) Ultrasonic scanning of the uterus will give a positive diagnosis of most cases of hydatidiform mole as early as ten to twelve weeks of gestation. At later stages of gestation, ie., fourteen weeks, ultrasound is considered to be 100 percent accurate. Also, the method is inexpensive, rapidly performed and is without danger to the mother or fetus. Its only drawback is that it requires a well trained technician to read and interpret the somagrams.

(4) The method which is generally accepted as the most accurate procedure for diagnosing hydatid mole is either arteriography and/or amniography. Either may be done as early as the mole is suspected with little immediate discomfort to the patient. However, any procedure which is associated with radiation also has potential hazards to the growing fetus and mother.

(5) Fetal heart detection, either by the doptone or ECG, determines viability but does not rule out a coexistent mole. Also, most fetal heart beats are not picked up until the fourteenth week of gestation. The passage of a uterine sound or amnioscopy would give a positive diagnosis but the consequence to a normal fetus could be dangerous. Certainly more investigation

is necessary to evaluate amnioscopy.

Any patient who presents with the signs and symptoms of a molar pregnancy and an elevated HCG titer should be quickly evaluated. Either ultrasound, amniography or arteriography would confirm the diagnosis. Thus, the complications of hydatidiform mole can be prevented.

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