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COMBINED PELVIC SONOGRAPHY AND SERUM BETA hCG, VERSUS LAPAROSCOPY FOR THE DIAGNOSIS OF STABLE PATIENT SUSPECTED OF ECTOPIC PREGNANCY

R. ACHIRON - E. SCHEJTER - H. ZAKUT

Department of Obstetrics and Gynecology,
The Sackler Faculty of Medicine, Tel-Aviv University,
The Edith Wolfson Medical Center, Holon 58100 (Israel)

Summary: The role of sonography in stable patients suspected of ectopic pregnancy is to establish the diagnosis using positive, suggestive or negative signs.

Establishing whether or not intrauterine gestation is present is crucial, as is the detection of any extrauterine abnormality. Sonography may be normal in ectopic pregnancy or when it is not abnormal findings are frequently nonspecific. Therefore, the sonographic results must be correlated and integrated with the clinical history and findings as well as with other diagnostic procedures.

The combination of ultrasound scanning with beta hCG was found highly contributory to the determination of the existence of an ectopic pregnancy.

Understanding the objectives and limitations of each diagnostic test involved is essential for logical and optimal sequences of diagnostic procedures to be employed in patient management.

During a twenty-month period, 138 patients were examined due to clinical suspicion of "sub-acute" ectopic pregnancy. Sixty-one patients were managed according to a non-invasive protocol composed of: a) ultrasound scanning alone and b) ultrasound scanning combined with serum beta subunit hCG.

Ultrasonograms for ectopic pregnancy diagnosis were coded: positive (fluid in cul-de-sac or extrauterine sac); suggestive empty uterus, adnexal mass and pseudo-gestational sac) and negative (intrauterine gestational sac and normal pelvis).

Surgical procedure was carried out immediately on nine patients with positive signs; all of them had ectopics. Suggestive signs were found in twenty-two patients. Beta subunit hCG was determined prior to interventional procedure; ectopic pregnancy was revealed in eighteen of them. Among thirty patients with negative signs, only two patients (7% of this sub-group or 3.5% of the general group) had ectopics.

The results obtained by this protocol were compared to the results of seventy-seven patients with the same clinical signs, who underwent immediate diagnostic laparoscopy on admission.

Thirty-four patients were found to have an ectopic pregnancy and were operated; thirty-two of them had ectopics. The laparoscopy examination excluded ectopic pregnancy in forty-three patients; one of them had ectopic.

Sensitivity and specificity of ultrasound scanning alone, laparoscopy alone, ultrasound scanning combined with beta subunit hCG were analyzed. Sensitivity was practically the same in the three groups (95%, 97% and 93%) respectively. The specificity was higher for ultrasound scanning combined with beta subunit hCG and for laparoscopy (97%, 95%) while the value of ultrasound scanning alone was low (87%). The important contribution of our results is that unnecessary laparoscopy is avoided. The morbidity of patients without ectopic pregnancy is thus reduced.

We suggest a rational management approach to the stable patient suspected of ectopic pregnancy, based on the orderly assemblage of non-invasive diagnostic findings.

INTRODUCTION

The clinical diagnosis of acute extrauterine pregnancy when a patient is in shock, showing signs of intra-abdominal emergency, seldom leads to problems. It is different with the hemodynamically stable patient in whom history and clinical examination establish the diagnosis in about 33% (¹). The classic triad of pain, irregular bleeding and pelvic mass occur only in 30% to 40% of ectopic pregnancies, and more reliable and accurate diagnostic methods are needed.

Initially the application of diagnostic laparoscopy seemed to be the method of choice as it confirms the diagnosis in 92% of the stable patients suspected of ectopic pregnancy (²). However, Samuelsson and Sjovell (³) reported that laparoscopy revealed no intra-abdominal pathologic condition in 40% of suspected patients. Furthermore, the liberal use of this invasive method exposes patients to severe operative and anaesthetic complications (⁴).

Over the past decade the introduction of pelvic sonography and serum beta subunit hCG assays, established a more conservative approach to clinical management of stable patients suspected of extrauterine pregnancy.

There is an extensive literature related to ultrasound criteria for diagnosing ectopic pregnancy (⁵⁻⁹). Most of the criteria are indirect evidence of the existence of ectopic pregnancies. Visualization of the actual ectopic gestation is an uncommon event and less specific diagnostic criteria are applied for sonographic diagnosis. Diagnostic accuracy of these nonspecific criteria are enhanced by the recent development of highly sensitive beta subunit hCG. However, only a few prospective investigations have been made in order to evaluate the diagnostic accuracy of each criteria, and to compare among the various methods used for ectopic pregnancy diagnosis.

We have tried to assess the prediction value of each sonographic criteria, the sensitivity and specificity of ultrasound scanning alone, ultrasound combined with serum beta hCG and laparoscopy on stable patients suspected of extrauterine pregnancy.

MATERIAL AND METHODS

Patients: One hundred and thirty-eight patients who were referred to the Department of Gynecology at the Edith Wolfson Hospital, Holon, Israel, with presumptive diagnosis of ectopic pregnancy during 20 months period were included in this study.

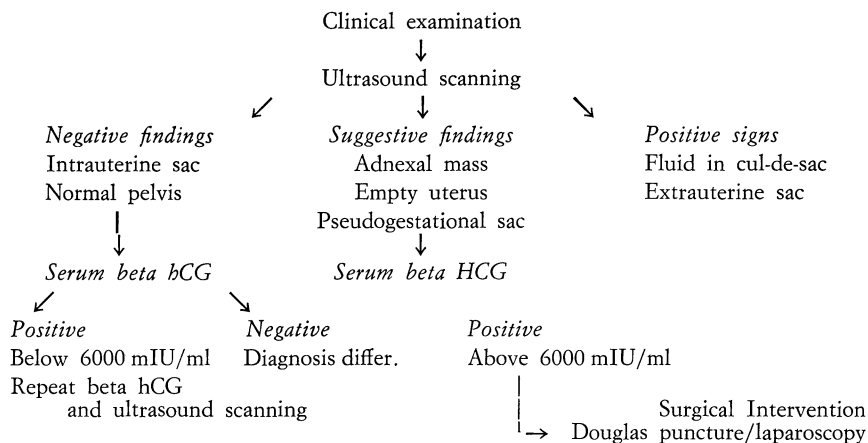


Fig. 1. — Prospective protocol for evaluating clinically stable patients ectopic pregnancy.

Group A: 61 patients were managed according to the prospective non-invasive protocol which is depicted in scheme 1.

Group B: 77 patients were evaluated in the same time period by other staff members using traditional invasive methods, i.e. dilatation and curettage, Douglas puncture and laparoscopy.

All 138 patients fulfilled the following criteria: *symptomatology* of mild to moderate intermittent *abdominal pain* with irregular vaginal bleeding and on gynecological examination, tenderness or a unilateral adnexal mass. All patients were clinically and hemodynamically stable.

Clinical and ultrasound examinations of Group A patients were carried out by the same physicians. The ultrasound scanning was performed with a standard full bladder technique using a Picker echoview 80L and a Unirad linear real-time equipment.

Quantitative beta hCG performed on a daily basis, was radioimmunoassayed using reagents produced by Serono Inc. (Switzerland). A positive pregnancy result was serum beta hCG level more than 10 mIU/ml. All results were reported within 8 hours after the specimen was taken.

In Group B, patients on admission and according to the suspicious index; dilation and curettage was performed, if material was not obtained, Douglas puncture was carried out. A positive Douglas puncture result, led directly to laparotomy, while on negative or equivocal results laparoscopy was undertaken.

Ultrasonographic criteria for diagnosis or exclusion of ectopic pregnancy are listed and classified in table 1.

Table 1. — Ultrasonographic criteria and final findings for the diagnosis of ectopic pregnancy in Group A.

Diagnosis criteria	No. of cases	Final diagnosis of ectopic pregnancy (No. of cases)
a. <i>Positive signs</i>		
fluid in cul-de-sac	6	6
extrauterine gestational sac	3	3
Total	9	9
b. <i>Suggestive signs</i>		
"empty uterus"	18	17
adnexal mass	3	1
pseudogestational sac	1	—
Total	22	18
c. <i>Negative signs</i>		
normal pelvis	23	—
missed abortion	4	—
intrauterine gestational sac	2	1
tuboovarian abscess	1	1
Total	30	2

Final diagnosis of ectopic pregnancy was accepted by histological findings, following laparotomy.

Ultrasound scanning alone, ultrasound scanning combined with serum hCG and laparoscopy were evaluated quantitatively by calculating sensitivity and specificity of the tests and rate of false negative and positive results were derived (10). χ^2 test was performed to determine whether the differences between tests were statistically significant.

RESULTS

Positive ultrasonographic signs proved to have positive predictive value of 100% (table 1); fluid in cul-de-sac was present in 6 patients, and definitive extrauterine sac was detected in 3 patients. Since these 9 patients were considered to have positive evidences of ectopic pregnancy, surgical procedure was performed without beta hCG assay test. All of them had tubal pregnancy on laparotomy.

Suggestive signs of ectopic pregnancy had lower diagnostic accuracy – 82% (18 patients). There were 18% (4 patients) with false positive diagnosis of suspected ectopic. Analysis of these 4 cases revealed two cases of pelvic inflammatory disease presented with adnexal mass; in the third case absence of intrauterine gestational sac at 6 weeks of amenorrhea coupled with hCG value above 250 mIU/ml led to laparoscopy on early intrauterine pregnancy, as it was proved later on; the fourth case had a central intrauterine sonolucent area which mimicked a pseudogestational sac of an ectopic pregnancy; a negative serum beta hCG, D&C and histologic examination proved that the intrauterine echoes were due to hyperplastic endometrium and blood within the uterine cavity. Among the 22 patients with suggestive signs, 18 demonstrated an enlarged uterus, absence of an intrauterine sac combined with linear endometrial or decidual hyperplasia ("Empty Uterus syndrome"). Since all the 18 patients had a positive serum beta hCG level above 250 mIU/ml, laparoscopy was performed. In

17 patients ectopic pregnancy was found. One patient had an early intrauterine pregnancy as was discussed above. Adnexal mass combined with an "empty uterus" was detected in 3 patients, only one of them had a positive beta hCG result and subsequently an ectopic pregnancy was found.

The predictive value of negative signs was 93%. A false negative diagnosis was made only in 2 patients (7%). In one patient, an ultrasound scan at six week's amenorrhea revealed a pseudogestational sac of ectopic pregnancy which was erroneously interpreted to be an early intrauterine pregnancy. In the second case adnexal mass was misdiagnosed as tubo-ovarian abscess. In both cases the persistence of abdominal pain coupled with the raising of blood beta subunit hCG levels led to laparoscopy and laparotomy.

The 77 patients of Group B underwent diagnostic laparoscopy on admission (table 2). 34 patients were suspected of ectopic pregnancy and, therefore, laparotomy was performed. In 2 out of these 34 patients histological specimens of the removed tubes failed to prove gestational tissue ("false positive"). On the other hand laparoscopy excluded ectopic pregnancy in 43 patients; however, one of them proved to have cornual pregnancy ("false negative"). The various conditions discovered at laparoscopy are listed in table 3.

Table 2. — Results of primary laparoscopy compared with the final diagnosis, suspected of ectopic pregnancy.

Diagnosis on laparoscopy	No. of cases	Ectopic pregnancy found at surgery and histologically proved	Surgery negative for ectopic
Positive for ectopic	34	32	2
Negative for ectopic	43	1	42
Total	77	33	44

Table 3. — Conditions diagnosed at laparoscopy when ectopic pregnancy was excluded.

	No.	%
Pelvic inflammatory disease without mass	12	29
Intrauterine missed abortion	8	19
Adnexal mass (inflammatory)	7	17
Early intrauterine pregnancy	4	10
Necrotizing myoma	1	2
Endometriosis	1	2
No pathological findings	9	21
Total	42	100

The results of ultrasound scanning alone are given in table 4 and those of ultrasound scanning combined with serum beta hCG, in table 5. The sensitivity and specificity of each test (table 6) were calculated. The sensitivity was practically the same in the three groups, 93%, 95% and 97% respectively. There were relatively few false positive tests. The specificity was high for the ultrasound scanning combined with beta hCG and for laparoscopy while the value of ultrasound scanning alone was low.

DISCUSSION

The results suggest that some of the sonographic criteria that have been used for the diagnosis of ectopic pregnancy are not sufficiently specific, as far as Robinson's statement that the absolute diagnosis of ectopic pregnancy by ultrasound alone

Table 4. — Results of Group A ultrasound scanning alone compared to final diagnosis.

Ultrasound scanning results	No. of cases	Final diagnosis	
		Ectopic pregnancy	Non ectopic
Suspected ectopic	31	27	4
Not suspected ectopic	30	2	28
Total	61	29	32

Table 5. — Ultrasound and serum beta hCG results of Group A compared to the final diagnosis.

Ultrasound and serum beta hCG	No. of cases	Final diagnosis	
		Ectopic	Non ectopic
Suspected ectopic	20	19	1
Not suspected ectopic	32	1	31
Total	52 *	20	32

* 9 patients with positive signs of ectopic pregnancy were excluded.

today is still the exception rather than the rule ⁽⁶⁾. (Therefore, there is a need for combined methods, particularly in the stable patients). In the present study an attempt was made to evaluate the predictive values of sonographic criteria and to sensitivity and specificity of invasive and non invasive methods. Predictive values represent the probability of normal or abnormal outcome in one patient with a known test result, while sensitivity and specificity describe a test's relationship to the total population of patients. The epidemiologist is interested in sensitivity and specificity while the clinician is interested in the predictive values of normal and abnormal results for each individual patient.

It is well known that many pelvic conditions can mimic ectopic pregnancy as was found in Group B (table 3).

Ectopic pregnancy was present in 45% of those in whom it was suspected. It seems that the first investigation to be performed is a sensitive radioimmunoassay for serum beta subunit hCG. Unfortunately during the study period beta hCG was not routinely assayed 24 hours around the clock in our hospital and therefore, after ultrasound scan was performed patients were divided into three groups: those who had positive signs for ectopic pregnancy, those who had suggestive and those who had negative signs. This policy

Table 6. — Diagnostic sensitivity and specificity of ultrasound combined with beta hCG and laparoscopy.

	Ultrasound	Ultrasound + hCG	Laparoscopy
* Sensitivity	27/29 = 93%	19/20 = 95%	32/33 = 97%
** Specificity	28/32 = 87%	31/32 = 97%	42/44 = 95%
False positive	4/31 = 13%	1/20 = 5%	2/34 = 6%
False negative	2/30 = 7%	1/32 = 3%	1/43 = 2%

* Sensitivity	=	$\frac{\text{True positive}}{\text{True positive} + \text{False negative}}$	$\chi^2 = 0.5$ (P > 0.5)
** Specificity	=	$\frac{\text{True negative}}{\text{True negative} + \text{False positive}}$	$\chi^2 = 1.9$ (P > 0.5)

allowed a tailoring of further patient-investigation which led to a more rational approach to the interpretation of the overall ultrasound findings. Patients presenting positive evidence of extrauterine pregnancy are uncommon. Identification of an extrauterine gestational sac is seen approximately in 15-20% of all cases (⁹). This study identified an unequivocal extrauterine gestational sac in three patients (10%).

We believe that this low rate of detection is predicted on a combination of inadequate ultrasonic technique, the size of the gestational sac, the presence of overlying structures, especially bowel, and the incorporation of the sac into a hemorrhagic mass. The identification of fetal structures in an extrauterine location is also a rare instance. Detection of fetal heart motion within the extrauterine gestational mass, utilizing a real time scanner is pathognomonic (¹¹).

Sonographic visualization of fluid in the cul-de-sac is especially significant since it can suggest recent hemorrhage. However, fluid in cul-de-sac is not synonymous with blood, and accumulated fluid may arise from a variety of sources, including the normal ovulation, rupture of an ovarian follicle or cyst, pelvic abscess or ascites.

In this study, fluid in cul-de-sac was demonstrated in 6 patients (21%). Since

it reinforced the diagnosis, a culdocentesis is suggested in cases in which serum beta subunit hCG is unknown (as in our patients), or laparoscopy in cases with positive serum beta subunit hCG.

The majority of patients (69%) with proven ectopic pregnancies fell into the group of suggestive evidence of extrauterine gestation.

The combination of uterine enlargement, absence of an intrauterine gestational sac and abnormal intrauterine echoes has been referred to as the "empty uterus" (⁸), once considered characteristic of ectopic pregnancy. However, the "empty uterus" has not proved to be pathognomonic since similar characteristics are noted: in situations such as early intrauterine pregnancy, a recent spontaneous abortion, a blighted ovum and pelvic inflammatory disease. Brown *et al.* (⁸) reported 27% of patients with positive pregnancy tests and an "empty uterus" but the diagnosis was other than ectopic pregnancy. Kadar *et al.* (¹²) determined the beta hCG level that distinguishes patients with *intrauterine pregnancies* in whom early gestational sac can be seen from those in whom it cannot be seen; they designated it as the discriminatory hCG zone, which varies between 6000 to 6500 mIU/ml. The absence of an intrauterine sac in conjunction with hCG values above

this level signifies ectopic pregnancy. Failure to demonstrate an intrauterine sac when the serum hCG is below 7000 mIU/ml is a non-diagnostic finding and may occur in normal or abnormal pregnancies including ectopics. However, repeated hCG estimations enable the assessment of normal pregnancies. The mean increase in serum hCG level is 113% in 48 hr, and the lower limit of normal is a 66% increase. For any given level of hCG the time of appearance of the intrauterine sac can be reliably predicted by a normogram constructed by Kadar and Romero⁽¹³⁾.

Intrauterine fluid collections, resembling an early intrauterine pregnancy, so called "pseudogestational sac" have been well reported in cases of ectopic pregnancy^(14, 15). It can vary from a very small sonolucent area equivalent to the size of five weeks pregnancy up to sizes equivalent to nine or ten week pregnancy. The large pseudosacs should present little difficulty in diagnosis since close and careful examination of the "sac" will show low level echoes from blood clots rather than the clear sonolucent appearance of a true gestational sac. The small pseudosacs, however, pose the greater diagnostic problem. We often consider it difficult to discriminate between those small pseudosacs and a normal five week gestational sac or an early blighted ovum. In this event the ring of echoes is usually incomplete or irregular, with less density in the pseudosac than in the true one. Furthermore, the true sac keeps an eccentric position in the uterus while the pseudosac is centrally located⁽¹⁶⁾.

Bradley *et al.*⁽¹⁷⁾ and Nyberg *et al.*⁽¹⁸⁾ recommend careful attention to the presence or absence of the "double sac" appearance in a true intrauterine pregnancy. The authors consider that this feature is created by echoes from the concentric decidua capsularis and decidua parietalis resulting in two layers being seen in the sac wall.

The ultrasound appearance of the adnexa in cases of ectopic pregnancy can range from well defined gestational sac to a mixed solid or cystic mass. Homogeneous solid demonstration may occur as a result of organized hematomas or "matting" of bowel loops with other pelvic viscera at the site of implantation. Although sonographic appearances of pelvic masses are nonspecific they have been relied on for the diagnosis of ectopic pregnancy⁽⁹⁾. Cystic or complex adnexal masses have been reported to be present only on the sonogram in 42% of ectopic pregnancies⁽¹¹⁾. However, 7% of our patients had complex masses on sonographic examination which may be due to the early time of examination. This suggests that perhaps the presence of pelvic masses in ectopic pregnancy depends on the time when the sonographic examination is performed. The presence of a complex adnexal mass combined with an empty uterus when serum beta hCG is positive may suggest an ectopic pregnancy and, therefore, laparoscopy is mandatory.

The 93% sensitivity of ultrasound scanning in Group A patients is in keeping with the results of Makland and Wright⁽⁷⁾ and Gleicher *et al.*⁽¹⁹⁾ who found diagnostic sensitivity of 82% and 84% respectively. The specificity of ultrasound scanning alone was 87% while diagnostic specificity of ultrasound alone in literature ranges from 77%⁽⁹⁾ to 95%⁽¹⁹⁾.

An analysis of the results obtained using a combination of ultrasound scan with serum beta subunit hCG indicates better sensitivity and specificity values which are similar to those of Bryson⁽²⁰⁾ and Kadar *et al.*⁽²¹⁾. Although there is no statistically significant difference between sensitivity and specificity of the combined examination versus laparoscopy, the major advantages of the non-invasive protocol are; avoidance of unnecessary interventive procedure, reducing morbidity and mortality rates. We would like to emphasize that among the 61 patients evaluated by the

invasive protocol only one unnecessary laparoscopic procedure was performed, while among the 77 patients who were traditionally treated, 42 laparoscopies were performed in order to exclude ectopic pregnancy diagnosis. Furthermore, two patients out of these 42 required laparotomy due to laparoscopic complications. One of these patients had a hypovolemic shock due to retroperitoneal vessel bleeding; the other had a bladder injury.

ACKNOWLEDGEMENTS

We are grateful to Mrs. S. Scharzt for the laboratory tests and to the staff and Department (Nurses and Physicians) for their help in collecting and following up the patients, and to Mrs. Linda Milner for typing the work.

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