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THE DIAGNOSIS OF ECTOPIC PREGNANCIES IN CASES OF LOWER ABDOMINAL PAIN USING BETA SUBUNIT ASSAY OF HUMAN CHORIONIC GONADOTROPIN

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Summary: The role of beta-subunit assay of human chorionic gonadotropin (hCG) in the early and accurate diagnosis and treatment of ectopic pregnancy was evaluated prospectively in a group of 57 women who presented with lower abdominal pains. A flow scheme for diagnosis work-up based primarily on hCG beta-subunit assay resulted in no false negative result. This enabled early and conservative treatment of the condition. Ectopic pregnancy was diagnosed early in more than one third of the patients. As a result conservative treatment was performed in cases where it was required and medically possible (33% of the cases).

INTRODUCTION

Ectopic pregnancy constitutes one of the few surgical emergencies in gynecology. The condition is relatively common, and the frequency is increasing (^{1, 2}). The major risks are directly related to the delay in establishing diagnosis and initiating treatment, mainly due to the inconsistency of signs and symptoms. Abdominal pain and irregular bleeding are the most fre-

quent symptoms of ectopic pregnancy, but they are also the most common complaints encountered in all gynecologic fields.

The immunologic test based on the inhibition of agglutination (HIT) by urinary human chorionic gonadotropin (hCG) has a sensitivity of approximately 1000 IU/l and has been reported to give positive results in only 50-80% of patients with ectopic pregnancy (^{3, 4}). Earlier and

more accurate diagnosis of pregnancy, including ectopic pregnancy, has been facilitated since the introduction of a specific, highly sensitive assay of the serum beta subunit of hCG (5).

The purpose of the study was to evaluate prospectively the value of beta-subunit assay of hCG in the early and accurate diagnosis of ectopic pregnancies in cases where patients presented undiagnosed lower abdominal pains.

symptoms). Beta-subunit of hCG was determined in serum with a commercial kit using radioactive iodinated 125 hCG as a tracer and anti-hCG serum calibrated against the second international standard; results were determined within 6-8 hours to a sensitivity as low as 6 IU/l (6,7). All patients also underwent ultrasonic scanning. In those cases in which serum beta-subunit of hCG was more than 10 IU/l and ultrasonic examination failed to show an intrauterine pregnancy, the patients were prepared for surgery. If dilatation and curettage (D & C), performed in most of these patients, did not show macroscopic-gestational products from the uterine ca-

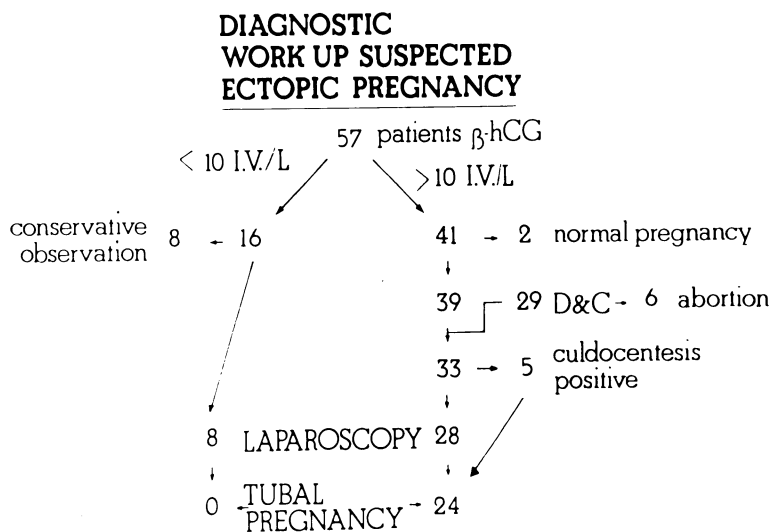


Fig. 1.

MATERIAL AND METHOD

The study population consisted of 57 patients admitted to the Department of Obstetrics and Gynecology, The Chaim Sheba Medical Center, Tel-Hashomer during 1982 with complaints of lower abdominal pain and a normal hemodynamic condition, in whom extrauterine pregnancy was suspected. Patients who presented symptoms requiring urgent intervention were not included in the study.

The scheme used for evaluating abdominal pain associated with suspected extrauterine pregnancy included an immunologic pregnancy test with a sensitivity of 1000 IU/l and radioimmunoassay of beta subunit of hCG which were performed in all patients. (Other routine laboratory tests, such as hemoglobin analysis and urinalysis, were performed according to the signs and

vity, culdocentesis and laparoscopy was immediately undertaken; positive culdocentesis was regarded as an indication for explorative laparotomy. Some patients with negative hCG beta-subunit values, also underwent laparoscopy, if the clinical picture required so.

RESULTS

To simplify assessment of the results, patients were divided into three groups:

Group A - patients with surgically proven ectopic pregnancy (N=24);

Group B - patients with positive hCG beta-subunit assay, but extrauterine pregnancy (N=17);

Group C - patients with negative hCG beta-subunit assay, and no pregnancy proven (N=16).

The diagnostic work-up of the women with abdominal pain and suspected ectopic pregnancy is shown in fig. 1.

Bet-subunit of hCG assay:

Results were positive in all cases later proven to be ectopic pregnancy. Of the 16 cases in which the assay was negative, laparoscopy failed to demonstrate tubal pathology in eight patients and, in the remaining eight D & C or culdocentesis was deemed unnecessary. Later follow-up did not show pregnancy in any of these 16 patients indicating that there were no false negative results with hCG beta-subunit assay with regard to either intra- or extra-uterine pregnancy.

Ultrasound:

Only two normal intrauterine pregnancies among the 57 patients were detected with ultrasound scanning, and in these cases no other measures were necessary. In another eight cases missed abortion was suspected.

D & C:

D & C was performed in 29 patients with positive hCG bet-subunit assay, in six women macroscopic products of conception were recovered from the uterine cavity. Further evaluation of these cases was deferred.

Culdocentesis:

Blood was revealed in five of the 33 patients who underwent this procedure, and laparotomy was subsequently performed without laparoscopy.

Other pregnancy tests and clinical data:

Table 1 indicates that while hCG beta-subunit assay was positive in all 24 patients with later proven ectopic pregnancy (Group A), HIT was positive in only six of these (25%). This difference is

Table 1. — *Menstrual history and laboratory findings in patients admitted with suspected ectopic pregnancy.*

	No. of patients	HIT positive	Beta-hCG positive	Amenorrh. or irregular bleeding	Adnexal Mass	Adnexal «fulness»
Group A	24	6	24	22	9	6
Group B	17	2	17	15	3	2
Group C	16	1	0	15	8	6

Group A - patients with later proven ectopic pregnancy.

Group B - patients with later proven intrauterine pregnancy.

Group C - no pregnancy found.

statistically significant ($P < 0.001$). Beta-subunit of hCG assay was also positive in an additional 17 patients with no extra-uterine pregnancy (Group B), whereas HIT was positive in only two of these (11.7%). In Group C (16 patients with negative hCG beta-subunit assay), the HIT was positive in one case, but to pregnancy could be proven.

Table 1 also demonstrates that clinical parameters of menstrual disorders and adnexal findings were equally distributed in all three groups. Most of the patients had signs and symptoms that could be attributed to extrauterine pregnancy, and all had abdominal pain; however, only hCG beta-subunit assay could objectively confirm the existence of a pregnancy.

Risk factors appeared randomly in the three groups and were of no help in establishing the diagnosis (table 2). Of the entire study population, seven patients (12.2%) has previous extra-uterine pregnancy, and eight (14%) had undergone previous tubal surgery. Thirty-four patients (59.6%) had other possible contributing factors, including current use of an intrauterine device (IUD) (seven patients), previous ovarian cystectomy or appendectomy (six patients), and previous abortion, either induced or spontaneous,

Table 2. — *Predisposing factors for ectopic pregnancy in patients with abdominal pain.*

	No. of patients	Mean age (yr)	Previous ectopic pregnancy	Previous tuboplasty	Previous abortion	Previous lower abdominal surgery	IUD in situ
Group A	24	31.6	3	4	6	2	3
Group B	17	29	2	1	11	1	2
Group C	16	26.1	2	3	4	3	2
Total	57		7	8	21	6	7

involving D & C (21 patients). Mean age was comparable in all three groups.

The decision to perform conservative surgery depended upon the will of the patient, her parity, and the extent of damage to the tubes. In this study, 8 patients (33.3%) underwent conservative tubal surgery (table 3). This was possible mainly because of the high rate of diagnosis of intact ectopic pregnancy.

Titers of beta-unit of hCG:

Low titers of beta-subunit of hCG cannot predict the location of the pregnancy, only its existence. The lowest titer associated with a diagnosis of ectopic pregnancy in the present study was 12 IU/l (table 4). Intact ectopic pregnancy was found in 11 cases (45.8%). All patients with low titers also showed negative HIT results, indicating that such pregnancies may have been undetected in the past.

Final diagnosis:

Final diagnosis other than ectopic pregnancy is presented in table 5. In Group B

Table 3. — *Operative procedures performed in patients with tubal pregnancy.*

	Salpin- gectomy	Conservative procedures
Tubal rupture	4	—
Tubal abortion	7	2
Intact tubal pregnancy	5	6
Total	16	8

Table 4. — *Titers of beta-hCG assay (IU/l) in patients with ectopic pregnancy (A) and without ectopic pregnancy (B).*

	10 - 50	50 - 100	100 - 250	> 250
Group A	4 (2)	2 (2)	4 (0)	14 (7)
Group B	3	0	1	13

Note: Number in brackets represent the number of intact ectopic pregnancies. The others were tubal abortions or ruptures.

(all with positive hCG beta-subunit assay) nine intrauterine pregnancies were discovered, but only two pregnancies were normal. Another five patients underwent D & C; in four no gestational products were recovered, and subsequent laparoscopy was negative; the remaining patient was proved to have an ovarian cyst, so that laparoscopy was unnecessary. In three patients, the first hCG beta-subunit assay was positive; however, a second assay performed 2-3 days after the symptoms had subsided, was negative and no further investigations were performed. In these patients the primary-positive result was attributed to an early complete abortion or to a missed tubal abortion (!).

In Group C (all with negative hCG beta-subunit assay) the final diagnosis was

Table 5. — *Final diagnosis in 33 of the 57 patients without ectopic pregnancy.*

	Positive beta-hCG (Group B)	Negative beta-hCG (Group C)
Normal pregnancy	2	—
Abortion	7	—
D & C without findings	4	—
Ovarian cyst	1	5
P. I. D.	—	5
Urinary tract infection	—	2
Undiagnosed pain	3 *	4 **
Total	17	16

* First beta-hCG assay positive; second assay negative; no further investigations performed.

** Laparoscopy without finding.

ovarian cyst in 5 patients, PID in 5 patients, and urinary tract infection in 2 patients. In 4 patients the cause of pain remained undiagnosed even after laparoscopy.

DISCUSSION

When clinical evidence of abdominal emergency exists and ectopic pregnancy is suspected, culdocentesis or preferably laparoscopy followed by laparotomy is immediately indicated. It has been recently noted that the incidence of ectopic pregnancies is increasing (^{1,2}) and that patients tend to present earlier than before. In many of these cases, the clinical manifestations are uncertain or irregular. Abdominal pain and irregular bleeding are by far the most frequent symptoms, but they are also the most common symptoms presented in all gynecological fields. This may cause delayed diagnosis and treatment, or sometimes over diagnosis due to the high index of suspicion required for early detection of ectopic pregnancy. In general, the young patient who presents with lower abdominal pain, irregular bleeding and predisposing factors for ectopic pregnancy, is considered at risk for ectopic pregnancy until otherwise proven.

In the present study it was shown that clinical history and presenting symptoms may be not only unreliable for diagnosis, but even misleading. All 57 patients presented with lower abdominal pain, and most (91.2%) also had irregular bleeding. Although none required urgent evaluation or showed hemodynamic instability, 86% had predisposing factors for ectopic pregnancy, including IUD *in situ* (⁸), previous tubal surgery or previous pelvic operation (⁹) or D & C for interruption of a pregnancy. However, the final diagnosis was other than ectopic pregnancy in 57.8% of cases. Hence, physicians very often face the dilemma of verifying which patient has an ectopic pregnancy, without increasing the suspicion index rate.

Beta-subunit assay of hCG has been proved to be a highly accurate diagnostic test in cases of abdominal pain and vague suspicion of ectopic pregnancy. In agreement with other studies (¹⁰), present results showed that hCG beta-subunit assay excludes the diagnosis of ectopic pregnancy: it is, therefore, suggested that this test be used as the primary tool in differentiating ectopic pregnancy from the other possible causes of lower abdominal pain. Those patients with positive results should be considered as high risk for ectopic pregnancy, requiring further steps to final diagnosis. Moreover, the flow schema demonstrated in fig. 1 was found simple and logical for diagnosis work-up of patients in whom ectopic pregnancy was suspected. Its use is recommended in order to prevent unnecessary hospitalization, surgical intervention or examinations. It might also lead to a decrease in the number of ruptured tubal pregnancies and to an increase in the possibilities of performing conservative surgery in selected cases.

The ultrasound technique is useful mainly for the exclusion of intrauterine pregnancy, rather than for positive confirmation of the existence of ectopic pregnancy. However, ultrasound scan cannot identify the intrauterine sac until week 6-7 of gestation.

Although culdocentesis had a 79% false-negative rate in the present study, the information thereby obtained was found useful; i.e. aspiration of nonclotting blood confirms the diagnosis in cases in which hCG beta-subunit assay is positive and ultrasound scan does not show intrauterine pregnancy. However, when culdocentesis is negative, ectopic pregnancy cannot be excluded before laparoscopy is performed.

Laparoscopy, on the other hand, is a far more accurate procedure than culdocentesis for the detection not only of hemoperitoneum, but also of the exact source of bleeding. It is noteworthy that of the

laparoscopies performed, 9 (32%) showed no tubal pregnancy. This rate is not high considering the benefit of early diagnosis and the possibility of performing conservative surgery before extensive tubal damage occurs. The false-positive hCG beta-subunit assays might be explained by an earlier complete abortion or a missed tubal abortion (¹). With these results in mind, laparoscopy is now used in our department in nonurgent cases, mainly when hCG beta-subunit assay is positive and rising.

In conclusion, serum hCG beta-subunit was found highly accurate and sensitive test in the early and accurate diagnosis of ectopic pregnancy when the clinical grounds were suggestive, its regular use can accelerate initiation of treatment in women at risk.

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