Provisionally accepted for publication

ORIGINAL ARTICLE

Serum human chorionic gonadotropin and ultrasound criteria in women with successful expectant management of tubal ectopic pregnancies: a retrospective cohort study

Ultrasound criteria and HCG levels as predictors for successful expectant management of tubal pregnancies

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Doi: 10.36129/jog.2025.211

ABSTRACT

Objective. To identify different variables associated with successful expectant management of tubal ectopic pregnancies.

Materials and Methods. A retrospective analysis was performed at a university hospital, examining the medical records of 88 cases of tubal ectopic pregnancy that were successfully managed through expectant management. Data regarding ultrasonographic criteria, peak serum β-hCG (human chorionic gonadotropin) levels, subsequent β-hCG trends during follow-up, and the duration (in days) required for resolution were analyzed.

Results. The mean diameter of the ectopic mass was 30.0 ± 9.73 mm and 26 ± 8.9 for the vertical and horizontal diameters, respectively. Twelve (18.5%) cases had no free fluid in the Douglas pouch. The median initial serum β-hCG concentration was 724.20

IU/L (IQR 361.95-1252.00, with the highest initial serum β-hCG concentration was 4617 IU/L.

The median time required for resolution was 15.0 days (IQR 12.0-18.0), whereas the median duration of hospitalization was 4.0 days (IQR 3-7.0).

Conclusions. Clinically stable women with tubal EP, ectopic mass up to 50 mm and those with variable degrees of hemoperitoneum and variable levels of β-HCG (up to 4617) can achieve successful expectant management. These findings provide valuable insights into identifying candidates suitable for expectant management in cases of tubal EP.

Key words

Ectopic pregnancy; expectant management; human chorionic gonadotropin; tubal pregnancy.

Introduction

Expectant management (EM) has gained growing recognition as an acceptable alternative for management of tubal ectopic pregnancies (EP). This strategy entails careful monitoring of EP without resorting to immediate medical or surgical intervention. This 'wait and watch' approach allows patients to avoid the potential complications associated with surgical procedures and the adverse effects of pharmacological treatments. [1, 2]

The aim of EM is to observe whether the tubal EP will resolve spontaneously, however; the main challenge for healthcare providers in embracing this line of treatment lies in the absence of a consensus regarding the selection criteria of women eligible for EM. [3]

To date, there is a significant difference in the recommendations across the literature along with the absence of standardized selection criteria for women eligible for EM. Nonetheless, most of the studies reported that eligible women should be willing and able to attend for follow-up, have minimal pain, have low or declining serum β-hCG levels. The success rates for EM are highly variable, ranging from 57% to 100%, and are strongly dependent on case selection. [4]

The National Institute for Health and Care Excellence suggested that EM can be offered for those with serum hCG levels of 1,000 IU/L or less and may be considered for women with serum hCG levels above 1,000 IU/L but less than 1,500 IU/L.[2] In contrast, the American College of Obstetricians and Gynecologists, did not specify a serum β-hCG level cut-off for offering EM, but noted an 88% success rate when the initial serum β-hCG level is below 200 IU/L. [5] Moreover, Tulandi, 2020 advised against EM for cases of EP with the serum hCG level exceeds 200 IU/mL at any point during follow-up or if levels are rising.[6]

A systematic review and meta-analysis of randomized controlled trials was performed to evaluate the efficacy and safety of EM for the treatment of tubal EP. The findings did not provide sufficient evidence to ascertain whether significant differences exist between EM and methotrexate in stable patients with serum β-hCG levels below 1500 IU/L regarding

the resolution of tubal EP, the avoidance of surgical intervention, or the duration required for tubal EP resolution. [7]

The aim of this study was to assess the initial serum β hCG levels and ultrasonographic criteria in women who had successful EM of tubal EP. This data can serve as a basis for establishing selection criteria for EM and may provide guidance for healthcare professionals in the management of tubal EP through expectant approaches.

Materials and Methods

This retrospective study was carried out at Ain-Shams University Maternity Hospital, analyzing the medical records of 88 tubal ectopic pregnancies that were successfully managed expectantly between January 2016 and December 2020. The women included in the study were those who were hemodynamically stable, with a confirmed diagnosis of tubal ectopic pregnancy based on ultrasound, showing no fetal heartbeats, no significant pelvic pain, and a serum hCG level of less than 5000 IU/L. The initial management approach offered to the patient, following comprehensive counseling, was expectant management.

In the process of planning the study, our original objective was to exclude cases involving hemoperitoneum. However, upon reviewing the medical records, we discovered that the majority of cases contained varying levels of fluid in the Douglas pouch. As a result, these cases were incorporated into the analysis.

The data extracted from the patients' medical records included maternal age, parity, duration of amenorrhea, history of prior abortion or ectopic pregnancy, presenting symptoms, clinical examination findings, and ultrasonographic results at both the initial presentation and at discharge.

Ultrasound findings included the measurements of the vertical and horizontal diameters of the ectopic masses and their morphological appearance that was graded according to Dooley et al., gestational sac containing an embryo with no visible cardiac activity, gestational sac containing only a yolk sac with no visible embryo, empty gestational sac with no visible additional structures, and solid homogenous mass.[8] The presence of free pelvic fluid or heamoperitonium and the measurements of the endometrial thickness at times of admission and discharge were reviewed.

β-hCG levels were documented during the initial visit and throughout the follow-up period. Initially, β-hCG measurements were taken at 48-hour intervals, with the frequency decreasing to once a week after confirming an adequate decline, defined as reaching non-pregnant levels of less than 10 IU/L.

The primary outcome was the resolution of hCG (upper limit of qualitative hCG levels associated with successful EM of ectopic pregnancy). Secondary outcomes included ultrasonographic markers indicative of successful EM, the time required for resolution of the ectopic pregnancy, the length of hospital stay, and reproductive outcomes following EM of ectopic pregnancy.

Ethical consideration:

The study was approved by the Ethical and Research Committee of the Council of Obstetrics and Gynecology Department, and Faculty of Medicine Ain Shams University Ethical Research Committee (FMASU ERC) (FMASU M S 304/2021) on 2/6/2021. An informed consent was obtained from each participant upon hospital admission as per the administration protocols and the hospital administration consent to review the needed data record was obtained. The study was reported in accordance with STROBE guidelines for reporting observational studies.

Results

Between January 2016 to December 2020; 556 women were diagnosed with a tubal ectopic pregnancy in Ain-Shams University Maternity Hospital and 88 (15.8%) of them underwent successful EM.

The mean age of women who had successful EM was 28.94 ± 5.36 years, with mean period of amenorrhea 46.83 ± 8.6 days. (Table 1)

Regarding the sonographic findings at admission, 53 (81.5%) women showed solid tubal mass, the mean diameter of the ectopic mass was 30.0 ± 9.73mm and 26 ± 8.9 for the vertical and horizontal diameters, respectively. Only 12 (18.5%) of the cases had no free fluid in the Douglas pouch. (Table 2)

The median initial serum β-hCG concentration was 724.20 IU/L (IQR 361.95-1252.00). The highest recorded initial serum β-hCG concentration was 4617 IU/L. (Table 3)

The median time interval from diagnosis to resolution was 15.0 days (IQR 12.0-18.0) and the median duration of hospital stay was 4.0 days (IQR 3-7.0).(Table 4)

Discussion

Ectopic pregnancy can be a life-threatening obstetrical emergency leading to catastrophic intra-abdominal hemorrhage that could also occur with spontaneous rupture of uterine vessels, or with uterine rupture. [9,10]

A small proportion of women with EP who are at minimal risk of tubal rupture may be considered for EM. However, there is no agreement among various professional societies regarding the clinical criteria that reliably predict the success of EM for tubal EP. The Society of Obstetricians and Gynecologists of Canada (SOGC) suggests offering EM if the initial β-hCG <1000 IU/L and decreasing (≥15%−20%) over 48 hours with no significant hematosalpinx, no fetal heart rate, and no significant free fluid. [11]

The criteria reported by the National Institute for Health and Care Excellence included clinically stable women with a tubal ectopic pregnancy measuring less than 35 mm with no visible heartbeat on transvaginal ultrasound scan and no haemoperitoneum with serum β-hCG levels of 1000 IU/L or less. EM can be considered if serum β-hCG levels above 1000 IU/L and below 1500 IU/L. [2]

American College of Obstetricians and Gynecologists (ACOG) reported that criteria for EM eligibility includes asymptomatic women without evidence of rupture or hemodynamic instability with objective evidence of resolution i.e., declining or plateauing β-hCG levels. ACOG does not specify a particular β-hCG threshold for initiating EM, but noted 88% success rate if EM offered in cases with the initial serum β-hCG level below 200 IU/l. [5]

The initial serum β-hCG is the most reliable predictor of the eventual outcome of EM. The higher the initial β-hCG levels are associated with less likelihood for spontaneous pregnancy resolution. Different studies suggested different maximum β-hCG thresholds beyond which EM may not be safe nor effective.

In the current study, the maximum initial serum β-hCG concentration was 4617 IU/L. The median initial concentration was 724.20 IU/L (IQR 361.95-1252.00), with 13 (14.8%), 43 (48.9%) and 15 (17.0%) women successfully managed expectantly had initial serum β-hCG concentration <200 IU/L, 200-1000 IU/L, and 1000-1500 IU/L, respectively. Similarly, Helmy et al., [12] found that among the 161 patients who had successful expectant management the mean initial serum β- hCG was 488 IU/L (range from 41 to 4883 IU/L).

In their clinical protocol for EM, Mavrelos and colleagues offered expectant management for women with an initial serum β-hCG level of < 1500 IU/L. [13]

Rodrigues et al. found no role for EM in cases with initial serum β- hCG exceeds 3,000 IU/l. In their study, 67% of the cases with an initial -hCG level above 2,000 IU/l developed symptoms during the follow up. [14]

The decline in serum β-hCG level is considered a reliable predictor of successful EM. The serum β-hCG at 48 hour/serum β-hCG at 0 hour ratio of less than 0.8 was associated with an overall success rate of 72%.[15] In the present study, this ratio was found to be below 0.8 in 53 women, accounting for 75.7% of the participants.

Our analysis revealed that 24 cases (37.5%) exhibited an ectopic mass with a size of ≥ 35 mm, with the largest vertical or horizontal diameter reaching 50 mm. Additionally, 81.5% of the cases involved solid masses. Furthermore, only 12 cases (18.5%) demonstrated an absence of free fluid in the Douglas pouch.

Mavrelos and colleagues found that solid heterogeneous mass was the main ultrasound finding in 70.2% of cases successfully managed expectantly with the median size of the mass 14.0 mm (11.4–18.25).[13] In contrast, Helmy et al. reported the successful EM in cases with a tubal mass measuring up to 57 mm. [12]

The guidelines set by the National Institute for Health and Care Excellence (NICE) are commonly applied when selecting women for expectant management [2]; however in contract to these recommendations, our findings indicated that 24 (37.5%) women with ectopic mass measuring ≥ 35 mm, and 32 (36.6%) women with β-hCG level > 1000 IU/L could be managed expectantly and avoiding the complications associated with both medical and surgical treatment.

As previously mentioned, the various guidelines recommend against EM in the presence of hemoperitoneum and it was considered an absolute contraindication for methotrexate.

In the current study, only 12 (18.5%) of the cases showed no hemoperitoneum. This was in line with Bignardi and Condous, 2009 who reported that the presence of hemoperitoneum was not an absolute contraindication to conservative treatment of EP. [16]

This could be explained by the fact that the presence of hemoperitoneum of any degree does not necessarily signify the diagnosis of tubal rupture or indicate hemodynamic instability. Rather, it may indicate a complete tubal abortion with the expulsion of the product of conception outside the fallopian tubes, without associated tubal rupture, accompanied by varying degrees of fluid. This would allow for conservative surgical management and preserving fertility. [17] Moreover, spontaneous hemoperitoneum in pregnancy has been reported in 100 cases within the literature, though the precise pathogenesis remains uncertain. Potential etiological factors, including hemodynamic and hormonal influences, have been suggested. [10]

Another advantage of EM is the potential to conceive more quickly compared to women receiving methotrexate, who are typically advised to wait for 3 months. [7]

In the current study, 14 women (15.9%) achieved normal pregnancy after EM and 2 women (2.3%) had recurrent EP.

Previous data reported that EM was associated with the highest cumulative incidence of clinical pregnancy, live birth rate, and the shortest time to achieve an intrauterine pregnancy when compared to medical and surgical treatment. [18] According to Kirk et al., ninety three percent of cases received EM of suspected EP has shown tubal patency during hysterosalpingography with subsequent intrauterine pregnancy rates of 63 - 88 percent. [19]

Due to the preservation of fertility provided by the conservative approach, trials of conservative management for both tubal and non-tubal ectopic pregnancies (EP) have been explored with varying success rates. In a recent case report and systematic review, Conte and colleagues discussed available treatment options for managing the rare condition of cervical twin pregnancy. They emphasized the lack of standardized criteria for implementing conservative management in such cases. They proposed that transvaginal ultrasound is a reliable and safe method for detecting hemoperitoneum. In their case report, they successfully terminated the pregnancies through dilation and curettage, followed by the placement of an intracervical Foley balloon, thereby preserving the patient's fertility without the need for methotrexate. [20]

Conclusions

Clinically stable women with tubal EP, ectopic mass up to 50 mm and those with variable degrees of hemoperitoneum and variable levels of β-HCG (up to 4617) can achieve successful expectant management. These findings can be useful for determining which women should undergo expectant management for tubal EP.

Strengths and limitation:

The main limitation of this study was the small sample size, also the retrospective nature of the study with some missing data in the medical records, but it opens up interesting openings for pilot and prospective studies. However, challenge the idea that surgery is mandatory in women with a tubal ectopic pregnancy and hemoperitoneum on ultrasound examination represents an interesting finding that could be the scope of future studies. Moreover, documenting the safety of EM in cases with higher β-HCG levels and larger ectopic mass could help in setting different selection criteria in EM clinical guidelines.

Authors' contributions:

E.T was responsible for Data curation, Formal Analysis, Investigation, Writing – review & editing.; **A.A** contributed in Conceptualization, Formal Analysis, Methodology, , Writing – review & editing.; **M.S** was responsible for Conceptualization, , Methodology, Resources, , Supervision, Validation, Visualization, Writing – review & editing ; and **R.A** contributed in Conceptualization, , Methodology, Resources, , Supervision, Validation, Visualization, Writing – original draft.

Funding:

This research received no external funding.

Study registration:

Clinical trials.gov: NCT04975984

Disclosure of interests:

The authors declare that they have no competing interests.

***Ethics approval*:**

The study was approved by the Ethical and Research Committee of the Council of Obstetrics and Gynecology Department, Faculty of Medicine Ain Shams University Ethical Research Committee (FMASU ERC) (FMASU MS 254/2021) on 17/4/2021 and Ethical Committee of the Council of Obstetrics and Gynecology Department and an informed consent was obtained from all subjects involved in the study.

Informed consent:
Informed consent for data collection for research purposes was obtained from all subjects involved in the study.

Data availability statement:

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Table 1: basic demographic and initial clinical characteristics of the study population

Age (Years)	
Mean ±SD	28.94 ± 5.36
Period of amenorrhea (days)	
Mean ±SD	46.83 ± 8.6
Parity N(%)	
0	20 (22.7%)
1	20 (22.7%)
2	26 (29.5%)
3 or more	22 (25.0%)
Previous Abortions	
N (%)	24 (27.2%)
Previous Ectopic pregnancy	
N(%)	3 (3.4%)
Clinical Presentation N(%)	
Pain	13 (15.1%)
Vaginal Bleeding	3 (3.5%)
Pain and vaginal bleeding	6 (7.0)
Referred from another unit	64 (74.4%)
Systolic blood pressure mmHg(Mean ± SD)	114.28 ±6.45
Diastolic blood pressure(Mean ± SD)	73.45 ±6.11
Pulse b/m (Mean ± SD)	84.88 ±6.44

Table 2: Participants' ultrasound findings at initial presentation

Ultrasound variable		
Endometrial Thickness (mm) Mean ± SD Median (IQR) (Minimum- Maximum)		 8.0 ± 2.95 8.0 (6.0-9.0) (4.0-18.0)
Size of Ectopic mass (vertical diameter) (mm) Mean ± SD Median (IQR) (Minimum- Maximum)		 30.0 ± 9.73 30.0 (23.0-37.0) (14.0-50.0)
Size of Ectopic mass (horizontal diameter) (mm) Mean ± SD Median (IQR) (Minimum- Maximum)		 26 ± 8.9 25.0 (20.0-30.0) (11.0-50.0)
Ectopic mass measuring ≥ 35 mm		24 (37.5%)
No free fluid in Douglas pouch		12 (18.5%)
Grading	Solid mass	53 (81.5%)
	Gestational Sac without fetal pole	11 (16.9%)
	Gestational Sac with fetal pole	1 (1.5%)

Table 3: criteria of serum β-hCG concentrations at the initial visit

Serum β-hCG concentrations at the initial visit (IU/L)	
Median (IQR)	724.20 (361.95-1252.00)
Minimum	55.60
Maximum	4617.00
Serum β-hCG categorization (IU/L) N(%)	
< 200	13 (14.8%)
200-1000	43 (48.9%)
1001-1500	15 (17.0%)
1501-2000	8 (9.1%)
2001-4000	7 (8.0%)
> 4000	2 (2.3%)
Serum β-hCG trend over 48 hours N(valid%)	
Decreasing ≥15%	60 (85.7%)
Decreasing <15%	9 (12.9%)
Increasing	1 (1.4%)
serum β-hCG at 48 hour/serum β-hCG on admission ratio	
N(valid%)	53 (75.7%)
< 0.8	17(24.3%)
≥ 0.8	

Table 4: Duration of follow up, hospitalization, and reproductive outcomes:

Variable	
Duration of follow up (days)	
Mean ± SD	16.5 ± 7.4
Median (IQR)	15.0 (12.0-18.0)
(Minimum- Maximum)	(4.0-45.0)
Duration of hospitalization (days)	
Mean ± SD	5.2 ± 3.6
Median (IQR)	4.0 (3-7.0)
(Minimum- Maximum)	(1.0-20.0)
Reproductive outcomes N(%)	
No pregnancy	23 (26.1%)
Normal pregnancy	14 (15.9%)
Ectopic pregnancy	2 (2.3%)
Not seeking fertility	49(55.7%)