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Fertility outcome after different treatment modalities of tubal ectopic pregnancy, Observational Study

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ABSTRACT
Objective:to assess the impact of expectant, medical, and surgical modalities for the management of tubal ectopic pregnancy (EP) on fertility and reproductive outcomes.
Methods: Our study included 159 patients with a history of tubal EP between December 2020 and November 2021 and actively planned to conceive following the EP. They were categorized into three groups: Group A (81 cases), who were treated surgically; Group B (34 cases), who received medical treatment; and Group C (44 cases), who received expectant therapy. They were asked to determine the fertility outcomes after EP, such as the mode of conception, the recurrence of EP, and the occurrence of abortion or live births. All patients who didn't conceive were subjected to hormonal profile and hysterosalpingography (HSG) evaluation.
Results: Among 159 patients, 44 (27.67%) had expectant management, 34 (21.38%) had medical treatment, and 81 (50.94%) had surgical treatment. Regarding the pregnancy outcome after EP, there was a significant difference between the groups (p-value <0.001). The highest clinical pregnancy rate was in the expectant group (72.73%), followed by the medical group (50%) and then the surgical group (34.57%). The tubal damage seen in hysterosalpingography was highest in the surgical group but was insignificant.
Conclusions: Expectant treatment was associated with the best reproductive outcome, followed by medical treatment, while surgical treatment had the lowest outcome with an increased risk of tubal complications.

Keywords: Ectopic pregnancy, Clinical pregnancy, Fertility outcome

INTRODUCTION

Ectopic pregnancy (EP) refers to a pregnancy that develops outside of the uterine cavity. The fallopian tube is the most common site of ectopic pregnancy. The majority of tubal ectopic pregnancy cases that are diagnosed early can be successfully managed either with minimally invasive surgery or with methotrexate-based medical treatment. On the other hand, tubal ectopic pregnancy in an unstable patient is a medical emergency requiring immediate surgical intervention [1].

Methotrexate, actinomycin D, potassium chloride, prostaglandins, and RU 486 are prescribed as a medical treatment for ectopic pregnancy. Considering the ambiguity of treatment efficacy and adverse consequences, the rationale for a conservative treatment must be carefully considered. It has to be known that in a large proportion of cases, surgical management is unavoidable. This takes many forms, including diagnostic laparoscopy (evacuation of the hemoperitoneum, followed by operative Laparoscopic treatment in the Same Session), tubal pregnancy milking through the fimbrial end, salpingostomy, evacuation by aqua-dissection or aspiration, partial salpingectomy and salpingectomy [2].

Treatment decisions comprise operative, medical management, and clinical and laboratory tests follow-up. It was reported that many cases of early ectopic pregnancy mayend in spontaneous termination and re-absorption, which may render aggressive treatment unnecessary. Therefore, modern monitoring may be adequate and enhances the preservation of tubal function and fertility[3].

Following EP, 20-60% of women may experience infertility, and the factors that impact reproductive prognosis are still debated. Several studies demonstrated that radical EP therapy has a negative impact on reproductive outcomes. Furthermore, the status of the contralateral tube may have a significant impact on subsequent fertility. Previous studies recommended preserving the damaged tube with a history of bilateral tubal disease because conservative management seems beneficial in such patients[4,5].In contrast, a previous studyon infertility risk

factors discarded the putative benefits of conservative management [6].
The ideal strategy to manage EP cases should be patient-tailoredaccording to patients' medical condition, success rate, side effects, the rate of complications, and costs.Still, fertility outcomes are essential to consider in determining the treatment approach [7]. Even though there are few studies on the efficacy of different management plans in terms of future fertility outcomes, the ideal management decision is indeterminate [8–11].Based onthose assumptions, the present study wasconducted to investigate thesuccess rate and the impact of surgical, medical, and expectant management of tubal EP on fertility performance and outcomes.

METHODS

All patients witha history of tubal ectopic pregnancy between December 2020 and November 2021 at the obstetrics & gynecology department at Minia University Hospitals were recruitedin this observational study.All cases were categorized into threegroups: GroupA (81 cases),who treated surgically; GroupB (34cases),who received medical treatment; and GroupC (44 cases) who receivedexpectant therapy.
The clinical suspicion of ectopic pregnancy was based on the presenceof two criteria in the medical records: suggestive βhCG titer(no doubling, slightdecrease, or stability of βhCG levels after 48 hours) and specific signs by direct transvaginal ultrasound (hemosalpinx or lateral uterine gestational sac and empty uterus).The cases were excluded if they were diagnosed beyond the trial period or managed outside the facility or those who used a contraceptive method after the treatment of EP. Cases with uncertain localization of EP or non-tubal EP were also excluded.
Medical records of the patients were used to acquire clinical data on their age, smoking status, body mass index (BMI), and parity before EP. Clinical data at the time of admission regarding gestational age, complaints, laboratory investigations, and ultrasound assessment were collected.
All eligible patients had a phone follow-up after 12 to 36 months of treatment. Patients who consented to participate in the study and actively planned to conceive following the EP incident were included. They were asked to determine the fertility outcomes after EP, such as the mode of conception, the recurrence of EP, and the occurrence of abortion or live births.
All patients who didn't conceive were subjected to hormonal profile evaluation to exclude patients having any other general cause of infertility. After that, hysterosalpingography (HSG) was done to spotlight the health condition of the tubes.
Statistical analysis was done using computer programs "Microsoft Excel 2007" and "IBM Statistical Package for the Social Science v25". Numerical data was presented as mean±standard deviation, while categorical data was presented as frequencies and percentages. Numerical variables were compared using the ANOVA test, while categorical variables were compared using the Chi-square or Exact test. P-values were considered statistically significant if less than 0.05.

RESULTS

This study was conducted at the Obstetrics & Gynecology Department of Minia University Hospital during the period from December 2020 to November 2021.Out of 216 patients, 159 patients with tubal EP were included, and others were excluded due to receiving contraception or missing the patient during follow-up. Expectant management was conducted on44 patients (27.67%).Medical treatment in the form of methotrexate was used to treat 34 out of 159 patients (21.38%), while 81 patients (50.94%) experienced surgical treatment.Demographic data shows no statistically significant difference between surgical, medical, and expectant groups regarding age, smoking status, body mass index (BMI), parity before EP, and gestational age (p-value >0.05) (Table 1).
Regarding the clinical data at the time of admission, there were no significant differences between groups regarding abdominopelvic pain and vaginal bleeding (P-value >0.05). In addition, there were no significant differences regarding the presence of ultrasound signs (Blob or bagel sign / Hemoperitoneum). In contrast, there was a statistically significant difference regarding hemoglobin (Hb), and βhCG levels showed a highly statistically significant difference among study groups (p-value <0.001). The βhCG levels were reported to be significantly higher in the surgical group rather than the other groups, while Hb levels were significantly lower in the surgical group rather than the other groups (Table 2).
According to the pregnancy outcome, there was a significant difference between the surgical, medical, and expectant groups regarding fertility outcomes after EP (p-value <0.001). The incidence of clinical pregnancy was highest in the expectant group (72.73%), followed by the medical group (50%) and then the surgical group (34.57%). However, there were no significant differences between groups regarding the rate of miscarriage and live birth. On the other hand, the incidence of infertility was the highest in the surgical group (65.43%), followed by the medical group (50%),and then the expectant group (27.27%). However, there were no significant differences between groups regarding the results of the hormonal profile (FSH, LH, E2, Progesterone). The tubal damage seen in hysterosalpingography was highest in the surgical group but was insignificant(Table 3).

DISCUSSION

Tubal ectopic pregnancy is a common medical obstetric problem. It is associated with a wide variety of complications, but the most important and alarming one is massive intra-abdominal hemorrhage with a high incidence of first-trimester mortality [13].Previous studies reported different treatment modalities, including close follow-up, methotrexate treatment, and surgical intervention. The widely applied surgical protocols for management are salpingectomy and salpingotomy [14]. However, it was reported that all treatment options are safe and effective regarding the hemodynamic status and clinical data of the patients [15]. Interestingly, few reports discussed the effect of type of management on subsequent fertility outcomes.

The current study aimed to shed light on the fertility outcomesofthese treatment options and determine the possible causes of infertility in patients who failed to get pregnant after treatment. The present study was performed in the Department of Obstetrics and Gynecology, Minia University Hospital, between December 2020 and November 2021. The study involved 159 patients categorized into three groups according to the management plan. About 50.94% of the patients (81/159) underwent surgical treatment (laparoscopic salpingectomy or laparotomy with salpingectomy); 21.38% of the patients (34/159) received medical treatment in the form of methotrexate; and 27.67% of the patients (44/159) had expectant management. Baggio et al. (2021) reported in a previous study that 49.8% of the cases underwent surgical management. In addition, 94.1% of the cases underwent laparoscopic salpingectomy. This could be explained by the fact that laparoscopy was the standard treatment of choice in the institution of the study [14].

According to complications, there weren't statistically significant differences regarding regarding abdominopelvic pain and vaginal bleeding. In line with our findings, a previous study reported the same observation [16]. Ranji et al.(2018) showed that the most common clinical manifestations of ectopic pregnancy were amenorrhea (90%), abdominal tenderness (68%) abdominal pain (64%), pelvic tenderness (44%) and vaginal bleeding/spotting (41%) [17].Women who are hemodynamically unstable or with signs or symptoms of a ruptured ectopic pregnancy require surgical management [18]. A previous study by Ibraheem et al.(2024) showed that surgical management was used in women who were hemodynamically unstable or with signs or symptoms of a ruptured ectopic pregnancy [19].

According to laboratory investigations, the current study revealed significantly higher βhCG levels and lower Hblevels in the surgical group compared to other groups. This agreed with Baggio et al.(2021), who revealed that surgical treatment was performed in case of high stable or increasing βhCG values or if previous treatments failed [14].

According to pregnancy outcome, the current study showed that the incidence of clinical pregnancy was highest in the expectant group (72.73%), followed by medical group (50%), then the surgical group (34.57%). On the other hand, the incidence of infertility was the highest in the surgical group (65.43%), followed by the medical group (50%), then the expectant group (27.27%).In concordance with the current study,Baggio et al.(2021) assessed the outcome after surgical, medical, and expectant management for 228 women with tubal ectopic pregnancy. Theyreported that the expectant treatment resulted in the highest rate of clinical pregnancy (65.3%), followed by the medical group (55.3%) and then the surgical group (39.5%) with statistical significance[14].Also, Shen et al.(2022) investigated the outcome of different treatments of tubal ectopic pregnancy expectant management, methotrexate, and laparoscopic surgery and revealed that the surgery group had the lowest rate of intrauterine pregnancy [20].Again,Török et al. 2023 retrospectively assessed the outcome of 312 patients with tubal ectopic pregnancy. They foundthat the patients managed expectantly and patients treated with salpingostomy had significantly higher rates of clinical pregnancy than patients treated with salpingectomy [21].Moreover, a systematic review and meta-analysis by Hao et al.(2023) included 20 articles to compare the effects of different treatment methods for tubal EP on natural pregnancy outcomes and revealed that for hemodynamically stable tubal ectopic pregnancy patients, methotrexate medical treatment has advantages over surgery, particularly salpingectomy, in improving natural pregnancy outcomes [22].

According to hysterosalpingography(HSG) in infertility investigations, the current study showed that tubal complications were significantly increased in the surgical group in comparison to other groups. This could be explained by the fact that surgery increases the risk of infection and postoperative adhesions [22]. A previous study by Helmy et al. (2022) stated that the rate of operative complications was higher in salpingectomy rather than in salpingotomy (34.9% and 23.4%, respectively) [23]. On the other hand, Machado et al.(2019) reported a low incidence of complications in post-surgical treatment of tubal ectopic pregnancy [24]. This could be attributed to different surgical protocols, as the cases in their study were managed laparoscopically only.The advantages of laparoscopy over laparotomy are more rapid access to the abdomen, shorter surgery, less blood loss, less extensive postoperative adhesions, faster recovery, and lower costs of hospitalization and rehabilitation [25].Moreover, Khatlani et al.(2016) showed that laparoscopic treatment of EP offers major benefits superior to laparotomy in terms of less blood loss, less need for blood transfusion, less need for postoperative analgesia, and a shorter duration of hospital stay [26].

Strengths and limitations: The main limitation is the retrospective study design, which introduces potential confounders and restricts statistical analysis by not randomly assigning patients to different treatments. The

small sample size is another restriction that could affect the results.

CONCLUSION

Expectant, medical, and surgical modalities were safe and effective methods in the treatment of tubal ectopic pregnancy.Expectant treatment was associated with the best reproductive outcome, followed by medical treatment, while surgical treatment had the lowest outcome with an increased risk of tubal complications.

DECLARATIONS

Declaration of interest

The authors declare that they have no competing interests.

Funding

There is no specific grant from any funding agency.

Informed consent

All participants gave their consent after being informed of the study's objective and design, and they were given the option to leave the study at any time.

Consent for publication

Not Applicable.

Availability of data and materials

The datasets used and/or analyzed during the current study available from the corresponding author on reasonable request.

Ethical approval

The Research Ethics Committee of the Faculty of Medicine approved the study. All methods were carried out per relevant guidelines and regulations.

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Table 1: Demographic data of the studied groups.

	Surgicalgroup N=81	**Medical group N=34**	**Expectant group N=44**	**p-value**
Age (years)	36.84 ± 5.96	38.32 ± 6.12	36.68 ± 5.97	0.413
BMI (kg/m2)	24.58 ± 3.19	24.51 ± 2.3	24.16 ± 3.01	0.749
Parity				
- Nullipara	43 (53.09%)	11 (32.35%)	19 (43.18%)	0.054
- No living birth	20 (24.69%)	11 (32.35%)	6 (13.64%)	
- Have living birth	18 (22.22%)	12 (35.29%)	19 (43.18%)	
Smoking	12 (14.81%)	6 (17.65%)	1 (2.27%)	0.061
GA (weeks)	6.68 ± 1.66	6.26 ± 1.26	6.02 ± 1.68	0.076

Table 2: Clinical data of the studied groups at the time of admission for ectopic pregnancy

	Surgicalgroup N=81	**Medical group N=34**	**Expectant group N=44**	**p-value**
Abdominopelvic pain	49 (60.49%)	23 (67.65%)	23 (52.27%)	0.382
Vaginal bleeding	50 (61.73%)	24 (70.59%)	25 (56.82%)	0.457
Ultrasound sign				
- Blob or bagel sign	59 (72.84%)	30 (88.24%)	30 (68.18%)	0.058
- Hemoperitoneum	12 (14.81%)	2 (5.88%)	3 (6.82%)	
- None	10 (12.35%)	2 (5.88%)	11 (25.00%)	
Hb (g/dL)	12.07 ± 1.31	12.94 ± 0.76	12.65 ± 0.96	**<0.001**
PLT	259.4 ± 53.77	268.89 ± 54.13	247.6 ± 38.12	0.171
ALT (U/L)	19.49 ± 5.19	18.43 ± 5.21	19.74 ± 5.19	0.506
βhCG (UI/L)	6217.65 ± 5438.75	934.59 ± 401.56	749.93 ± 554.44	**<0.001**

Table 3: Pregnancy and fertility outcomes of the studied groups.

	Surgicalgroup N=81	**Medical group N=34**	**Expectant group N=44**	**p-value**
Clinical pregnancy	28 (34.57%)	17 (50.00%)	32 (72.73%)	**<0.001**
Live birth	25/28 (89.29%)	12/17 (70.59%)	23/32 (71.88%)	0.191
Miscarriage	3/28 (10.71%)	5/17 (29.41%)	9/32 (28.13%)	0.191
Ectopic pregnancy	0 (0%)	0 (0%)	0 (0%)	NA
Infertility	53 (65.43%)	17 (50.00%)	12 (27.27%)	**<0.001**
High FSH	19/53 (35.85%)	10/17 (58.82%)	7/12 (58.33%)	0.139
High LH	21/53 (39.62%)	9/17 (52.94%)	7/12 (58.33%)	0.384
High E2	18/53 (33.96%)	7/17 (41.18%)	7/12 (58.33%)	0.289
Low progesterone	20/53 (37.74%)	8/17 (47.06%)	7/12 (58.33%)	0.394
HSG				
- Tubal damage	25/53 (47.17%)	3/17 (17.65%)	3/12 (25.00%)	0.212
- Peritubal adhesions	7/53 (13.21%)	3/17 (17.65%)	2/12 (16.67%)	
- Normal	21/53 (39.62%)	11/17 (64.71%)	7/12 (58.33%)	