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Management of nontubal ectopic pregnancies-single center experience

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ABSTRACT

Aims: Ectopic pregnancies can be defined as pregnancies in which the growing blastocyst implants outside the endometrial cavity. However, it is assumed that 0.5-1% of all pregnancies are ectopic pregnancies. The most common extrauterine implantation site is the fallopian tube. Non-tubal pregnancies (NTG Non-tubal pregnancies) account for less than 5% of all ectopic pregnancies but cause 8 times higher maternal mortality than tubal pregnancies. The study aimed to determine the frequency of nontubal ectopic pregnancies in a tertiary care unit in Turkey and the differences that may differentiate patients from tubal ectopic pregnancies.

Methods: The purpose of this retrospective study was to analyze and describe the treatments of patients who were hospitalized for ectopic pregnancy in the Gynecology and Obstetrics Clinic of Mengücekgazi Training and Research Hospital from May 2014 to May 2024. Obstetric/gynecologic history, risk factors for previous ectopic non-tubal pregnancy, serum-hCG levels at the moment of diagnosis, ultrasound findings, surgical or medical treatment and treatment outcomes were presented.

Results: In our institutional records, 240 patients received an ectopic pregnancy diagnosis. and n=23 nontubal ectopic pregnancies were identified. Cervical pregnancy (CP) (n=2), interstitial pregnancy (IP) (n=2), cesarean scar pregnancy (ScP) (n=10), ovarian pregnancy (OvP) (n=9) were detected.

Conclusion: It emerges from our sample that NT-EP needs to be diagnosed quickly. This can assist in the conservative use of a medical or minimally invasive method. The significant advance in imaging technologies allows for a faster diagnosis, allowing the patient to be transferred to a referred center from where the best procedures can be selected, reducing the potential impact of surgery on the patient's fertility.

Keywords: Ectopic pregnancy, cervical pregnancy, scar pregnancy, interstitial pregnancy, ovarian pregnancy

INTRODUCTION

Ectopic pregnancies can be defined as pregnancies in which the growing blastocyst implants outside the endometrial cavity.[1] Since their occurrence varies among various communities and research, it is impossible to pinpoint their incidence with precision. Nonetheless, 0.5–1% of all pregnancies are thought to be ectopic gestations.[2] The fallopian tube is the most often used location for extrauterine implantation.[3] Just under five percent of all ectopic pregnancies are non-tubal pregnancies (NTG Non-tubal Pregnancies) but cause maternal mortality 8 times higher than tubal pregnancies.[4]

The most typical clinical sign of an ectopic pregnancy is discomfort in the abdomen accompanied by vaginal bleeding in the first trimester.[5] A retrospective study revealed that 376 (18%) of the 2026 pregnant patients who came to the emergency room complaining of stomach pain and vaginal bleeding in the first trimester were indeed pregnant with an ectopic pregnancy. Among these 376 patients, 76% reported vaginal bleeding and 66% reported abdominal pain.[6] The usual time for ectopic pregnancy symptoms to manifest is six to eight weeks following the previous regular menstrual cycle. The discomforts of normal pregnancy (e.g. nausea, breast tenderness, frequent urination) are sometimes present. Though progesterone, estradiol, and human chorionic gonadotropin (HCG) levels may be lower in ectopic pregnancy patients than in normal pregnant patients, early pregnancy symptoms may be less common in these individuals.[7]

The main reason why ectopic pregnancy occurs is the disruption of their normal tubal anatomy due to factors such as infection, by surgery, from congenital anomalies or neoplasms. Anatomical disruption may be preceded by functional

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disturbance due to damaged ciliary activity. The higher risk is associated with a history of previous ectopic pregnancy or tubal surgery. In addition, periconceptional smoking, vaginal douching and endometriosis are also related to an increased risk of ectopic pregnancy.[1]

The fallopian tube is the site of 96% of ectopic pregnancies. In a series of 1800 surgically treated patients, the distribution of sites was ampullary (70%), isthmic (12%), fimbrial (11.1%), ovarian (3.2%), interstitial (2.4%) and abdominal (1.3%).[3] Non-tubal pregnancies include interstitial, rudimentary horn, angular, abdominal, cesarean scar, ovarian and heterotopic pregnancies. The proximal section implanted in the uterine muscle is the interstitial portion of the Fallopian tube. A pregnancy located in this area is called an interstitial pregnancy. Roughly 1% to 3% of all ectopic pregnancies are these uncommon pregnancies.[8] Rudimentary horn pregnancy is an intrauterine pregnancy located in the rudimentary uterine horn of the unicornuate uterus. In the uterine cavity, an angular pregnancy implants medially to the uterotubal junction at the lateral angle, in close proximity to the proximal ostium of the fallopian tube. An angular pregnancy is situated medially to the round ligament, unlike interstitial pregnancy.[8] An abdominal pregnancy is an uncommon kind of ectopic pregnancy where the pregnancy implants itself in the peritoneal cavity, external to the fallopian tubes, ovaries, broad ligament, and cervix. Cervical pregnancy refers to a specific kind of ectopic pregnancy when the trophoblast inserts itself into the cervical tissue surrounding the endocervical canal. Caesarean scar pregnancy is a pregnancy within or on the scar of a previous caesarean section. Pregnancies implanted on or within myomectomy scars (also called intramural pregnancy) can also occur.[9]

Primary diagnostic test for women suspected of having an ectopic pregnancy is serum ß-hCG measurement.[10] For patients with a baseline hCG level <10,000 mIU/mL, the actual expected rate of increase within 48 hours depends on the baseline hCG level; the projected growth rate is 49 percent for a baseline hCG level <1500 mIU/mL, 40 percent for a baseline hCG level 1500 to 3000 mIU/mL and 33 percent for a baseline hCG level >3000 to <10,000 mIU/mL. An increase of less than these values raises suspicion of ectopic pregnancy.[11] When the ß-HCG level is above 1500 IU/L, the absence of an intrauterine gestational sac on ultrasonography, douglas fluid, coagulum and adnexal mass suggest ectopic pregnancy.

Ultrasound is more reliable for intrauterine pregnancy confirmation because the incidence of heterotopic pregnancy is 1/7000.[12] Color Doppler can show an ectopic pregnancy as a ring-like formation. Color Doppler could offer vital information when other ultrasound data lead to a diagnostic conundrum or unclearty.[13]

Treatments for ectopic pregnancy include follow-up, medical therapy (methotrexate MTX) and surgery. Preoperative MTX treatment is now widely used in early diagnosed non-ruptured patient groups and has the advantages of less tubal damage, low cost, and less effect on subsequent conception.[14] MTX application can be performed in pregnancies without fetal heartbeat, ß-HCG less than 5000 mlU/ml, and ectopic mass diameter less than 3 cm on ultrasound.[15] In patients with advanced gestational week, adnexal mass larger than 3 cm, and unstable hemodynamics, the treatment is surgery. Salpingectomy, cornual excision, salpingooferectomy, hysterectomy are among these methods.[16]

Even though non-tubal ectopic pregnancies represent only %5 of all ectopic pregnancies, they are responsible for approximately %20 of ectopic pregnancy-related deaths.[10] New research suggests that we are not as successful in diagnosing and treating non-tubal ectopic pregnancies as tubal ectopic pregnancies.[17] Diagnosis and management of non-tubal ectopic pregnancies is clinically challenging and there are alternative treatment options that traditionally involve major surgical procedures affecting future fertility.[18]

This research aims to assess the frequency of non-tubal ectopic pregnancies in a tertiary care facility in Turkey and the features that may separate patients from tubal ectopic pregnancies.

METHODS

The study was set up with the permission of Erzincan Binali Yıldırım University clinical research ethics committee (Date: 04.07.2024, Decision No: 369119).

The study aimed to retrospectively review the data of the patients who were hospitalized in the department of obstetrics and gynecology of Mengücekgazi Training and Research Hospital between May 2014 and May 2024 due of ectopic pregnancy and who were proven to have a non-tubal location and to present the treatments used in detail. Permission to publish was obtained in accordance with the 1964 Declaration of Helsinki and its subsequent amendments or similar ethical standards. Obstetric/gynecologic history, previous risk factors for ectopic non-tubal pregnancy, serum-hCG levels at diagnosis, ultrasound findings, surgical or medical treatment and treatment outcomes are presented.

Interstitial pregnancy was diagnosed by transvaginal ultrasonography according to the criteria defined by Timor-Tritsch. Criteria for a diagnosis of caesarean scar pregnancy include the absence of fetal fragments in the uterus or cervix, visualization of a gestational sac covering the scar area or completely within the myometrium, and failure to visualize the myometrium layer between the gestational sac and the bladder on the anterior wall. Ovarian pregnancy was diagnosed during laparoscopic surgery in patients with high serum Hcg levels and hemoperitoneum.

RESULTS

Between the specified dates, a total of 240 patients were diagnosed with ectopic pregnancy in the records of our institution and n=23 nontubal ectopic pregnancies were detected. Table 1 summarizes the clinical features and history of the study group members. In hemodynamically stable individuals, serum hcg levels and transvaginal ultrasonic results formed the diagnosis. Emergency surgical procedures were performed in n=6 cases due to hemoperitpneumonia. We classified n=23 nontubal ectopic pregnancies into four categories based on implantation place: cervical pregnancy (CP) (n=2), interstitial pregnancy (IP) (n=2), cesarean scar pregnancy (ScP) (n=10), ovarian pregnancy (OvP) (n=9). (figure 1) At diagnosis, the research cohort's average age was 33.18 years. Although serum beta hcg levels were significantly higher in cesarean scar pregnancies ($p<0.005$), the mean Hcg level at diagnosis was 1896. Serum hcg levels according to treatment groups are shown in table 2.

Table 1. Demographic characteristics, obstetric and gynecological history and ectopic pregnancy risk factors in the study population.

Ectopic pregnancy	Age	Obstetric history	Gravidity (g) Parity (p) Viabil (v)	Treatment
İnterstisyel pregnancy				
Case 1	35	Nsvl	G1p1v1	Laparotomy
Case 2	29	Nsvl	G1p1v1	Laparoscopy
Ovarian pregnacy				
Case 1	36		G1	Laparoscopy
Case 2	31	1cs, 1 nsvl	G4p2v2a1	Medical
Case 3	31		G1	Laparoscopy
Case 4	28	1cs	G2p1v1	Laparotomy
Case 5	35	2cs	G3p2v2	Laparotmy
Case 6	37	2cs	G7p4v4a2	Laparoscopy
Case 7	24		G1	Laparoscopy
Case 8	36		G1	Medical
Case 9	35	1cs	G2p1v1	Laparotomy
Cervikal pregnancy				
Case 1	29		G2p0v0a1	Laparotomy
Case 2	24		G1	Medical
Scar pregnancy				
Case 1	39	2cs	G4p2v2a1	Medical
Case 2	33	1cs	G2p1v1	Medical
Case 3	43	1cs	G3p1v1a1	Medical
Case 4	29	1cs	G3p1v1ect1	Medical
Case 5	41	3cs	G4p3v3	Medical
Case 6	28	2cs	G5p2v3a1ect1	Medical
Case 7	40	1cs	G2p1v1	Medical
Case 8	32	2cs	G3p2v2	Medical
Case 9	33	2cs	G3p2v2	Medical

Cs: caserean section, g: gravidity, p: parity, v: viabil, a: abortus, ect:ektopic pregnancy, nsvl:normal spontanous vaginal labour

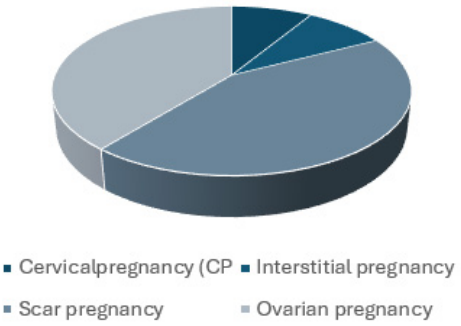

Figure 1. Non-tubal ectopic distribution by location in our center: Cervical pregnancy (CP); Interstitial pregnancy (IP); Scar pregnancy (ScP); Ovarian pregnancy (OvP)

Among the primary treatments, n=12 women were managed conservatively with medial treatment only. Surgical treatment was required in n=2 patients due to failure of initial medical treatment. In n=10 patients who were hemodynamically stable, curettage was performed following medical treatment.

Interstitial pregnancy was diagnosed by transvaginal ultrasonography according to Timor-Tritsch criteria. Cornual resection was performed for interstitial pregnancies detected in the whole study group with n=2 surgeries.

The norms for the diagnosis of caesarean scar pregnancy included the absence of fetal fragments in the uterus or cervix, visualization of a gestational sac covering the scar area or completely within the myometrium, and failure to visualize the myometrium layer between the gestational sac and the bladder on the anterior wall. For cesarean scar pregnancies n=10, vacuum curettage was performed following im MTX treatment as in cervical pregnancies.

Table 2. Non-tubal ectopic pregnancies: a single center experience. For each subtype of NT-EP are reported clinical presentation, gestational age, basal-hCG levels, ultrasound findings, treatment details(medical or surgical or medical combined with surgical)and outcome

Ectopic Pregnancy	Outset	Beta-hcg levels before treatment	Ultrasonography	Outcome
İnterstisyel pregnancy				
Case 1	Asymptomatic	2356	7 cm hematoma in the douglas	Laparotomy
Case 2	Asymptomatic	2502	GS 28mm; right horn	Laparoscopy
Ovarian pregnacy				
Case 1	Hemoperitoneum	2097	GS 29mm on the right ovary	Laparoscopy
Case 2	Asymptomatic	100	Gs 30 mm on teh left ovary	Medical
Case 3	Hemoperitoneum	5460	Ectopic on the left ovary and 2cm hematoma in the douglas	Laparoscopy
Case 4	Acute abdomen	890	5cm hematoma	Laparotomy
Case 5	Brownish vaginal discharge and mild pelvic pain	6900	Normally located ria in the cavity, left ovarian pregnancy	Laparotomy
Case 6	Hemoperitoneum	134	Gs 38 mm on the right ovary	Laparoscopy
Case 7	Mild pelvic pain	657	Ectopic on the left ovary and 3,5 cm hematoma in the douglas	Laparoscopy
Case 8	Asymptomatic	299	Ectopic on the left ovary	Medical
Case 9	Mild pelvic pain	331	Ectopic on the left ovary	Laparotomy
cervikal pregnancy				
Case 1	Vaginal bleeding and acute abdomen	---	5cm hematoma in the douglas	Laparotomy
Case 2	Vaginal bleeding	331	3cm ectopic focus at the level of the cervix	Medical
Scar pregnancy				
Case 1	Asymptomatic	70000	Crl 9 mm fhb +	Medical
Case 2	Asymptomatic	5920	6w scar pregnancy	Medical
Case 3	Asymptomatic	37460	7w fhb + scar pregnancy	Medical
Case 4	Asymptomatic	2282	10 mm gs on the scar	Medical
Case 5	Asymptomatic	31220	6w scar pregnancy	Medical
Case 6	Asymptomatic	13836	10mm gs	Medical
Case 7	Asymptomatic	7817	20 mm gs on scar	Medical
Case 8	Asymptomatic	2115	5w gs	Medical
Case 9	Asymptomatic	11641	7w fhb+	Medical

Gs: gestasyonel sac, CRL: Crown rump length, FHB: fetal heart beat

Ovarian pregnancy was diagnosed during laparoscopic surgery in patients with high serum Hcg levels and hemoperitoneum. In the ovarian pregnancies detected in the study group (n=9), laparoscopic approach was used in 3 patients, laparotomic approach in 3 patients, (oophorectomy in 1 patient, partial resection in 2 patients) and systemic methotrexate treatment in 3 patients.

Fertility preserving treatment was applied in all cervical pregnancies. MTX's one dosage im 50 mg/m2 was administered followed by ultrasonography-guided vacuum curettage.

DISCUSSION

Non-tubal ectopic pregnancies represent a considerable challenge to gynecologists because to the rarity of the condition and the current absence of recommendations for its care. With the widespread use and application of ultrasonography, it has become possible to locate the gestational sac earlier, leading to earlier diagnosis and choice of treatment without complications of ectopic pregnancies. Management of each patient should be personalized depending on clinical symptoms, viability of the pregnancy, gestational week, serum Hcg level and the woman's wishes. Specialization in the care of NT-EPs allows for faster diagnosis, giving a better chance for successful medical treatment or minimal invasive surgery including local injection of one of many agents such as MTX, potassium chloride, hyperosmolar glucose, etoposide, curettage, hysteroscopy or laparoscopy, and in the majority of instances a fertility-sparing approach becomes feasible. We describe data from a 10 year assessments of all diagnosed NT-EPs and their management thereafter. This series contributes to the growing evidence that sonography-guided curettage combined with systemic MTX is a safe and effective first-line treatment for women with high-risk NT-EP who wish to preserve future fertility.

In generally, the main treatment for interstitial and ovarian pregnancies is surgery, while systemic or local methotrexate is preferred for cesarean scar pregnancy and cervical pregnancies. In this method, it is feasible to treat patients with sufficient hcg reduction, although surgical treatments should be added in situations of excessive bleeding and treatment failure.

The status of the contralateral fallopian tube and the desire for future fertility should be considered when choosing the surgical approach. In recent years, laparoscopy has been considered a minimally invasive surgical procedure that may better preserve normal ovarian tissue and reduce pelvic adhesions.[19]

Cervical Pregnancy

The frequency of CP has been observed to be 1 in 1000-18,000 pregnancies. Because of the high hemorrhage risk of CP, it has been treated with hysterectomy in the past and resulted in loss of fertility.[20] The ease of diagnosis using the sonographic diagnostic criteria indicated by Jurkovic et al.[13] has facilitated the treatment options and especially the preservation of fertility with a conservative approach. For CP, the hysteroscopic approach is also recommended in patients with serum HCG levels greater than 5000 UI/mL, either alone or in conjunction with systemic MTX .[21] It has been shown in the study by Fowler et al.[22] that a single treatment option is not sufficient in cervical pregnancies and more than half of the patients require more than one intervention. Tremmel et al.[23] showed that treatment of cervical pregnancy with methotrexate only in 87.5% of cases was achieved. In our study, all cervical pregnancies underwent a two-stage treatment consisting of systemic methotrexate therapy followed by vacuum curettage.

Interstitial Pregnancy

IP is a very rare form of EP that causes uterine rupture, typically in advanced gestational age. It is a life-threatening illness with a 6-7 times greater fatality rate. Quantitative HCG levels and TVUS are essential to safely manage this condition. Empty uterine cavity, a separated chorionic sac at Least 1 cm from the side of the uterine cavity, lack of myometrium surrounding the gestational sac (<5 mm) and an interstitial line are diagnostic for IP.[24] Early diagnosis with TVUS leads to conservative treatment with methotrexate; surgical treatment may be required later in pregnancy. Despite studies suggesting that systemic methotrexate treatment is more successful than surgery in interstitial pregnancies, surgery was preferred in 2 cases of interstitial pregnancy detected in our study.[25] The study by Reis et al.[26] also showed cases requiring surgery due to methotrexate failure. Mao et al.[27] argued that systemic methotrexate was not beneficial and surgery should be preferred especially in cases of interstitial pregnancy larger than 1.5 cm.

Scar Pregnancy

The prevalence is predicted to grow in the next years owing to declining vaginal delivery rates and increasing cesarean section rates, and there are studies showing that the probability increases when the number of cesarean sections exceeds 2. Diagnosis is relatively easy in early pregnancy, but as the gestation continues, the differentiation between ScP, CP and low intrauterine pregnancy is more difficult. Several management options are available to treat CP, but it is unclear which is the best choice. Operative procedures alone or in combination with medical management have high success rates, but more surgical skill is required. Medical therapy is not regarded the treatment of choice for ScP, perhaps because the resorption and effectiveness of MTX is hampered by the fibrous tissue surrounding the GS, which is placed at a unique position inside the uterine cavity. MTX appears to be more effective when combined with curettage or hysteroscopy.[28] A recent intervention review concluded that it is uncertain if there is a difference between vacuum curettage under hysteroscopy and vacuum curettage under ultrasonography in terms of treatment success rates, complications, side effects or time to normalization of HCG (very low quality evidence).[29] In some studies, expectant treatment is not recommended in cesarean scar pregnancies, and if possible, operative hysteroscopy is recommended to remove the pregnancy.[30] According to some opinions, laparoscopic or laparatomic surgery in scar pregnancies is considered necessary for complete excision of the pregnancy material and restoration of the scar line.[23] In the study conducted by Altay et al.,[31] it was suggested that surgery should not be performed for cesarean scar pregnancies and vacuum curettage was performed under ultrasound guidance instead of using a sharp curette. However, other studies have shown that the success of vacuum curettage decreases in the presence of concomitant pelvic inflammatory disease, enlargement of the gestational sac and fetal heartbeat.[29] In our study, we treated all scar pregnancies with systemic methotrexate, and 9 patients underwent vacuum curettage for complete removal of chorionic tissue.

Ovarian Pregnancy

OvP is an uncommon occurrence, with frequency estimates ranging from 1 in 2100 pregnancies to 1 in 7000 pregnancies or 3% of all EPs. Ultrasonographic findings for OvP include a large echogenic ring, yolk sac or fetal fragments that are more echogenic on the ovary compared to the ovarian tissue. Surgical criteria as defined by Spiegelberg: fallopian tubes are intact and separate from the ovary, the GS in the ovary is attached to the uterus via the utero-ovarian ligament, and placental tissue appears mixed with the ovarian cortex. Surgical treatment is the most common approach and oophorectomy or wedge resection of the ovary is generally necessary.[32] In ovarian pregnancies, some studies suggest that surgery is more successful than systemic methotrexate treatment.[25] When surgery is required to preserve fertility, wedge resection rather than oophorectomy seems to be more valuable and there are studies including subsequent pregnancy outcomes.[33] The study of Reis et al.[26] showed that surgery was performed in all ovarian pregnancies detected. In our study, 5 patients were treated with partial resection and 3 with systemic methotrexate to preserve ovarian reserve.

Limitations

The main limitations of this research are the limited sample sizes owing to the rarity of the condition and the variation in therapies on the basis of clinical particular characteristics and in order to individualize the appropriate care.

CONCLUSION

It emerges from our sample that NT-EP needs to be diagnosed quickly. This may aid a conservative management with a medicinal or least invasive approach. The significant advance in imaging technologies allows for a more rapid diagnosis, allowing the patient to be transferred to a reference center where the best procedures can be selected, reducing the impact of surgery on the patient's fertility. For NT-EP management, a reference center with surgeons well trained in minimally invasive surgery with specific skills that reduce the risks of life-threatening bleeding and hysterectomy and preserve future fertility is essential.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was set up with the permission of Erzincan Binali Yıldırım University clinical research ethics committee (Date: 04.07.2024, Decision No: 369119).

Informed Consent

Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

The authors declared that this study has received no financial support.

Author Contributions

Conceptualization: Betül Kalkan YILMAZ
Data curation: Betül Kalkan YILMAZ
Formal Analysis: Betül Kalkan YILMAZ
Funding acquisition: Betül Kalkan YILMAZ, Okay ALPTEKİN
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Supervision: Okay ALPTEKİN
Validation: Betül Kalkan YILMAZ, Okay ALPTEKİN
Visualization: Betül Kalkan YILMAZ
Writing -original draft: Betül Kalkan YILMAZ, Okay ALPTEKİN
Writing-review& editing: Betül Kalkan YILMAZ, Okay ALPTEKİN

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In 2012, I graduated from Erciyes University Faculty of Medicine. Between 2012-2017, I received specialty training at the doctor zekai tahir burak women's health training and research hospital. Afterwards, I worked as a specialist doctor in Erzincan. Since 2021, I have been working as a doctor faculty member in the department of gynecology and obstetrics at Erzincan Binali Yıldırım University.