







Original Article

A retrospective review of non-tubal ectopic pregnancies in a tertiary unit in Turkey

Türkiye’de bulunan tersiyer bir merkezdeki non-tubal ektopik gebeliklerin retrospektif değerlendirilmesi

Ömer Lütfi Tapisiz*^{1,2} , Sabri Cavkaytar^{1,3} , Hakan Aytan^{1,4} , Görkem Tuncay^{1,5} , Turgut Var^{1,6} , Hüseyin Yeşilyurt^{1,7} 

¹Kadın Hastalıkları ve Doğum Bölümü, Dr. Zekai Tahir Burak Kadın Sağlığı Eğitim ve Araştırma Hastanesi, Ankara

²Sağlık Bilimleri Üniversitesi, Etlik Zübeyde Hanım Kadın Hastalıkları Eğitim ve Araştırma Hastanesi, Ankara

³Bahçeci Sağlık Grubu, Umut Tüp Bebek Merkezi, İstanbul

⁴Kadın Hastalıkları ve Doğum AD, Mersin Üniversitesi Tıp Fakültesi, Mersin

⁵Kadın Hastalıkları ve Doğum AD, Üreme ve Reprodüktif Endokrinoloji Bilim Dalı, Tüp Bebek Merkezi, İnönü Üniversitesi Tıp Fakültesi, Malatya

⁶Kadın Hastalıkları ve Doğum AD, İstinye Üniversitesi Tıp Fakültesi, İstanbul

⁷Kadın Hastalıkları ve Doğum Bölümü, Ankara Şehir Hastanesi, Ankara

Abstract

Aim: Although non-tubal ectopic pregnancies represent 5% or less of all ectopic pregnancies, they account for approximately 20% of the mortalities attributed to ectopic gestations. Diagnosis and management of non-tubal ectopic pregnancies are clinically challenging and the treatment alternatives have traditionally included major surgical procedures, which affect future fertility. The aim of this study was to establish the incidence of non-tubal ectopic pregnancies in a tertiary unit in Turkey and to elucidate any differences that may discriminate patients from those with tubal ectopic pregnancy.

Material and Method: This was a retrospective review of cases; comparing patient features and special investigation in patients with tubal and non-tubal ectopic pregnancies. The records of the 197 histologically confirmed ectopic pregnancies and two cervical and one term abdominal gestations were analyzed.

Results: Eleven of 200 (5.5%) ectopic pregnancies were found to be non-tubal and the remaining 189 were tubal pregnancies. There was no significant difference between non-tubal and tubal ectopic pregnancies except for vaginal bleeding and rectal pain symptoms. Vaginal bleeding and rectal pain were observed significantly more frequent in the non-tubal group ($p=0.004$ and 0.016 , respectively).

Conclusion: Non-tubal location may be considered in patients with the suspicion of ectopic pregnancy especially if there are vaginal bleeding and rectal pain.

Key words: Non-tubal; ectopic pregnancy; vaginal bleeding; rectal pain.

Öz

Amaç: Non-tubal ektojik gebelikler tüm ektojik gebeliklerin %5 veya daha azını oluştursa da ektojik gebeliğe bağlı ölümlerin yaklaşık %20'sinden sorumludurlar. Non-tubal ektojik gebeliklerin klinik olarak tanı ve tedavisi zordur ve tedavi seçenekleri geleneksel olarak gelecekteki fertilitiyi etkileyecek temel cerrahi prosedürleri içermektedir. Bu çalışmanın amacı, Türkiye'de bulunan üçüncü basamak bir merkezdeki non-tubal ektojik gebeliklerin insidansını tespit etmek ve bu hastaları tubal ektojik gebeliklerden ayırt edebilmemizi sağlayacak olası farklılıkları ortaya koymaktır.

Gereç ve Yöntem: Bu çalışmada olgular retrospektif olarak taranarak tubal ve non-tubal ektojik gebeliklerdeki hasta özellikleri ve özel incelemeleri kıyaslanmıştır. Histolojik olarak doğrulanmış 197 ektojik gebelik, iki servikal ve bir term abdominal gebelik olgusunun kayıtları analiz edilmiştir.

Bulgular: İkiyüz ektojik gebelik olgusunun 11'i (%5.5) non-tubal, 189'u tubal ektojik gebelik şeklinde tespit edilmiştir. Non-tubal ve tubal ektojik gebelikler arasında vajinal kanama ve rektal ağrı semptomları dışında anlamlı bir fark bulunmamıştır. Vajinal kanama ve rektal ağrı non-tubal grubunda anlamlı şekilde fazla görülmüştür (sırasıyla, $p=0.004$ ve $p=0.016$).

Sonuç: Ektojik gebelik şüphesi olan bir hastada özellikle vajinal kanama ve rektal ağrı mevcutsa, non-tubal lokalizasyonun olabileceği akılda tutulmalıdır.

Anahtar kelimeler: Non-tubal; ektojik gebelik; vajinal kanama; rektal ağrı.

Introduction

Ectopic pregnancy is any pregnancy in which the fertilized ovum implants outside the intrauterine cavity (1,2). Ectopic pregnancy accounts for 2% of all pregnancies, 3-10% of ectopic pregnancies are non-tubal (3-5), and constitutes 4-9% of all maternal deaths in developed countries (6). The increased use of assisted reproduction techniques has been accompanied by an increase in ectopic pregnancies of unusual locations (7). Non-tubal implantations most frequently occur in the ovaries, cervix, abdominal cavity, uterine interstitium, rudimentary uterine horn, and between the leaves of the broad ligament. The literature also includes reports of the vaginal, cesarean scar and heterotopic pregnancies (8, 9).

Although non-tubal ectopic pregnancies represent 5% or less of all ectopic pregnancies, they account for approximately 20% of the mortalities attributed to ectopic gestations (10). Available reports indicate that we may not have been equally successful in the diagnosis and management of non-tubal ectopic pregnancies such as tubal ectopic pregnancies (11). Diagnosis and management of non-tubal ectopic pregnancies are clinically challenging, and the treatment alternatives have traditionally included major surgical procedures, which affect future fertility (8).

The aim of this work was to establish the incidence of non-tubal

ectopic pregnancies in a tertiary unit in Turkey and elucidate any differences that may discriminate patients from those with tubal ectopic pregnancy.

Material and Method

This study was based on hospital records from the Department of Obstetrics and Gynecology at Dr. Zekai Tahir Burak Women's Health Education and Research Hospital, Ankara, Turkey. We reviewed the histologically confirmed ectopic pregnancy case notes retrospectively for a 3-year period and patients were excluded in the absence of histological confirmation of ectopic pregnancy. The tubal and non-tubal groups were compared in terms of demographic features, historical predisposing factors, presenting symptoms and signs, β -HCG levels, characteristics of hemoglobin concentration and clinical findings. This study protocol was approved by the ethical committee of Dr. Zekai Tahir Burak Women's Health Education and Research Hospital, Ankara, Turkey. Data were stored and analyzed by using SPSS (Statistical Package for Social Science; release 10.0) for Windows. Variables were tested with the Kolmogorov-Smirnov test with Lilliefors's significance correction for normal distribution. Normally distributed data were expressed as means \pm standard deviation and data that was non-normally distributed were expressed as the median and interquartile range (IQR) for descriptive



statistics. To compare the groups; Student’s t-test was used for normally distributed data, while the Mann-Whitney U test for non-normally distributed data and X² test was used for the categorical data (Fisher’s exact test was used where the frequencies were less than 5 in > 20% of cells). The level of statistical significance was set at 0.05.

Results

A total of 223 patient records were identified and twenty-three patients were excluded from the study because of incomplete data and the lack of histological confirmation. The records of the 197 cases of histologically confirmed ectopic pregnancies and two cervical and one term abdominal gestations were analyzed retrospectively. Eleven of 200 (5.5%) ectopic

pregnancies were found to be non-tubal and the remaining 189 were tubal pregnancies. The non-tubal pregnancies consisted of 4 (2%) ovarian, 1 (0.5%) abdominal, 2 (1%) cervical, 1 (0.5%) intraligamentary, 2 (1%) cornual and 1 (0.5%) heterotopic pregnancies.

Demographic features, β-HCG levels, characteristics of hemoglobin concentration, historical predisposing factors and presenting symptoms of two groups are shown in **Table 1**. No significant difference was found with respect to these parameters between the groups (p>0.05) except for the vaginal bleeding and rectal pain. The vaginal bleeding and rectal pain symptoms were observed significantly more frequent in the non-tubal group (p= 0.004 and 0.016, respectively).

Table 1. Demographic features, β-HCG levels, characteristics of hemoglobin concentration, historical predisposing factors, and presenting symptoms of two groups

	Non-Tubal Pregnancies (n=11)	Tubal Pregnancies (n=189)	p values
Features			
Age (years)	29.27 ± 5.19	27.88 ± 5.43	0.409 ^a
Gravidity	2 [1-4]	2 [1-3]	0.927 ^b
Parity	1 [0-3]	1 [0-2]	0.216 ^b
Gestational age (weeks)	5.20 ± 2.97 *	5.50 ± 2.2	0.667 ^a
Laboratory results			
β-HCG	1680 [215-4750] *	2345 [605-3240]	0.165 ^b
Anemia (Hb <10.5 gr/dl)	4 (36.4%)	64 (33.9%)	0.549 ^c
History			
Previous ectopic pregnancy	0 (0%)	9 (4.8%)	0.550 ^c
Previous PID	2 (18.2%)	55 (29.1%)	0.347 ^c
Infertility treatment	1 (9.1%)	4 (2.1%)	0.249 ^c
Abdominopelvic surgery	4 (36.4%)	70 (37.1%)	0.617 ^c
IUD in situ	1 (9.1%)	3 (1.6%)	0.204 ^c
Presentation			
Abdominal pain	9 (81.8%)	130 (68.8%)	0.293 ^c
Vaginal bleeding	8 (72.7%)	53 (28%)	0.004^c
Missed period	6 (54.5%)	146 (77.2%)	0.093 ^c
Nausea/Vomiting	1 (9.1%)	21 (11.1%)	0.654 ^c
Syncope	3 (27.3%)	72 (38.09%)	0.353 ^c
Palpitation	3 (27.3%)	30 (15.9%)	0.265 ^c
Rectal pain	3 (27.3%)	8 (4.2%)	0.016^c
Pre-shock	2 (18.2%)	37 (19.6%)	0.634 ^c
Urinary tract symptoms	1 (9.1%)	23 (12.2%)	0.611 ^c

Hb: Hemoglobin concentration, PID: Pelvic inflammatory disease, IUD: Intrauterine device, Values are mean ± S.D, median [interquartile range] or n (%), ^a: Student’s t-test, ^b: Mann-Whitney U test, ^c: Fisher’s exact test were used, P<0.05: statistically significant, * : n=10, term abdominal pregnancy is excluded.

The most common abdominal findings in both groups were abdominal distension (71.7% in the non-tubal group and 63.5% in the tubal group), abdominal tenderness (81.8% in the non-tubal group and 76.2% in the tubal group), and rebound tenderness (54.5% in the non-tubal group and 57.1% in the

tubal group). There was no significant difference between the groups (p>0.05).

Demographic and clinical features, ultrasonographic findings, and the treatment modalities of the 11 non-tubal ectopic pregnancies are shown in **Table 2** in detail.

Table 2. Demographic and clinical features, ultrasonographic findings, and the treatment modalities of the non-tubal ectopic pregnancies

n	Age	GA	Clinical symptoms on admission	Initial USG Findings	Non-tubal location	Treatment
1	20	3	-Abdominal pain -Vaginal bleeding	70x50 mm gestational sac at right adnexa	Right ovarian pregnancy	Laparoscopy
2	25	12	-Abdominal pain -Missed period -Syncope -Nausea/ Vomiting	22 mm left ovarian cystic lesion	Left ovarian pregnancy	MTX followed by laparoscopy
3	36	7	-Abdominal pain -Vaginal bleeding -Missed period	CRL 7 mm, FHR (-), in a 13mm gestational sac at right adnexa	Right cornual pregnancy	Laparotomy
4	30	5	-Abdominal pain -Vaginal bleeding -Missed period -Syncope -Rectal pain	Free fluid accumulation in the abdomen	Right ovarian pregnancy (ruptured)	Laparotomy
5	32	3	-Abdominal pain -Vaginal bleeding -Palpitation -Rectal pain	54x38 mm heterogeneous appearance at right adnexa	Right intraligamentary pregnancy (ruptured)	Laparotomy
6	27	2	-Abdominal pain -Palpitation -Syncope -Pre-shock	42x24 mm hematoma formation in the left adnexa	Left cornual pregnancy (ruptured)	Laparotomy
7	26	3	-Abdominal pain -Vaginal bleeding -Palpitation -Pre-shock	CRL 8 mm, FHR (-), in a 22x17 mm gestational sac at left adnexa	Left ovarian pregnancy (ruptured)	Laparotomy
8	30	4	-Abdominal pain -Vaginal bleeding -Urinary tract symptoms -Rectal pain	CRL 12 mm, FHR (-) intrauterine gestation and 13x8 mm gestational sac at left adnexa	Heterotopic pregnancy (intrauterine and left ovarian pregnancy)	Laparotomy
9	35	7	-Vaginal bleeding -Missed period	CRL 6.8 mm FHR (+) embryo, with a 41x21 mm gestation sac in cervix	Cervical pregnancy	Intraembryonic KCl + MTX administration
10	36	6	-Vaginal bleeding -Missed period	CRL 7,2 mm FHR (+) embryo, with a gestational sac of 22 mm in cervix	Cervical pregnancy	Intraembryonic KCl + MTX and systemic MTX
11	25	38	-Abdominal pain -Missed period -Decrease in fetal activity	38-39 weeks of gestation FHR (+) fetus	Abdominal pregnancy	Laparotomy +Systemic MTX

GA: Gestational age, USG: Ultrasonography, CRL: Crown-rump length, FHR: Fetal heart rate, KCl: Potassium chloride, MTX: Methotrexate.

Discussion

In this study, our primary aim was to establish the incidence of non-tubal ectopic pregnancies, the second aim was to compare the non-tubal ectopic pregnancies with the tubal ones. The incidences of the non-tubal pregnancies were found to be 2% for ovarian, 0.5% for abdominal, 1% for cervical, 0.5% for intraligamentary, 1% for corneal and 0.5% for heterotopic pregnancies in the current study. These ratios were not

consistent with the literature. The incidence for ovarian pregnancies is approximately 3% of all ectopic pregnancies (12); for interstitial pregnancies 2.5% of ectopic pregnancies (12); for cervical pregnancies incidence accounting for less than 1% of all ectopic pregnancies (8, 13); for abdominal pregnancies 1.3% of ectopic pregnancies (12); and for the remaining heterotopic ectopic pregnancies, an incidence of 1/3-4000 pregnancies (14). Since patients were excluded in the absence of histological



confirmation of ectopic pregnancy, our incidences may be over or under estimated. Here, the different ratios might be explained by the study population's different demographic characteristics. Although the small sample size and unequal number of groups were our main limitations, this study included a group of Turkish women admitted to a tertiary hospital for three years which were the strengths of our study. Prevalence of ectopic pregnancies may be different due to many factors including ethnicity, culture, religion, sexual behavior, and contraceptive usage.

In the current study, among the presenting symptoms, the vaginal bleeding and rectal pain symptoms were observed significantly more frequently in the non-tubal group than in the tubal group. Here, a higher incidence of rectal pain and vaginal bleeding in the non-tubal group is probably important. There had been a few reports of ectopic pregnancy presenting as rectal pain (15-17). Most cases were secondary to abdominal ectopic pregnancy, with a few cases due to interstitial ectopic pregnancy (18, 19). The pathogenesis of rectal pain in ectopic pregnancy is not clear but probably involves both trophoblastic villous invasion of the bowel wall and infection (15, 16). In the current study, the rectal pain was frequently observed in non-tubal patients with ruptured ectopic pregnancies which might be due to Douglas pouch irritation. This condition may explain the rectal pain. On the other hand, the higher incidence of vaginal bleeding in non-tubal ectopic pregnancy when compared to tubal may be explained by delayed diagnosis and frequently ruptured condition of non-tubal ectopic pregnancies. Furthermore, we speculate that inadequate space for gestational development in the implanted area may cause more vaginal bleeding, especially in cervical and cornual pregnancies. However, further investigations are needed to clarify this subject.

Ectopic pregnancy is still the most common cause of first-trimester maternal deaths (6). In Turkey, the maternal mortality ratio has decreased to 16.4/100.000 live births in 2010 from 28.5/100.000 live births in 2005 and it has been published that the mortality rate from ectopic pregnancy was 0.9%. (20,21). In our study, there was no maternal death due to ectopic pregnancy. Confidential inquiries into maternal deaths (CEMD) make extensive efforts to identify all maternal deaths and the United Kingdom has the longest history of CEMD, dating back to the 1950s. The eighth report of the CEMD in the United Kingdom has been published in 2011 (22). In that report, there has been a decline in mortality rate from ectopic pregnancies, although the incidence of ectopic pregnancy remained unchanged. The mortality rate from ectopic pregnancy has almost halved from

an estimated 31.2 (95% CI 16.8-57.9) per 100000 estimated ectopic pregnancies for 2003-2005 to 16.9 (95% CI 7.6-37.6) for 2006-2008 ($p=0.23$) (22). This decline in mortality rate may be explained by advances in ultrasound technology and the development of specialized early pregnancy assessment units over recent years has led to an increase in the early diagnosis of ectopic pregnancies. Despite this, patients may still present late in pregnancy and the diagnosis always needs to be suspected in women admitted with a positive pregnancy test and hemorrhagic shock (11). On the other hand, with the suspicion of ectopic pregnancy, the clinician should keep in mind the unusual ultrasonographic features of tubal as well as non-tubal pregnancies (23).

A large body of literature describes associations and risk factors for ectopic pregnancy in the long run (24-26). However, there is no study comparing risk factors and clinical symptoms for ectopic pregnancies in non-tubal locations because of low incidence. To the best of our knowledge, the present study is the first report in the literature that evaluates and compares non-tubal ectopic pregnancies. Based on the current study, it was demonstrated that there was no significant difference exhibited in clinical findings between the non-tubal and tubal ectopic pregnancies, except for vaginal bleeding and rectal pain symptoms. These results may help the clinicians in the diagnosis process. However, our study had some limitations. The first limitation was our small sample size and the unequal number of groups, so it is difficult to suggest changes in clinical practice based on this sample size. The second limitation was our retrospective design and incomplete data for some cases, therefore possibly introducing some degree of bias. But there can be no randomized controlled studies about this topic, but a system including national or international online registration of patients may be valuable in the follow-up.

Conclusion

The incidence of non-tubal ectopic pregnancy was 5.5% (11/200) among ectopic pregnancies and vaginal bleeding, rectal pain symptoms were observed significantly higher in the non-tubal group. These findings may discriminate non-tubal ectopic pregnancies from the tubal ones. But the small number of non-tubal ectopic pregnancies and one center-based retrospective study design were our main limitations and so how these findings will add something to clinical practice remain uncertain. Further studies with larger case series are needed to clarify this subject.

Declaration of Interest

The authors report no conflicts of interest.

References

1. Bakken IJ, Skjeldestad FE. Time trends in ectopic pregnancies in a Norwegian country 1970-2004, a population-based study. *Hum Reprod* 2006; 21:3132-3136.
2. Alalade AO, Smith FJE, Kendall CE, Odejinmi F. Evidence-based management of non-tubal ectopic pregnancies. *J Obstet Gynaecol* 2017; 37:982-991.
3. Fylstra DL. Ectopic pregnancy not within the (distal) fallopian tube: etiology, diagnosis, and treatment. *Am J Obstet Gynecol* 2012; 206:289-299.
4. Parker VL, Srinivas M. Non-tubal ectopic pregnancy. *Arch Gynecol Obstet* 2016; 294:19-27.
5. Ramkrishna J, Kan GR, Reidy KL, Ang WC, Palma-Dias R. Comparison of management regimens following ultrasound diagnosis of nontubal ectopic pregnancies: a retrospective cohort study. *BJOG* 2018; 125:567-575.
6. Khan KS, Wojdyla D, Say L, Gülmezoglu AM, Van Look PF. WHO analysis of causes of maternal death: a systematic review. *Lancet* 2006; 367:1066-1074.
7. Malak M, Tawfeeq T, Holzer H, Tulandi T. 2011. Risk factors for ectopic pregnancy after in vitro fertilization treatment. *J Obstet Gynaecol Can* 2011; 33:617-619.
8. Oliver R, Malik M, Morris J. Management of extra-tubal and rare ectopic pregnancies: case series and review of current literature. *Arch Gynecol Obstet* 2007; 276:125-131.
9. Chang Y, Kay N, Chen YH, Chen HS, Tsai EM. Resectoscopic treatment of ectopic pregnancy in previous cesarean delivery scar defect with vasopressin injection. *Fertil Steril* 2011; 96:e80-2.
10. Dorfman SF, Grimes DA, Cates W Jr, Binkin NJ, Kafrisen ME, O'Reilly KR. Ectopic pregnancy mortality, United States, 1979 to 1980: clinical aspects. *Obstet Gynecol* 1984; 64:386-390.
11. Chetty M, Elson J. Treating non-tubal ectopic pregnancy. *Best Pract Res Clin Obstet Gynaecol* 2009; 23:529-538.
12. Bouyer J, Coste J, Fernandez H, Pouly JL, Job-Spira N. Sites of ectopic pregnancy: a 10-year population-based study of 1800 cases. *Hum Reprod* 2002; 17:3224-3230.
13. Gun M, Mavrogiorgis M. Cervical ectopic pregnancy: a case report and literature review. *Ultrasound Obstet Gynecol* 2002; 19:297-301.
14. Pisarska MD, Carson SA. Incidence and risk factors for ectopic pregnancy. *Clin Obstet Gynecol* 1999; 42:2-8.
15. de Boer CN. Ectopic pregnancy presenting as intermittent rectal bleeding and anemia. A case report. *Int J Gynaecol Obstet* 1986; 24:379-381.
16. Saravanane C, Robinson Smile S, Chandra SS, Habeebullah S. Rectal bleeding: a rare complication of abdominal pregnancy. *Aust N Z J Obstet Gynaecol* 1997; 37:124-125.
17. Erwin EA, Counselman FL. Ectopic pregnancy presenting as rectal pain. *Am J Emerg Med* 2007; 25:221-222.
18. Atrash HK, Friede A, Hogue CJ. Abdominal pregnancy in the United States: frequency and maternal mortality. *Obstet Gynecol* 1987; 69:333-337.
19. Warshal DP, Fultz PJ, Dawson AE, Del Priore G, DuBeshter B. Interstitial pregnancy complicated by rectal bleeding. *Am J Obstet Gynecol* 1996; 175:1373-1375.
20. Koc I, Schumacher R, Campbell O, Turkyilmaz AS, Ergocmen B. 2005. The Turkey national maternal mortality study. Page: 62. [http://www.hips.hacettepe.edu.tr/uaop_ankara/UAOC_ana_rapor.pdf (accessed on 16.05.2012)]
21. National Maternal Mortality Survey, Turkey, 2010. [www.tusak.saglik.gov.tr/EN/dosya/healthstatisticsyearbook.2010.pdf (accessed on 16.05.2012)]
22. Cantwell R, Clutton-Brock T, Cooper G, Dawson A, Drife J, Garrod D, et al. Saving Mothers' Lives: Reviewing maternal deaths to make motherhood safer: 2006-2008. The Eighth Report of the Confidential Enquiries into Maternal Deaths in the United Kingdom. *BJOG* 2011;118 Suppl 1:1-203.
23. Hunt SP, Talmor A, Vollenhoven B. Management of non-tubal ectopic pregnancies at a large tertiary hospital. *Reprod Biomed Online* 2016; 33:79-84.
24. Bouyer J, Coste J, Shojaei T, Pouly JL, Fernandez H, Gerbaud L, Job-Spira N. Risk factors for ectopic pregnancy: a comprehensive analysis based on a large case-control, population-based study in France. *Am J Epidemiol* 2003; 157:185-194.
25. Karaer A, Avsar FA, Batioglu S. Risk factors for ectopic pregnancy: a case-control study. *Aust N Z J Obstet Gynaecol* 2006; 46:521-527.
26. Menon S, Sammel MD, Vichnin M, Barnhart KT. Risk factors for ectopic pregnancy: a comparison between adults and adolescent women. *J Pediatr Adolesc Gynecol* 2007; 20:181-185.