

Risk factors for ectopic pregnancy: A case–control study

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Background: Ectopic pregnancy (EP) is a condition presenting as a major health problem for women of childbearing age. This study aimed to identify potential risk factors for EP and to evaluate the contribution of the risk factors associated to EP.

Materials and Methods: This retrospective nested case–control study was conducted from 2006 to 2011. In case group, there were a total of 83 women diagnosed with EP, while in the control group; there was a total of 340 women who gave birth. The basic recorded information included surgical, gynecological, obstetrics, sexual, contraceptive, and infectious histories; demographic characteristics; smoking habits; fertility markers; as well as reproductive outcome after EP. The association between EP and the factors studied was analyzed by logistic regression. **Results:** The findings reveal that the following factors were associated with increased risk of EP, including: Maternal age (odds ratio [OR] = 1.11, confidence interval [CI] [1.06–1.16], $P < 0.0001$), spouse's cigarette smoking (OR = 1.73, CI [1.05–2.85], $P = 0.02$), gravidity (OR = 1.50, CI [1.25–1.80], $P < 0.0001$), prior spontaneous abortions (OR = 1.93, CI [1.11–3.36], $P = 0.01$), history of EP (OR = 17.16, CI [1.89–155.67], $P = 0.01$), tubal blockage (OR = 10.85, CI [2.02–58.08], $P = 0.01$), use of intrauterine device (IUD) (OR = 4.39, CI [1.78–10.81], $P = 0.001$), tubal damage (OR = 2.704, CI [1.26–5.78], $P = 0.01$), first pregnancy interval (OR = 1.01, CI [1.00–1.02], $P < 0.0001$) and history of infertility (OR = 6.13, CI [2.70–13.93], $P < 0.0001$). **Conclusion:** By identifying risk factors being amenable to modification, such as cigarette smoking and use of IUD and first pregnancy interval the effective risk-reduction strategies can be devised.

Key words: Ectopic pregnancy, intrauterine device, tubal damage

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INTRODUCTION

Ectopic pregnancy (EP) is a condition presenting as a major health problem for women of childbearing age.^[1] The incidence of EP varies with the population, but it has been accounted for 1–2% of all reported pregnancies.^[2–5] Numerous studies have attempted to explain the risk factors for EP.^[3,6–9] Accordingly, it is speculated that the main risk factors for EP are conditions or procedures, which can result in tubal damage.^[1,6,10,11] Despite these insights, much remains to be learned about these factors. For instance, the exact role and strength of these factors have not been definitively determined due to sample size problem or other design issues.^[6,7] On the other hand, extrapolation of results from studies conducted before is difficult, owing to the variation in incidence and risk factor associated with EP among populations studied.^[6] Moreover, searching on PubMed revealed that there are no publications on incidence or risk factors for EP in Iran. Obviously, successful implementation of risk-reduction counseling program before conception

provides high-risk patients with screening to identify and manage EP;^[6] therefore, the current study was designed to identify potential risk factors and to evaluate the contribution of the risk factors associated EP in women attending a referral women's hospital in Tehran, capital of Iran.

METHODS

Study design and participants

This retrospective nested case–control study performed at Arash Women's Hospital, Tehran, Iran between 2006, and 2011. The study was approved by the Institutional Review Board of the Royan Institute Research Center and the Royan Ethics Committee. The case-patients were 83 women in their first trimester of pregnancy presenting to the hospital with a diagnosis of EP in order to receive the treatment of medical or surgical procedure. Control group consisted of 340 randomly selected women (systematic sampling method) giving birth at Arash Hospital.

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Study variables

The basic recorded information included surgical (abdominal surgery), gynecological (tubal damage, tubal situation), obstetrics (gravidity, first pregnancy interval, history of live birth, history of abortion, history of induced abortion, history of EP), contraceptive (contraceptive methods) and infectious histories (history of pelvic inflammatory disease [PID]), demographic characteristics (age, body mass index [BMI]); smoking habits (smoking, spouse's cigarette), fertility markers (history of infertility, duration of infertility), as well as reproductive outcome after EP. The severity of vaginal bleeding and pain as a symptom of EP were also recorded. A clinical intrauterine pregnancy was defined as the presence of an intrauterine gestational sac, confirmed by ultrasound.^[12] Furthermore, coexistence of intrauterine and extrauterine gestation is a definition for heterotopic pregnancy.^[12] We considered a pregnancy as ectopic if it was reported as either ectopic only or heterotopic. Ectopic and heterotopic pregnancies were diagnosed by detection of conception products within the fallopian tube, visualization of an extrauterine gestational sac, or by a rise in human chorionic gonadotropin level after dilatation and evacuation.^[13]

Statistical analysis

Statistical analysis was performed with SPSS software, version 18.0 (SPSS Inc., Chicago, IL, USA). For comparison of the patient and cycle characteristics, appropriate statistical analysis methods were performed using Student's *t*-test or Mann-Whitney U-test for continuous variables, while Pearson's Chi-square test or Fisher's exact test for categorical variables. The *P*<0.05 was considered statistically significant. Quantitative variables were expressed as mean ± standard deviation while qualitative variables were presented with number and percent. The association between EP and the factors studied was measured by odds ratio (ORs) and 95% confidence interval (CI). We used logistic regression analysis to calculate ORs and 95% CI for them. Subsequently, multiple logistic regression was used to select independent predictors for EP.

RESULTS

Of the 11174 women have been referred during pregnancy; a total of 140 patients presented with warning signs of an EP in the first trimester of pregnancy. Of these, 83 patients were diagnosed with EP (0.74%), in which one of them was heterotopic (1.2%). Table 1 shows the distribution of the sites of EP. Only 4.8% of EPs were extratubal, while the most common site of the tubal pregnancies was ampullary region of the fallopian tube (62.7%). No cervical and abdominal pregnancies were observed.

The general characteristics of all couples are provided in Table 2. There was no difference in racial distribution

between two groups and approximately 97.6% of the population was Iranian. Overall, the mean age of the cases was significantly higher than that of the controls (30.3 ± 5 vs. 27.1 ± 5.3 ; *P*<0.0001). Accordingly, there was a considerable increase in crude risk of EP with age [Table 2]. Although the number of women used tobacco was small (*n*=6), the difference between the two groups was marginally significant at the 0.1 level (*P*=0.08). On the other hand, spouse's cigarette smoking was associated with EP, while odds of EP in women with smoker husband was 1.738 times more than nonsmokers (*P*=0.02). There was no association between EP and BMI [Table 2].

Most of the parameters given in the patients' obstetric histories were associated with EP [Table 3]. We found a close

Table 1: Distribution of the site, location and direction of EP

Variable	(%)
Site of EP	
Fimbrial	16 (19.3)
Isthmic	8 (9.6)
Ampullary	52 (62.7)
Ovarian	4 (4.8)
Interstitial	1 (1.2)
NA*	2 (2.4)
EP location	
Tubal	77 (92.8)
Ovarian	4 (4.8)
NA*	2 (2.4)
Direction of EP	
Right	51 (61.4)
Left	29 (34.9)
NA*	3 (3.6)

EP=Ectopic pregnancy; *NA=Not available

Table 2: EP and demographic characteristics

	Study group (n=83) (%)	Control group (n=340) (%)	OR	95% CI	P value
Age					
□26	15 (18.1)	163 (47.9)	1*		<0.0001
27-32	44 (53)	123 (36.2)	3.88	2.06-7.30	
33-38	19 (22.9)	48 (14.1)	4.30	2.03-9.10	
□39	5 (6)	6 (1.8)	9.05	2.47-33.20	
BMI (mean)*	25.9±3	26±4.3	0.98	0.93-1.05	0.72
Smoking					
Yes	3 (3.6)	3 (0.9)	4.21	0.83-21.26	0.08
No	80 (96.4)	337 (99.1)	1*		
Spouse's cigarette smoking					
Yes	34 (41.0)	97 (28.5)	1.73	1.05-2.85	0.02
No	49 (59.0)	243 (71.5)	1*		

OR=Odds ratio; CI=Confidence interval; *BMI=Body mass index; EP=Ectopic pregnancy

Table 3: The association between EP and surgical, gynecologic and obstetric histories

	Study group (n=83) (%)	Control group (n=340) (%)	OR	95% CI	P value
Gravidity (mean)	2 (1.8)	1.3 (1)	1.50	1.25-1.80	<0.0001
History of live birth					
Yes	45 (54.2)	144 (42.4)	1.61	0.99-2.61	0.05
No	38 (45.8)	196 (57.6)	1*		
History of abortion					
Yes	24 (28.9)	59 (17.4)	1.93	1.11-3.36	0.01
No	59 (71.1)	281 (82.6)	1*		
History of induced abortion					
Yes	1 (1.2)	8 (2.4)	0.50	0.06-4.10	0.52
No	82 (98.8)	332 (97.6)	1*		
History of EP					
Yes	4 (4.8)	1 (0.3)	17.16	1.89-155.67	0.01
No	79 (95.2)	339 (99.7)	1*		
History of abdominal surgery					
Laparotomy	15 (18.1)	30 (8.8)	2.28	1.16-4.47	0.05
Appendectomy	2 (2.4)	9 (2.6)	1.01	0.21-4.80	
No surgery	66 (79.5)	301 (88.5)	1*		
Tubal damage					
Yes	12 (14.5)	20 (5.9)	2.70	1.26-5.78	0.01
No	71 (85.5)	320 (94.1)	1*		
Tubal situation					
Both open tube	38 (45.8)	165 (48.5)	1*		0.01
One open tube	5 (6)	2 (0.6)	10.85	2.02-58.08	
Both block tubal	1 (1.2)	1 (0.3)	4.34	0.26-70.98	
NA*	39 (47)	172 (50.6)			

OR=Odds ratio; CI=Confidence interval; EP=Ectopic pregnancy; NA=Not available

association between EP and gravidity. Prior spontaneous abortions, the risk of EP also increased, but this was not true about induced abortion. The risk of EP was higher among women with histories of EP, with an OR of 17.16 ($P = 0.01$). According to our results if one or both fallopian tubes are blocked, the risk of EP increased at least 10- and 4-fold respectively. We also observed that, the risk of EP is higher in women with tubal damage ($P = 0.01$) [Table 3].

The women with a longer interval between marriage and first pregnancy had a higher risk of EP ($P < 0.0001$). Since the number of women with a history of laparoscopically-confirmed PID was small ($n = 3$), we could not find any association between prior PID and EP. Among contraceptive methods, use of intrauterine device (IUD) was associated with an increased risk of EP compared with those who used no birth control. History of infertility, especially primary infertility was strongly associated with the risk of EP with an OR of 6.135 ($P < 0.0001$) compared with women with no history of infertility [Table 4].

Table 4: The association between EP and sexual history, infectious history, contraceptive history and fertility markers

	Study group (n=83) (%)	Control group (n=340) (%)	OR	95% CI	P value
First pregnancy interval (month)	35.9±42.6	19.6±21.4	1.01	1.00-1.02	<0.0001
History of PID					
Yes	2 (2.4)	1 (0.3)	8.37	0.75-93.44	0.08
No	81 (97.6)	339 (99.7)	1*		
Contraceptive methods					
IUD	10 (12)	11 (3.2)	4.39	1.78-10.81	0.001
Oral contraceptive	2 (2.4)	14 (4.1)	0.69	0.15-3.11	
Condom	8 (9.6)	18 (5.3)	2.14	0.89-5.16	
Other	3 (3.6)	7 (2.1)	2.07	0.52-8.24	
Non	60 (72.3)	290 (85.3)	1*		
History of infertility					
Primary	14 (16.9)	12 (3.5)	6.13	2.70-13.93	<0.0001
Secondary	11 (13.3)	23 (6.8)	2.51	1.16-5.43	
No infertility	58 (69.9)	305 (89.7)	1*		
Duration of infertility (year)	1.8±3.7	0.5±2	1.17	1.08-1.28	<0.0001

EP=Ectopic pregnancy; OR=Odds ratio; CI=Confidence interval; PID=Pelvic inflammatory disease; IUD=Intrauterine device

Table 5: The backward logistic regression analysis with OR and 95% CI on the factors affecting the EP

Variables	OR	95% CI for OR		P
		Lower	Upper	
Gravidity	1.461	1.17	1.81	0.001
History of infertility	3.181	1.54	6.53	0.002
First pregnancy interval	1.012	0.001	1.02	0.033

OR=Odds ratio; CI=Confidence interval; EP=Ectopic pregnancy

In other to build a prediction model and find the most predictive factors of EP, we used the multiple logistic regressions. The results of multivariate analysis showed that three factors were associated with a significant increase in the risk of EP that is listed in Table 5.

Our analysis demonstrated that 68 (81.9%) and 48 (57.8%) of women with EP have moderate/severe vaginal bleeding and pain respectively. We also evaluated the reproductive outcome after EP. Accordingly, the outcomes of 50 out of 83 patients were available due to subsequent loss to follow-up ($n = 33$). Out of 50 patients, there were 15 (30%) patients who didn't intend to get pregnant and used contraceptive methods after EP (8 patients with tubal ligation and 7 patients with other methods of birth control) and 12 women were infertile. The remaining 23 had subsequent intrauterine pregnancies, of these, 17 resulted in a live birth and five ended in miscarriage. One patient had EP in her subsequent pregnancy.

DISCUSSION

There is extensive research on potential risk factors for EP.^[6] Our results confirm some of these supposed risk factors.

Previous ectopic pregnancy

Similar to other studies,^[6,14,15] we found that, among all the possible risk factors of EP, the strongest evidence is for an association between previous EP and sequent EP. According to our results, the risk of EP was almost 17 times higher for women who had prior EP compared to controls (OR = 17.165, 95% CI = 1.89–155.67). Barnhart *et al.*^[6] indicated that the risk of facing a repeat EP increases intensely with the number of prior EP (OR = 2.98 for one prior EP and OR = 16.04 for 2 or more). Other research studies also estimated the risk of facing a repeat EP to be between 2.4 and 25.0.^[6,14,15]

Prior pelvic inflammatory disease

Previous studies have reported a strong association between prior PID and EP with OR ranging from 2.0 to 10.1.^[6,16–18] In our study, although the number of women with a history of laparoscopically-confirmed PID was small ($n = 3$), it was close to statistical significance ($P = 0.08$).

Previous tubal surgery

It has been reported that previous tubal surgery is a major risk factor for EP with an estimated OR of 4.7 (2.4–9.5) according to a meta-analysis.^[19] Similarly, we observed that the women with tubal damage were almost 2.5–3 times more likely to have an EP than controls. It is uncertain whether the increased risk is arising from a surgical procedure or from the underlying problem.^[20]

Abdominal surgery

Previous studies have reported different results about the association between nontubal abdominal or pelvic surgery and subsequent EP from no association to OR ranging from 2.4 to 5.0.^[6,16,21,22] In our study, the women with histories of laparotomy and appendectomy were more likely to have EP compared with controls. However, this difference was not statistically significant ($P = 0.05$).

Tubal blockage

Tubal pregnancy may occur in a blocked tube with contralateral tubal patency. In this case, the sperm migrates across the abdomen to fertilize an egg released from the blocked side.^[20] It is demonstrated that when a woman becomes pregnant after a tubal ligation, the risk of EP is higher in women not using this contraceptive method.^[23] Although, the number of cases with tubal blockage was small ($n = 9$), our analysis showed that the risk of EP is approximately 11-fold higher for women with one blocked tube. This association was found to be weaker for those with two blocked tubes (OR = 4.34, 95% CI = 0.26–70.98).

Maternal age

Our result is consistent with some previous studies which found that the risk of EP increases with advancing maternal age.^[24,25] Based on our results, the average maternal age was significantly higher for women with EP than controls. Furthermore, compared with women aged ≤ 26 years, the risk of EP for women aged 27–32 and aged 33–38 were 3.9 and 4.3 times higher respectively, while women aged ≥ 39 years approximately had a 9-fold risk of EP.

Existing evidence on how advanced maternal age has an effect on EP risk remains unclear. It is improbable that the higher risk of EP in older age cohorts is due to chromosomal abnormalities in the trophoblastic tissue.^[7,26] Some researchers attributed it to some age-related factors, such as: Possible tubal scarring from PID^[1,27] major gonococcal and chlamydial epidemics^[1,28] and changes in tubal function leading to delay in ovum transport and tubal implantation.^[7] However, these hypotheses need to be investigated.

Cigarette smoking

Several contemporary studies have reported a strong association between tobacco use and EP.^[7,29,30] In a meta-analysis, Waylen *et al.*^[2,31] revealed that smoking patients demonstrated significantly higher odds of EP (OR = 15.69, 95% CI = 2.87–85.76). In our study, despite the small number of women used tobacco ($n = 6$), the difference between the two groups was significant at the 0.1 level ($P = 0.08$). We also could find that there is an association between spouse's cigarette smoking and EP with an OR of 1.7 (95% CI: 1.05–2.85). Although, the reason that smoking causes EP remains unknown,^[2] animals studies have shown that inhalation of cigarette smoke may impair fallopian tube function by affecting on ciliary beat frequency and smooth muscle contraction.^[2,32]

Intrauterine device

According to our results, among contraceptive methods only after use of IUD, there was a 4–5 fold increased risk of a subsequent EP. Early studies on risk factors of EP indicated that OR greater than one belonged to current IUD use.^[7,33] Although the exact mechanism by which implantation is occurring outside the uterus is not well understood, it is thought that IUD-induced inflammation may result in deciliation of the endosalpinx and then delays ovum transport, which leads to EP.^[34,35]

In a case-control study comparing 243 women using an IUD and suffering from EP to 140 IUD users with an intrauterine pregnancy, Bouyer *et al.*^[36] have described that progesterone IUD, duration of IUD use, and pelvic pain after the insertion of the IUD are the factors increasing the risk of EP in IUD users. In addition, other influencing factors associated with decreasing risk of EP are the displacement of the IUD and

use of anti-inflammatory drugs including paracetamol or aspirin before the pregnancy. In our study, we didn't evaluate the impact of these variables.

Prior abortions

In the case of spontaneous abortion, the results are conflicting. Several other studies^[36,37] and our study have showed the association of prior spontaneous abortion with increased risk of EP. Another study, however, failed to find an association between the two mentioned variables.^[36] With regard to the available evidence, the cause of this relationship is most likely due to infection,^[7,38] hormonal imbalance,^[7,36,39] or immunologic factors.^[7]

Multiple studies have produced conflicting results regarding the association between EP and a history of induced abortions.^[7,17,22,24,40,41] A large case-control study including 803 cases of EP, however showed an increased risk of EP for women with a history of two or more prior induced abortion with an adjusted OR of 1.9 (95% CI = 1.0-3.8).^[6] This is contrary to our findings and some other published reports.^[24,41] However, because of the small number of cases with induced abortion history in our study, we cannot do a powerful test for a relationship between induced abortion and EP.

Gravidity and prior live birth

Furthermore, we observed an association between prior live birth and risk of a subsequent EP which was close to the threshold of statistical significance. Also, our results showed that first pregnancy interval and first birth is another important risk factor for EP. We did also find a close association with gravidity, which is similar to findings of one study.^[6]

History of subfertility

A strong association between history of subfertility and risk of EP was also detected which may be due to a significant role of hyperstimulation, with high estrogen levels.^[20,42] This finding is further supported by other studies.^[4,19] In our study, we found that the same relationship is true for the duration of infertility. However, not all studies have revealed such relationship.^[43]

Symptoms

We also evaluated the signs and symptoms of EP. Our analysis demonstrated that 81.9% and 57.8% of women with EP have moderate/severe vaginal bleeding and pain respectively. This is consistent with the finding of Barnhart *et al.*, which reported moderate and/or severe bleeding and the presence of pain were significantly and positively associated with the presence of an EP. Therefore, it is essential to evaluate all women with complaints of considerable pain or bleeding after a period of amenorrhea as a patient with a potential EP.^[6]

CONCLUSION

The clinician can help patients to improve their health status by detection of historical and clinical risk factors of EP in order to provide early intervention. By identifying risk factors being amenable to modification, such as cigarette smoking, the effective risk-reduction strategies can be devised. Additional studies are needed to be performed on hormonal and immunologic factors possibly involved in EP.^[7,39]

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AUTHORS' CONTRIBUTIONS

AM contributed in the conception of the study, revising the draft, approval of the final version of the manuscript, and agreed for all aspects of the work. RH contributed in acquisition of data, revising the draft, approval of the final version of the manuscript, and agreed for all aspects of the work. NJ contributed in conducting the study, drafting the work and approval of the final version of the manuscript, and agreed for all aspects of the work. MSh contributed in the conception of the work, and approval of the final version of the manuscript, and agreed for all aspects of the work. MA contributed in analysis and interpretation of data for the work, revising the draft, approval of the final version of the manuscript, and agreed for all aspects of the work.

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