

Risk Factors for Ectopic Pregnancy: A Multi-center Case Control Study

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Abstract

Background: Ectopic pregnancy (EP) is defined as a pregnancy in which fertilized oocyte implants outside the endometrial cavity. Although there is no known etiology for ectopic pregnancy, some risk factors of EP have been determined. It has been evident that ectopic pregnancy can be of multifactorial origin. This multicenter research aims to study risk factors associated with increased risk of ectopic pregnancy in women living in Kabul.

Methods: A multicenter case control study was conducted in five tertiary maternity hospitals located in Kabul, Afghanistan. A total of 457 pregnant women were included in this study. In the case group, women with diagnosed ectopic pregnancy, while in control group women with intrauterine pregnancy were included. For each case in this study, two controls were enrolled.

Results: The mean (SD) age of women in case group was 27.9 (6) years while in control group it was 26.4 (5.5) years. This difference was not statistically significant. We found a significant association between history of abortion and EP (Adj. OR=1.57; 95%CI: 1.02, 2.42). Having history of abdominal/pelvic surgery was a risk factor for EP with adjusted OR 1.94 (95%CI: 1.15, 3.30). In this study we found an increasing risk of EP in women of 35 years or older compared to younger women (Crude OR=2.26; p= 0.024). In women reporting prior EP, the chance of its recurrence was increased (Crude OR= 9.64; 95%CI: 1.1, 83.2). No association of gravidity and parity was found with EP incidence.

Conclusions: In this study we found a statistically significant association between history of abdominal/pelvic surgery and EP. In addition, history of abortion was suggested as a risk factor for ectopic pregnancy. In case of having a previous EP probability of its recurrence will be increased. Women with advanced age having other potential risk factors will be facing higher risk of EP.

Background

Ectopic pregnancy is a condition in which fertilized oocyte implants outside the endometrial cavity i.e., in the uterine tubes, ovaries, uterine cervix, and abdominal or pelvic cavity. This is one of the life threatening problems usually diagnosing in the first trimester of pregnancy(1)(2). The incidence of ectopic pregnancy varies in different countries settings. However globally, it has been reported that 1–2% of all pregnancies are ectopic(3). Several risk factors have been identified for this complication of pregnancy including pelvic inflammatory disease (PID), previous ectopic pregnancy, previous pelvic surgery, induction of ovulation, assisted reproductive technologies, intrauterine contraceptive device, advanced maternal age, history of abortion and smoking at the time of conception. It has been evident that ectopic pregnancy is can be of multifactorial origin(4)(5).

Evidences from several studies indicate that key role in development of ectopic pregnancy belongs to conditions and processes leading to fallopian tubes damages(6).

Worldwide, its incidence has shown a significant increase lately. This increase has been attributed to increase in some of the risk factors such as advance gestational age, excessive use of assisted reproductive technologies (ART), smoking, surgical operations, induced abortions (3).

Mortality of ectopic pregnancy in developing countries is higher compared to the developed countries. Studies have highlighted its case fatality rates of 1–3% in developing countries, which is 10 times higher than developed countries(7). To prevent its mortality, early diagnosis and treatment of ectopic pregnancy is fundamental(8). Additionally, early diagnosis and treatment of ectopic pregnancy is associated with minimized morbidity(9). Evidences show that in the majority of cases (98%) implementation occurs in uterine tubes and its most common complication is rupture of the ectopic pregnancy and life threatening hemorrhage(8).

Despite several published articles about ectopic pregnancy risk factors there is lack of studies to search for its risk factors in Afghan women. This multicenter study aims to look for the risk factors associated with increased risk of ectopic pregnancy in Afghan women.

Methods

This multicenter case control study was conducted in five tertiary maternity hospitals located in Kabul, Afghanistan. A total of 457 pregnant women were included in this study. Of them, 159 women were included in case group while 298 women were included in control group. The data was collected from March 2017 to January 2018.

Inclusion criteria: In the case group, women with diagnosed ectopic pregnancy who have been admitted to the above mentioned hospitals were included. In the control group women with intrauterine pregnancy were included. In this study for each case, two controls were enrolled.

Exclusion criteria: From case group, women with heterotopic pregnancy were excluded, while from the controls women with multiple pregnancy and those with gestational age lower than 28 weeks were excluded.

In this study, diagnosis of ectopic pregnancy was confirmed by menstrual history, physical examinations, beta-human chorionic gonadotropin (β -hCG) level's testing, and abdominal/transvaginal ultrasonography.

Main variables of the study were; maternal age, gravidity, parity, history of abortion, history of abdominal/pelvic surgery, and previous ectopic pregnancy. In addition, demographic information such as patients' education, residence, employment statues etc. has also been recorded.

All data were collected from the hospitals' medical records. The collected data was organized and analyzed in SPSS program, version 23. Initially, descriptive measures are presented according to the variables' type and distribution. Odds ratio (OR) and 95% confidence intervals (CI) were calculated to find association between exposure and outcome variables. After univariate analysis, multivariable modelling

(logistic) was conducted to determine association between ectopic pregnancy and the potential risk factors included in this study.

In the multivariate analysis, we only added variables that were significantly associated with the risk of ectopic pregnancy in univariate analysis. In this study significance level of 0.05 has been considered.

The proposal of this study was reviewed and approved by Ethical Committee of Kabul University of Medical Sciences (KUMS). In this study, the participants were not directly contacted. Considering this, using informed consent form had been waived by Kabul University of Medical Sciences-Ethical Committee in protocol #5–12/09/1396. Confidentiality was taken care of, and no personal information that may lead to patient’s identification has been included in this study. All methods were carried out in accordance with relevant guidelines and regulations for observational studies in KUMS and the hospitals.

Results

The study included a total of 457 women with mean (SD) age of 27 (5.7) years, ranging from 17 to 50 years. Almost half of the participants (49.4%) of this study were 25 years old or younger. All of the women included in this study were married and majority of them (97.6) were housewives (Table 1).

Table 1
Descriptive figures of demographic variables

Variable	Group	N (%)
Age (N = 457) Mean (SD): 27 (5.7)	Case	159 (35)
	Control	298(65)
Age groups	≤ 25 Yrs	224 (49.4)
	26- 35Yrs	192 (42.4)
	≥ 36 Yrs	37 (8.2)
Residence	Kabul	386 (85.7)
	Provinces	71 (14.3)
Marital Status	Married	
	Widow/Single	
Occupation	Housewife	446 (97.6)
	Employee	8 (1.8)
	Student	3 (0.3)
SD: Standard Deviation; Yrs: years		

Mean age of the women in case group was 27.9 (6) years, but in controls it was 26 (5.5). However the difference was not statistically significant ($p = 0.56$).

Median pregnancy number in case group was reported as 4 (IQR, 2 to 6) and in the control group it was reported as 3 (IQR, 2 to 5). This difference in median pregnancy numbers was not statistically significant ($p = 0.16$). Meanwhile, women in the case and control groups reported similar number of deliveries (Table 2).

Table 2
Association of Age and obstetric variables with ectopic pregnancy

Variable	Group	Mean/Median	p-value
Age (yrs) Mean (SD)	Case	27.9 (6)	0.86
	Control	26.4 (5.5)	
Pregnancy median (IQR)	Case	4 (2–6)	0.16
	Control	3 (2–5)	
Delivery median (IQR)	Case	2 (1–4)	0.5
	Control	2(1–3)	
SD: standard Deviation; IQR: interquartile range			

To find association between advanced maternal age and risk of ectopic pregnancy, the participants were divided in to three groups of (≤ 25 years), (26 to 35 years) and (≥ 36 years). The odds of ectopic pregnancy among women above 35 years is two times higher than in women aged 25 years or younger (crude OR, 2.26); whereas this chance in women between 26 and 35 years is increased by a crude OR = 1.53. This association was found to be statistically significant ($p = 0.04$) in univariate analysis (Table 3).

Table 3
Association of ectopic pregnancy with demographic variables.

	Case	Control			
Variable	N (%)	N (%)	Crude OR	95% CI	p- value
Age groups					
≤ 25 Yrs	66 (41.5)	195 (53.7)			
26- 35Yrs	75 (47.2)	117(39.7)	1.53	1.02–2.30	0.02
≥ 36 Yrs	18 (11.3)	19 (6.5)	2.26	1.12–4.59	0.04
Occupation					
Housewife	157 (99)	289 (97)			
Employee	1 (0.6)	7 (2.3)	0.26	0.03–2.2	0.46
Student	2 (0.6)	2 (0.7)	0.92	0.08–10.23	0.21
Yrs: years; OR: Odds ratio; CI: confidence interval					

Around 33% of women in case group reported at least one prior abortion, while this number in control group was 23.5%. This indicates that history of abortion is associated with increased risk of ectopic pregnancy (crude OR = 1.58; p = 0.034).

More than 20% of women in case group reported past abdominal/pelvic surgery. In controls, this was only 11.4%. This difference was statistically significant (crude OR = 2.03; p = 0.008). Univariate analysis of our data (Table 4) shows that women with a previous ectopic pregnancy are at higher risk of having EP once more (crude OR = 9.64; p = 0.01).

Table 4
Association of ectopic pregnancy with abortion, history of surgery and prior EP

Variable	Case		Control		Crude OR	95% CI	p-value
	N (%)	N (%)	N (%)	N (%)			
H/O Abortion	No	53 (32.7)	70 (23.5)		1.58	1.03–2.42	0.034
	Yes	107 (67.3)	228 (76.5)				
H/O surgery	No	33 (20.8)	34 (11.4)		2.03	1.2–3.43	0.008
	Yes	126 (79.2)	264 (88.6)				
H/O EP	No	5 (3.1)	1 (0.3)		9.64	1.11–83.2	0.01
	Yes	154 (96.9)	297 (99.7)				

EP: Ectopic Pregnancy; OR: Odds ratio; CI: Confidence Interval; H/O: history of

To find independent risk factors for EP, all the variables with statistically significant result ($p > 0.05$) in the univariate analysis were included in a multivariate analysis.

After controlling with other potential risks, the association between ectopic pregnancy and age was disappeared (Table 5). Adjustment did not affect the association between prior abdominal/pelvic surgeries and EP (Adj. OR = 2.03; 95% CI, 1.15–3.3). Meanwhile, prior abortion history remained a risk factor for ectopic pregnancy (Adj. OR = 1.57; 95%CI; 1.02, 2.42). However having prior history of ectopic pregnancy lost its significance after controlling for surgery (Table 5).

Table 5
Risk factors for Ectopic pregnancy, Univariate vs Multivariate analysis

Variables	Univariate Analysis			Multivariate Analysis		
	C.OR	95% CI	p-value	Adj. OR	95%CI	p-value
H/O Abortion	1.58	1.03–2.42	0.034	1.57	1.02–2.42	0.04
H/O Surgery	2.03	1.2–3.43	0.008	1.94	1.15–3.3	0.01
H/O EP	9.64	1.11–83.2	0.01	5.97	0.65–54.5	0.11
Age groups						
26- 35Yrs	1.53	1.02–2.30	0.04	1.38	0.9–2.11	0.13
≥ 36 Yrs	2.26	1.12–4.59	0.02	1.83	0.88–3.8	0.1

Adj. OR: Adjusted Odds Ratio; C. OR: Crude Odds Ratio; CI: Confidence interval; EP: Ectopic pregnancy

Discussions

This study was an attempt to evaluate ectopic pregnancy risk factors in women living in Kabul. To our knowledge no studies had been published on ectopic pregnancy risk factors in our locality. Our findings indicate that having prior abdominal/pelvic surgery and abortion increases risk of EP in women. Advanced age, though appeared significant risk in the univariate analysis, but not in the multivariate.

This study indicated that risk of Ectopic pregnancy is 2 times higher for women who had previous abdominal/pelvic surgery compared to controls (Adj. OR = 1.94; 95%CI; 1.15, 3.3). Literature is consistent on history of abdominal/pelvic surgery as a risk factor for EP. Ragab et.al. found this association significant in Egypt (OR = 4.4; 95%CI; 1.3 13.3) (10). Moini et.al. also have provided similar findings (OR = 2.28; 95% CI. 1.16, 4.47)(6). In China, Li et. al. presented association between history of abdominal/pelvis surgery and risk of ectopic pregnancy with OR = 2.9; 95% CI; 1.39, 2.13 (11). Karaer et.al in a study conducted in Turkey found women having prior cesarean section are at higher risk of having ectopic pregnancy(12). The observed association between abdominal/pelvic surgery and increased risk of EP can be explained by peritoneal and peri-tubal adhesions. The developed adhesions and infections after surgery might disturb the normal function of the uterine tubes and increase risk of EP.

This study indicates that there is association between history of abortion and incidence of ectopic pregnancy (Adj; OR = 1.57; 95% CI. 1.02, 2.42). In other words, this study found abortion history as a risk factor for ectopic pregnancy. Results about this association in the literature are inconsistent. Moini and et.al. has found this association significant (OR = 1.8; 3. 95%CI; 1.11, 3.36)(6). Also, similar findings has been reported by li et.al. (OR = 1.53; 95% CI; 1.12, 2.11) and Bouyer et.al (11)(1).

However, Ragab et.al. failed to find association between history of abortion and increased risk of ectopic pregnancy(10). Parashi et al. also failed to find this association(4).

Considering the above evidences, we can highlight the role of harmonic disturbance, immunity and infections among women with abortion history; which can expose these women to ectopic pregnancy(6).

Consistent with other studies, this study documented that women with history of prior ectopic are at increased risk of having it again (crude OR = 9.64). However, this association- in our study- lost its significance in the multivariate analysis. In this study we had only six participants with prior history of Ectopic pregnancy (five in case and 1 in the control group), and likely this was the reason for the lost significance.

Other studies found an increased risk of EP among women with prior ectopic pregnancy. Karaer et.al. with an OR = 13 has presented this association(12). Studies have been carried out in Iran, China, France and United States indicate prior EP as an independent risk for its recurrence(6)(11)(1)(13).

It can be concluded that the risk factors and pathologies which once caused ectopic pregnancy may lead to its recurrence. Furthermore, surgical treating of ectopic pregnancy can increase likelihood of adhesions in the pelvis, and subsequently increase the higher risk of its recurrence(14).

With a crude OR = 2.26, this study found an association between ectopic pregnancy and advanced maternal age. However, this association lost its significance after controlling for history of abdominal/pelvic surgery, abortion and prior EP. Moini et.al. explained this association with OR = 4.3 (6). However, a number of other studies failed to find this association(11)(14)(1). Our multivariable analysis presents similar unstable association (Adj. OR = 1.83; 95% CI: 0.88, 3.8). Reason behind association between advanced age and risk of EP has not explained clearly. But, considering the above evidences, it can be concluded that increase of age can change physiology of female reproductive system. Additionally, advance age is associated with many confounding factors including history of abortion, surgery, infections, etc.(6).

Median number of pregnancies and deliveries were not significantly different in case and control groups. This was consistent with findings available in the literature(11)(6)(1).

Being a hospital-based case-control study, selection bias must be acknowledged in this study. The multi-centered design carried out across five maternity hospitals covering the urban and rural areas in Kabul was the strength of this study, which helped to have a relatively good representation of the population and minimizing the selection bias.

Conclusions

In this multi-center case control study, we were able to conclude that history of abdominal/pelvic surgery and prior abortion are independent risk factors for ectopic pregnancy. It has been found that in case of prior ectopic pregnancy, the possibility of its recurrence is higher. Presence of multiple risk factors in women with advanced age can increased the risk of EP. Identifying potential risk factors in women can be useful for early proper medical treatment.

List Of Abbreviations

β-hCG Beta-human chorionic gonadotropin

CI Confidence interval

EP Ectopic pregnancy

KUMS Kabul University of Medical Sciences

OR Odds ratio

SD Standard division

IQR Interquartile range

Declarations

Ethics approval and consent to participate

The proposal of this study was reviewed and approved by Kabul University of Medical Sciences (KUMS) Ethical Committee (Protocol#5-12/09/1396). All methods were carried out in accordance with relevant guidelines and regulations for observational studies in KUMS and the hospitals. As the participants were not directly contacted and all data was collected from medical records, informed consent form was not used in this study. The informed consent was waived by Kabul University of Medical Sciences Ethical Committee in protocol #5 – 12/09/1396. Confidentiality was taken care of, and no personal information that may lead to patient's identification has been included in this study.

Consent for publication

Not applicable.

Availability of data and material

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

Competing interests

The author(s) declare(s) that they have no competing interests

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Authors' contributions

NA designed the study as well as the questionnaire and supervised the data collection and entry. NA did data cleaning, editing and analysis. NA, FA, NN and MS wrote the first draft of the manuscript. NA critically reviewed the draft and revised it. All authors read and approved the final manuscript.

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Overlapping publications on submission

Not applicable

References

1. Bouyer J. Risk Factors for Ectopic Pregnancy: A Comprehensive Analysis Based on a Large Case-Control, Population-based Study in France. *Am J Epidemiol* [Internet]. 2003 Feb 1 [cited 2020 Dec 25];157(3):185–94. Available from: <https://academic.oup.com/aje/article-lookup/doi/10.1093/aje/kwf190>
2. Madhra M, Otify M, Horne AW. Ectopic pregnancy [Internet]. Vol. 27, *Obstetrics, Gynaecology and Reproductive Medicine*. Churchill Livingstone; 2017 [cited 2020 Dec 25]. p. 245–50. Available from: <http://www.obstetrics-gynaecology-journal.com/article/S1751721417301252/fulltext>
3. Taran F-A, Kagan K-O, Hübner M, Hoopmann M, Wallwiener D, Brucker S. The Diagnosis and Treatment of Ectopic Pregnancy. *Dtsch Aerzteblatt Online* [Internet]. 2015 Oct 9;70(41):591–4. Available from: <https://www.aerzteblatt.de/10.3238/arztebl.2015.0693>
4. Parashi S, Moukhah S, Ashrafi M. Main risk factors for ectopic pregnancy: A case-control study in a sample of Iranian women. *Int J Fertil Steril*. 2014;8(2):147–54.
5. Khin-Nwe-Oo, Wah-Wah-Aung, Moe-Thida, Khin-Thet-Wai, Hta-Hta-Yi, Win-Win-Mya. Case-control study of ectopic pregnancies in Myanmar: Infectious etiological factors. *Southeast Asian J Trop Med Public Health*. 2011;42(2):347–54.
6. Moini A, Hosseini R, Jahangiri N, Shiva M, Akhoond MR. Risk factors for ectopic pregnancy: A case-control study. *J Res Med Sci* [Internet]. 2014 Sep;19(9):844–9. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/25535498>
7. Shetty S, Shetty A. a Clinical Study of Ectopic Pregnancies in Atertiary Care Hospitalof Mangalore, India. *Innov J Med Heal Sci* [Internet]. 2014;4:305–9. Available from: <http://www.innovativejournal.in/index.php/ijmh>
8. Lee R, Dupuis C, Chen B, Smith A, Kim YH. Diagnosing ectopic pregnancy in the emergency setting. *Ultrasonography* [Internet]. 2018 Jan 1;37(1):78–87. Available from: <https://doi.org/10.14366/usg.17044>
9. Ranji GG, Usha Rani G, Varshini S. Ectopic Pregnancy: Risk Factors, Clinical Presentation and Management. *J Obstet Gynecol India* [Internet]. 2018;68(6):487–92. Available from: <https://doi.org/10.1007/s13224-017-1075-3>
10. Ragab A, Mesbah Y, El-Bahlol I, Fawzy M, Alsammani MA. Predictors of ectopic pregnancy in nulliparous women: A case-control study. *Middle East Fertil Soc J* [Internet]. 2016 Mar;21(1):27–30. Available from: <https://linkinghub.elsevier.com/retrieve/pii/S1110569015300273>
11. Li C, Meng C-X, Zhao W-H, Lu H-Q, Shi W, Zhang J. Risk factors for ectopic pregnancy in women with planned pregnancy: a case–control study. *Eur J Obstet Gynecol Reprod Biol* [Internet]. 2014 Oct;181:176–82. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/25150957>
12. Karaer A, Avsar FA, Batioglu S. Risk factors for ectopic pregnancy: A case-control study. *Aust New Zeal J Obstet Gynaecol* [Internet]. 2006 Dec [cited 2020 Dec 25];46(6):521–7. Available from: <https://pubmed.ncbi.nlm.nih.gov/17116058/>
13. Barnhart KT, Sammel MD, Gracia CR, Chittams J, Hummel AC, Shaunik A. Risk factors for ectopic pregnancy in women with symptomatic first-trimester pregnancies. *Fertil Steril*. 2006 Jul 1;86(1):36–

43.

14. Butts S, Sammel M, Hummel A, Chittams J, Barnhart K. Risk factors and clinical features of recurrent ectopic pregnancy: A case control study. *Fertil Steril*. 2003 Dec 1;80(6):1340–4.