

## Original Article

## Risk Factors and Outcomes in Ectopic Pregnancy : Insights from a Case-Control Study

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## Abstract

**Background :** Ectopic pregnancy is a major life-threatening complication and identification of its risk is critical for avoiding mortality and morbidity. It is also essential to identify factors that may influence adverse outcomes in Ectopic pregnancies. Although different studies have identified several risk factors that might be associated with Ectopic pregnancy, there is a lack of evidence in perceiving their value as an independent predictor of Ectopic pregnancy and its complications.

**Materials and Methods :** A case-control study was designed with 65 patients as cases with an equal number of matched controls. Probable risk factors and adverse outcomes have been identified from the literature. Linear and logistic regression analyses were performed to identify independent risk factors for the occurrence of Ectopic pregnancy. Sub-analysis was also conducted to identify independent risk factors for adverse outcomes.

**Results :** The study identified Hb on Admission, No of PRBC Transfusion, History of Intrauterine Device (IUD) Usage, Previous History of Ectopic Pregnancy, and Previous History of Pelvic Inflammatory Disease (PID) as independent risk factors of occurrence of Ectopic pregnancy. No of PRBC Transfusion, History of IUD Usage and Previous History of Ectopic Pregnancy were identified as the most significant risk factors for adverse outcomes.

**Conclusion :** This study identified potential risk factors associated with Ectopic pregnancy and adverse outcomes. It also provided a clear guideline to identify the risk factors associated with ectopic pregnancy and to mitigate adverse outcomes. Although further studies are required to reinforce these findings, this study will help identify the crucial risk factors during patient monitoring and reduce adverse outcomes.

**Key words :** Ectopic Pregnancy, Risk Factors, Adverse Outcomes, Pelvic Inflammatory Disease, Blood Transfusion.

Ectopic pregnancy refers to the complication of pregnancy when the fetus is implanted outside the uterine cavity<sup>1</sup>. The classical triad of Ectopic pregnancy comprises abdominal pain, vaginal bleeding, and amenorrhea. However, symptoms may vary depending on the site<sup>2</sup>. In developed nations, the rate of Ectopic pregnancies is approximately 1-2%, while it might be as high as 20% among people with history of tubal surgery or previous Ectopic

## Editor's Comment :

- History of IUD use, previous ectopic pregnancy, and prior PID are strong independent predictors of ectopic pregnancy.
- Adverse outcomes such as ruptured ectopic pregnancy and HDU admission are most strongly associated with IUD use, prior ectopic pregnancy, and increased PRBC transfusion requirement.
- The study offers a practical evidence-based framework for early risk identification, which can help clinicians intervene promptly and reduce maternal morbidity.

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pregnancy<sup>3</sup>. In India, there are regional differences in the frequency of ectopic pregnancy. It usually varies between 0.9 to 2.5%, close to the rates reported in developed countries<sup>4</sup>. However, the rate of ruptured Ectopic pregnancies was relatively high in most studies<sup>4-6</sup>. Ectopic pregnancy is the primary cause of maternal morbidity and decreased childbearing potential in women of reproductive ages. It is also the leading cause of pregnancy-related deaths during the first trimester<sup>7</sup>. These findings indicate that identifying the risk factors of Ectopic pregnancy and early diagnosis is crucial in preventing complications arising from Ectopic pregnancy.

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The risk factors for Ectopic pregnancy include Pelvic Inflammatory Disease (PID), intrauterine device use, previous exposure to diethylstilbestrol, tubal or intrauterine surgery, smoking, advanced maternal age, previous Ectopic pregnancy, endometriosis, tubal ligation, history of infertility, and infertility treatment<sup>8</sup>. A history of specific sexually transmitted infections, such as chlamydia, is also associated with Ectopic pregnancy. However, in most cases, the exact risk factors for Ectopic pregnancy remain unclear<sup>9</sup>. The cause of Ectopic pregnancy varies in countries or regions, depending on socio-economic conditions, contraceptive practices, sexual behaviors, and cultural norms<sup>10</sup>. The Eastern region of India has a separate demographic profile from the rest of the country, and disease risk factors vary significantly. However, conclusive evidence does not predict the risk factors for Ectopic pregnancy in Eastern India. Most studies focused on the demographic trends of Ectopic pregnancy in West Bengal<sup>11,12</sup>. All of them identified multigravida as a common risk factor. Barik, *et al* also identified previous cesarean section as a potential risk factor<sup>11</sup>. Therefore, we identified a lack of studies focusing on identifying the risk factors for Ectopic pregnancy in the Eastern region of India. In this study, we attempted to identify various risk factors associated with Ectopic pregnancy through a prospective case-control study conducted in a Tertiary Hospital in West Bengal.

## MATERIALS AND METHODS

### Study Design :

This institution-based prospective case-control study was conducted between March, 2021 and July, 2022 in the Department of Obstetrics & Gynaecology of the institution. This study was conducted with ethical approval from the Institutional Ethics Committee.

### Study Population :

The study was conducted on patients who were admitted to the Obstetrics and Gynaecology Department of NRS Medical College & Hospital through the Emergency or Outpatient Department after obtaining informed consent from the patients who fulfilled inclusion and exclusion criteria. Ectopic pregnancy was diagnosed by history taking, clinical physical examination, laboratory tests (urine pregnancy test/serum beta HCG) and Ultrasonography.

### Sample Size :

The sample size was calculated as 63 subjects at an alpha error of 0.5 and power of 80%, assuming a 5.4 odds ratio of and a 6% prevalence. We conducted this study with 65 patients as cases (with ectopic pregnancy), and for each case of Ectopic Pregnancy, one control, ie, a woman with first-trimester intrauterine pregnancy, was included in the study as a control. The inclusion and exclusion criteria were as follows:

### Inclusion Criteria :

- (1) Patients who presented with the classic triad in their history included amenorrhea, abdominal pain, and vaginal bleeding.
- (2) Positive Urine Pregnancy Test results and absence of Intrauterine Pregnancy in Transvaginal Sonography (TVS).
- (3) TVS showing fluid (echogenic) in the Pouch of Douglas.
- (4) Lower concentration of  $\beta$ -Human chorionic gonadotropin ( $\beta$ -hCG) compared to normal Intrauterine Pregnancy and a doubling time of more than two days.

### Exclusion Criteria :

1. Miscarriage
2. Twisted Ovarian Tumor.
3. Ruptured Chocolate Cyst
4. Corpus luteum Rupture
5. Pelvic Inflammatory Disease
6. Perforated Peptic Ulcer

For each case and control, the following outcomes were considered:

### Outcome Definitions :

#### (A) Risk factors :

- (1) Age.
- (2) Pulse (Pulse rate)
- (3) Diastolic Blood Pressure (DBP)
- (4) Systolic Blood Pressure (SBP)
- (5) Hb on admission (Hemoglobin on admission)
- (6) Number of packed Red Blood Cell transfusions (No of PRBC Transfusion)
- (7) Period of Amenorrhea (POA)
- (8) Parity
- (9) Previous History of (H/O) Ectopic Pregnancy.
- (10) Previous H/O Pelvic Inflammatory Disease (PID).

- (11) H/O infertility
- (12) Use of Intrauterine Contraceptive Devices (IUD).
- (13) H/O abortion.
- (14) H/O Dilation & Curettage (D&C).

#### (B) Adverse outcomes:

- (1) Ruptured Ectopic
- (2) Hemodynamic shock.
- (3) Requirement of blood transfusion.
- (4) Maternal death.
- (5) HDU admission.

#### Statistical Methods:

The following assumptions were made regarding the data:

- (1) Cases of the samples should be independent,
- (2) The populations from which the samples are drawn have the same variance (or standard deviation),
- (3) Samples were randomly drawn from different populations.

The normality of the data was tested using the Anderson-Darling test, Shapiro-Wilk test, Kolmogorov-Smirnov test and visually by QQ plot.

Linear regression was used to assess whether quantitative data were associated with Ectopic pregnancy and adverse outcomes. Similarly, logistic regression analysis was performed for ordinal data.

Among the adverse outcomes, hemodynamic shock and maternal death were excluded because there were no cases. All Ectopic pregnancy cases required blood transfusion; therefore, blood transfusion was not considered. Finally, for Ectopic pregnancy, the need for HDU admission and Ruptured Ectopic Pregnancy was considered.

All statistical analyses were performed using Epi Info™ software (Version 7.2, Centers for Disease Control and Prevention (CDC), Atlanta, Georgia, USA, <https://www.cdc.gov/epiinfo/pc.html>)

## RESULTS

#### Linear Regression Analysis :

Linear regression analysis was performed on the quantitative data (Age, DBP, SBP, Hb on admission, Parity, Pulse, No of PRBC Transfusion and Period of amenorrhea (POA in Weeks) to determine the independent association between the occurrence of

Ectopic pregnancy and adverse events [need for High Dependency Unit (HDU)] admission and ruptured Ectopic pregnancy)(Table 1).

In the linear regression analysis, most variables were not significantly associated with any of the outcomes. For the prediction of ectopic pregnancy, Hb levels at admission and No of PRBC Transfusion can be considered an independent predictive factor with a p-value less than 0.05. Even though SBP and POA also have a significant p-value, the coefficient is too low to draw any meaningful correlation with the occurrence of ectopic pregnancy.

#### Logistic Regression Analysis :

Logistic regression was used to analyze ordinal data and evaluate their association with Ectopic pregnancy and adverse outcomes (Table 2).

In the logistic regression analysis, we find a significant association between IUD usage and past history of

Table 1 — Linear Regression analysis of nominal data (Three outcomes were evaluated)

Variable	Coefficient	95% Confidence	STD Error	F-test	P-value*
<b>(A) Ectopic Pregnancy</b>					
Age	0	-0.01	0.005	0.0021	0.963646
DBP	-0.01	-0.017	0.004	8.6357	0.003949
SBP	-0.007	-0.013	0.003	4.7902	0.030542
Hb on admission	0.135	0.064	0.036	14.3207	0.000241
Parity	0.05	-0.001	0.026	3.7035	0.056647
Pulse	0.003	-0.001	0.002	2.7826	0.09788
No of PRBC Transfusion	0.349	0.249	0.05	47.6724	0.00001
POA (Weeks)	-0.033	-0.061	0.014	5.1217	0.025411
<b>(B) Need for HDU admission</b>					
Age	0.002	-0.01	0.007	0.1451	0.703972
DBP	-0.001	-0.01	0.004	0.0912	0.763208
SBP	-0.003	-0.011	0.004	0.6945	0.406291
Hb on admission	0.012	-0.075	0.044	0.0797	0.778199
Parity	-0.01	-0.074	0.032	0.0888	0.766176
Pulse	0.001	-0.004	0.003	0.1298	0.719281
No of PRBC Transfusion	0.335	0.211	0.063	28.5619	0.00001
POA (Weeks)	-0.006	-0.041	0.018	0.1046	0.746923
<b>(C) Ruptured Ectopic</b>					
Age	-0.01	-0.023	0.006	2.4005	0.123912
DBP	0.002	-0.007	0.004	0.1281	0.720991
SBP	-0.007	-0.015	0.004	3.6353	0.058939
Hb on admission	-0.046	-0.131	0.043	1.133	0.289253
Parity	0.056	-0.007	0.032	3.1206	0.07983
Pulse	0.001	-0.004	0.002	0.1508	0.698443
No of PRBC Transfusion	0.278	0.157	0.061	20.629	0.000013
POA (Weeks)	0.016	-0.019	0.018	0.8316	0.363622

\*P<0.05 is considered significant.

Table 2 — Logistic Regression analysis of original data (Three outcomes were evaluated)

Term	Odds Ratio	95%	CI	Coefficient	SE	Z-Statistic	P-Value
<b>(A) Ectopic Pregnancy</b>							
H/O D & C (Yes/No)	3.8425	0.8459	17.4538	1.3461	0.7722	1.7433	0.0813
H/O Abortion (Yes/No)	0.6868	0.2617	1.8029	-0.3757	0.4924	-0.763	0.4455
H/O Infertility (Yes/No)	1.5588	0.2581	9.4158	0.4439	0.9176	0.4838	0.6285
IUD Usage (Yes/No)	11.2138	2.3137	54.3507	2.4171	0.8053	3.0016	0.0027
Previous H/O Ectopic (Yes/No)	20.605	2.1561	196.9103	3.0255	1.1517	2.6271	0.0086
Previous H/O PID (Yes/No)	3.9077	1.463	10.4374	1.3629	0.5013	2.7191	0.0065
<b>(B) Need for HDU admission</b>							
H/O D & C (Yes/No)	2.2599	0.5569	9.1706	0.8153	0.7147	1.1408	0.2539
H/O Abortion (Yes/No)	0.6978	0.263	1.8512	-0.3599	0.4978	-0.7229	0.4697
H/O Infertility (Yes/No)	2.3234	0.4073	13.2537	0.843	0.8884	0.9489	0.3427
IUD Usage (Yes/No)	3.8856	1.2441	12.1353	1.3573	0.581	2.3359	0.0195
Previous H/O Ectopic (Yes/No)	6.9993	1.3768	35.5832	1.9458	0.8296	2.3454	0.019
Previous H/O PID (Yes/No)	2.0929	0.8328	5.2593	0.7385	0.4701	1.5709	0.1162
<b>(C) Ruptured Ectopic</b>							
H/O D & C (Yes/No)	2.184	0.5361	8.8975	0.7812	0.7166	1.09	0.2757
H/O Abortion (Yes/No)	0.8172	0.3072	2.1739	-0.2018	0.4992	-0.4044	0.686
H/O Infertility (Yes/No)	2.2439	0.3792	13.278	0.8082	0.9071	0.891	0.3729
IUD Usage (Yes/No)	4.079	1.3099	12.7021	1.4058	0.5796	2.4257	0.0153
Previous H/O Ectopic (Yes/No)	11.6349	1.9523	69.3392	2.454	0.9107	2.6945	0.007
Previous H/O PID (Yes/No)	1.2475	0.4768	3.2639	0.2211	0.4907	0.4506	0.6523

*P* < 0.05 is considered significant.

Ectopic pregnancy in the occurrence of Ectopic pregnancy along with its complications (HDU) admission and ruptured ectopic. A previous history of PID was associated with the occurrence of Ectopic pregnancy but not with its complications.

## DISCUSSION

In this study, we aimed to identify the risk factors associated with Ectopic pregnancies in Eastern India. We also attempted to identify the risk factors responsible for adverse outcomes of Ectopic pregnancies in this region. Understanding the risk factors of Ectopic pregnancy can provide a means of early detection and prediction of adverse outcomes. This study evaluated all established risk factors of Ectopic pregnancy and analyzed them using linear or logistic regression to determine the independent risk factors of ectopic pregnancy. We identified Ruptured Ectopic, Hemodynamic shock, Requirement of blood transfusion, Maternal death, and HDU admission as five important adverse outcomes and analyzed their relationship with the risk factors.

Our analysis identified that Hb on Admission, No of PRBC Transfusion, History of IUD Usage, Previous History of Ectopic Pregnancy, and Previous History of Pelvic Inflammatory Disease (PID) are independent

risk factors for the occurrence of Ectopic pregnancy. No of PRBC Transfusion, History of IUD Usage, and Previous History of Ectopic Pregnancy were identified as the most significant risk factors for adverse outcomes (Ruptured Ectopic and Need of HDU admission). Among these, No of PRBC Transfusion had the strongest correlation with the occurrence of Ectopic pregnancy and its complications. It had an extremely low p-value, which means that the number of PRBC transfusions is strongly associated with the occurrence of Ectopic pregnancy and its complications. PRBC transfusion is one of the primary management strategies for ectopic pregnancy and its associated complications<sup>13</sup>. Therefore, it is logical that the number of PRBC transfusions was strongly associated with them. However, this finding is of less predictive value since Ectopic pregnancy and its complications are often identified beforehand and PRBC transfusion is administered later. Nevertheless, this proves the validity of the analysis and conclusions of this study.

## CONCLUSION

This study proves that past medical history has a more excellent predictive value in predicting the occurrence of Ectopic pregnancy and its complications. Several studies have previously tried to identify the risk factors



associated with Ectopic pregnancy<sup>14-16</sup>. These studies have mostly identified the history of IUD Usage, Previous History of Ectopic Pregnancy, and Previous History of Pelvic Inflammatory Disease as having a significantly higher association with Ectopic pregnancy. However, none of these studies accounted for all these factors. Risk Factors for ectopic pregnancy are mostly ignored by the Scientific Community and most of the recent meta-analysis mostly focused on the management rather than prevention<sup>17-19</sup>. One recent meta-analysis on Ectopic pregnancy concluded that a history of past Ectopic pregnancy, age, tubal diameter, and infertility had strong association with the occurrence of Ectopic pregnancy<sup>20</sup>. Additionally, they found that Hemoglobin level and beta-HCG levels are associated with high risk of rupture. While the conclusions of recent studies are aligned with our results, we additionally identified the association of adverse outcomes with these risk factors, which makes our study unique. The incidence and risk factors of disease change significantly in different populations, and our study population has significantly different epidemiological characteristics. Very little data is available for our study population, which makes our study more critical for healthcare providers and policymakers.

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