

# Modifiable risk factors of ectopic pregnancy

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## Abstract

**Background:** To identify women with high risk of ectopic pregnancy and identify modifiable risk factors. **Materials and methods:** It was an observational prospective case-control study conducted in the OBGY Department of B.R.D Medical College, Gorakhpur, Uttar Pradesh, India. A total of 144 cases who were diagnosed with ectopic pregnancy (EP) and 200 controls with intrauterine pregnancies were recruited for the study from January 2019 to February 2020. Social, obstetrical, gynecological, surgical history, and information on previous and current use of contraceptives use was collected from all patients. **Observation:** The study revealed that the incidence of EP was 23.67/1,000 antenatal admissions in our institution. Risk of EP was associated with maternal age of  $\geq 30$  years,  $\geq 2$  full-term deliveries, infertility of  $>1$  year duration,  $\geq 1$  spontaneous abortion, history of postabortion infection, history of puerperal infection, previous adnexal surgery, previous appendectomy, previous cesarean section, genital tuberculosis, previous extragenital TB, and tubal corrective surgery. In women with current use of contraception, EP risk was increased only with the failure of permanent sterilization. The levonorgestrel emergency contraception in current cycle was associated with increased risk of EP. Present study does not show any association between traditional risk factors like previous EP and previous or current use of intrauterine device. **Conclusion:** By identifying risk factors being amenable to modification, such as postabortion and puerperal infection, the effective risk-reduction strategies should be devised that helps in safe motherhood. Guidelines for adnexal surgeries and appendectomy should be targeted for reduction of postoperative adhesion. Over-the-counter availability of LNG EC should be stopped because irrational and inappropriate use of LNC EC has come out as an important emerging risk factor for EP. Tuberculosis has come out as a major risk factor of EP.

**Keywords:** Ectopic pregnancy, Intrauterine devices, Intrauterine pregnancy, Levonorgestrel emergency contraception.

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## INTRODUCTION

An ectopic or extrauterine pregnancy (EP) is one in which the blastocyst implants anywhere other than the endometrial cavity. Ectopic pregnancy is the leading cause of early pregnancy-related morbidities and mortalities. While there has been a fourfold increase in incidence over the couple of decades, the mortality is reduced by 80%. In

the United States, EP comprises 1 to 2% of all first trimester pregnancies. This small proportion accounts for 6% of all pregnancy-related deaths.<sup>1,2</sup> The incidence in India varies from 1 in 300 to 1 in 150 deliveries.<sup>3</sup> The most common site of ectopic implantation is the fallopian tube. Other sites, such as the abdomen, ovary, or cervix are far less common, but are associated with higher mortality. This higher mortality is due to greater detection difficulty and massive bleeding that can result if rupture occurs at these sites. The increase in incidence in the past few decades is thought to be due to two factors: (1) Increased incidence of salpingitis and (2) improved ability to detect ectopic pregnancies. Blood loss is the major cause (about 85%) of death in ectopic pregnancies. Misdiagnosis leading to delayed treatment contributed to about half of deaths. Better understanding of EP risk factors can help in prevention of its occurrence. Ectopic pregnancy also affects future reproductive function of women. It has been shown to reduce future fertility of women. We carried a

case-control study to evaluate the risk factors for EP in B.R.D. Medical College of eastern Uttar Pradesh, India. It remains to be a condition presenting as a serious health problem for women of childbearing age. It has been shown to reduce subsequent fertility and increase the chances of subsequent EP.<sup>4</sup> There is extensive literature regarding the potential risk factors for EP. The identified risk factors for EP include age, previous EP, previous pelvic surgery, use of intrauterine devices (IUDs), female sterilization, history of pelvic inflammatory disease (PID), history of infertility, and smoking at the time of conception.<sup>4</sup> However, the study designs of previous researches focused on women not using contraception at the time of conception to explore the risk factors for EP comprehensively, which failed to evaluate the association between EP and contraceptive use in the current cycle of conception. This might make the results in an overall ambiguity, because fertility intention might have a great impact on pregnancy outcome when the study of the risk factors for EP is undertaken.<sup>5</sup> Furthermore, with the increased incidence of EP and variance in population structure and regional differences, the risk factors of EP may have changed. Most of the previous studies assessed risk factors only in cases of EP. This study is designed to compare the prevalence of risk factors in cases of EP and patients with intrauterine pregnancy (IUP), so that we can better understand the causation of EP.

### MATERIALS AND METHODS

This prospective observational case-control study was conducted in B.R.D. Medical College, Gorakhpur, Uttar Pradesh, India. Written informed consents were obtained from all the participants before they were interviewed. From January 2019 to Feb 2020, women who had been diagnosed with EP in the obstetrics and gynecology department of the hospital were interviewed as potential

candidates for the case group. A total of 200 women with IUP attending the antenatal clinic of the hospital were enrolled randomly in the study as controls. All participants were interviewed via a questionnaire according to a standard protocol to obtain information on social (age, education, and smoking) and obstetrical, gynecological, and surgical history (including number of previous abortions, PID, parity, history of previous EP, previous infertility, previous cesarean section, previous adnexal surgery, and previous appendectomy). History of previous use of contraceptives [including levonorgestrel emergency contraception (LNG EC), IUD, oral contraceptive pills, and condoms] and current use of contraceptives (IUD, barrier, oral contraceptive pills, LNG EC, female sterilization) was taken from patients.

### OBSERVATION

Totally 144 patients of EP were admitted during the period of 1 year. Incidence of EP was 23.67/1,000 ante natal checkup admissions in our institution. Out of 144 cases, 132 cases had ruptured ectopic, and laparotomy was performed. About 12 cases were managed conservatively. Table 1 compares age of patients of EP and IUP. We found that women who are <30 years of age are at increased risk of EP ( $p < 0.05$ ). Table 2 shows association between previous full-term deliveries and EP/IUP. We observed that women with <2 full-term deliveries are at increased risk of occurrence of EP ( $p < 0.05$ ). In Table 3, we compare previous history of EP and history of infertility among the patients with EP and IUP. We found that history of previous EP was not present in a single patient of EP, but was present in 5 patients of IUP ( $p > 0.05$ ). Previous history of infertility is a major risk factor for EP ( $p < 0.001$ ) in our study. Table 4 compares previous history of spontaneous abortion, puerperal infection, and post abortion infection.

**Table 1:** Age of patients of EP and IUP

| Age (years) | Cases (144) | Controls (200) | $\chi^2$ test | p-value |
|-------------|-------------|----------------|---------------|---------|
| <20         | 2           | 4              | 0.1824        | >0.05   |
| ≥20         | 142         | 196            |               |         |
| <25         | 46          | 73             | 0.7679        | >0.05   |
| ≥25         | 98          | 127            |               |         |
| <30         | 100         | 158            | 4.077         | <0.05   |
| ≥30         | 44          | 42             |               |         |
| <35         | 141         | 195            | 0.0639        | >0.05   |
| ≥35         | 3           | 5              |               |         |
| <40         | 143         | 200            | 0.0273        | <0.05   |
| ≥40         | 1           | 0              |               |         |

**Table 2:** Full term deliveries in enrolled patient

| Full term deliveries | Cases (144) | Controls (200) | $\chi^2$ test | p value |
|----------------------|-------------|----------------|---------------|---------|
| None                 | 58          | 96             | 2.019         | >0.05   |
| ≥1                   | 86          | 104            |               |         |
| <2                   | 105         | 165            | 4.554         | >0.05   |

|    |     |     |       |       |
|----|-----|-----|-------|-------|
| ≥2 | 39  | 35  |       |       |
| <3 | 131 | 188 | 1.139 | >0.05 |
| ≥3 | 13  | 12  |       |       |

**Table 3:** Association of previous EP and infertility with EP in cases and controls

|                               | Cases (144) | Controls (200) | χ <sup>2</sup> test | p-value |
|-------------------------------|-------------|----------------|---------------------|---------|
| <i>Previous EP</i>            |             |                |                     |         |
| None                          | 144         | 195            | 2.116               | >0.05   |
| ≥1                            | 0           | 5              |                     |         |
| <i>History of infertility</i> |             |                |                     |         |
| Absent                        | 105         | 178            | 14.85               | <0.001  |
| Present                       | 39          | 22             |                     |         |

**Table 4:** History of spontaneous abortion, puerperal infection, and postabortion infection among the enrolled patients

|  | Cases (144) | Controls (200) | Odds ratio | 95% Confidence interval |
|--|-------------|----------------|------------|-------------------------|
| <i>Previous spontaneous abortion</i>     |             |                |            |                         |
| None                                     | 98          | 157            | 6.879      | 0.3760–125.9            |
| ≥1                                       | 46          | 43             |            |                         |
| <i>History of puerperal infection</i>    |             |                |            |                         |
| Absent                                   | 141         | 191            | 4.064      | 0.4181–35.50            |
| Present                                  | 3           | 9              |            |                         |
| <i>History of post abortal infection</i> |             |                |            |                         |
| Absent                                   | 133         | 196            | 4.053      | 1.263–13.00             |
| Present                                  | 11          | 4              |            |                         |

**Table 5:** Comparison of appendicectomy, tubal corrective surgery, C-section, and adnexal surgery among enrolled patients

|  | Cases (144) | Controls (200) | Odds ratio | 95% Confidence interval |
|--|-------------|----------------|------------|-------------------------|
| <i>History of appendicectomy</i>           |             |                |            |                         |
| Present                                    | 2           | 2              | 1.394      | 0.1940–10.02            |
| Absent                                     | 142         | 198            |            |                         |
| <i>History of tubal corrective surgery</i> |             |                |            |                         |
| Present                                    | 3           | 0              | 9.919      | 0.5080–193.7            |
| Absent                                     | 141         | 200            |            |                         |
| <i>History of C-section</i>                |             |                |            |                         |
| Present                                    | 32          | 33             | 1.446      | 0.840–2.486             |
| Absent                                     | 112         | 167            |            |                         |
| <i>History of adnexal surgery</i>          |             |                |            |                         |
| Present                                    | 4           | 3              | 1.876      | 0.4133–8.578            |
| Absent                                     | 140         | 197            |            |                         |

**Table 6:** History of genital and extragenital TB among the enrolled patients

|                                   | Cases (144) | Controls (200) | Odds ratio | 95% Confidence interval |
|-----------------------------------|-------------|----------------|------------|-------------------------|
| <i>History of genital TB</i>      |             |                |            |                         |
| Present                           | 2           | 1              | 2.803      | 0.2516–31.23            |
| Absent                            | 142         | 199            |            |                         |
| <i>History of extragenital TB</i> |             |                |            |                         |
| Present                           | 9           | 3              | 4.378      | 1.163–16.47             |
| Absent                            | 135         | 197            |            |                         |

**Table 7:** History of IUCD, tubectomy, and current use of LNG EC among enrolled patients

| Risk Factor                      | Cases (144) | Controls (200) | Odds ratio | 95% Confidence interval |
|----------------------------------|-------------|----------------|------------|-------------------------|
| <i>History of tubal ligation</i> |             |                |            |                         |
| Present                          | 4           | 2              | 2.829      | 0.5108-15.66            |
| Absent                           | 140         | 198            |            |                         |

|         |     | History of LNG EC current user |        |              |
|---------|-----|--------------------------------|--------|--------------|
| Present | 7   | 5                              | 1.993  | 0.6194-6.411 |
| Absent  | 137 | 195                            |        |              |
|         |     | Past IUCD user                 |        |              |
| Yes     | 5   | 11                             | 0.6181 | 0.2099-1.82  |
| No      | 139 | 189                            |        |              |
|         |     | Current IUCD user              |        |              |
| Yes     | 1   | 5                              | 0.2727 | 0.0315-2.361 |
| No      | 143 | 195                            |        |              |

Among both groups, we found that previous history of  $\geq 1$  spontaneous abortion is associated with significantly high risk of EP [odds ratio (OR) = 6.879, 95% confidence interval (CI) = 0.3760–125.9]. Previous history of puerperal infection and post abortion infections also shows association with EP (OR = 4.064, 95% CI = 0.4181–35.50 and OR = 4.053, 95% CI = 1.263–13.00 respectively). We took the history of PID, but almost every patient had a history suggestive of PID at least once in their life-time. So, we specified the history to only post abortion and puerperal period. Table 5 compares the surgical history of all enrolled patients of EP and IUP as risk factor assessment. We compared the history of appendectomy, tubal corrective surgeries, C-section, and adnexal surgery among both groups with EP and IUP. We found that previous history of tubal corrective surgery was present in 3 out of 144 patients of EP, and none of enrolled patients of IUP had history of tubal corrective surgeries. Among these three tubal corrective surgeries, two were recanalization and one was peritubal adhesiolysis. This finding shows strong association between tubal corrective surgery and EP (OR = 9.919, 95% CI = 0.5080–193.7). We also found association between history of appendectomy, C-section, adnexal surgery, and occurrence of EP (appendectomy: OR = 1.394, 95% CI = 0.1940–10.02, C-section: OR = 1.446, 95% CI = 0.840–2.486, adnexal surgery: OR = 1.876, 95% CI = 0.4133–8.578). Adnexal surgery included cystectomy and ovarian drilling for polycystic ovarian disease. Table 6 compares history of genital TB and extra genital TB among the patients of EP and IUP. All the patients had received antitubercular treatment (ATT). A total of 3 out of 15 patients were still taking ATT. We found increased risk of EP in patients of genital and extragenital TB (OR = 2.803, 95% CI = 0.2516–31.23 and OR = 4.378, 95% CI = 1.163–16.47 respectively). In Table 7, we can see a strong association between failed tubectomy and EP (OR 2.829, 95% CI = 0.5108–15.66). We also found association between EP and use of LNG EC in current cycle (OR = 1.993, 95% CI = 0.6194–6.411). Four out of seven women who had EP and used LNG EC in current cycle took LNG EC  $\geq 2$  times in same cycle and did not use any other contraception. We did not find any association between EP and past and current use of IUD.

## DISCUSSION

In the current study, we found the incidence of EP to be 23.67/1,000 ANC admissions in our institution. Patel *et al.*<sup>6</sup> found mean rate of EP as 11.41/1,000 births. Incidence of EP was found to be 3.99/1,000 deliveries by Mufti *et al.*<sup>7</sup> and 5.6/1,000 deliveries by Shetty and Shetty<sup>8</sup>. We found that the risk of EP increases in women over 30 years of age. Similarly, in a case-control study by Karaer *et al.*<sup>9</sup> they found that an increase in rate of EP coincides with an increase in the age of women before reaching age 40. Bouyer *et al.*<sup>10</sup> also reported a significant relation between age and EP. The mean age of the cases was significantly higher than that of the controls (30.3  $\pm$  5 vs. 27.1  $\pm$  5.3) as indicated by Moini *et al.*<sup>11</sup> The role of age in the incidence of EP has been suggested by researchers. However, studies have produced conflicting results in this respect. The peak age of incidence was 26 to 30 years in Majhi *et al.*<sup>12</sup> Gupta *et al.*<sup>13</sup> found a maximum 72.5% cases were in the age group of 21 to 30 years. The precise physiological impact of advanced maternal age on EP risk is unclear.<sup>10</sup> It has been reported that the age-related changes in tubal function may delay ovum transport, leading to tubal implantation. However, these hypotheses remain to be tested. Furthermore, Coste *et al.*<sup>14</sup> found that this association refers to the probability of exposure to most risk factors, which increase with age. Conversely, another study by Pulkkinen and Talo<sup>15</sup> has suggested that age plays a more important role as compared with other risk factors. We observed that women with  $\geq 2$  full-term deliveries are at increased risk of occurrence of EP ( $p < 0.05$ ). Similarly Cheng Li *et al.*<sup>16</sup> showed association of EP with parity (once: OR = 1.14, 95% CI: 1.02–1.30; more than twice: OR = 1.58, 95% CI: 1.27–1.96). The highest incidence of EP was found among women who were Para 2, 32.9% by Pal *et al.*<sup>17</sup> Parashi *et al.*<sup>18</sup> found that the case and control groups had similar parity. Majhi *et al.*<sup>12</sup> found that most sufferers were primi. So, correlation with parity and EP is not consistent. As we can see in Table 3, traditional risk factor like history of previous EP was not present in a single patient of EP, but was present in 5 (2.5%) cases of IUP. Malathi *et al.*<sup>19</sup> found history of EP in 7.8% of EP cases and Shetty and Shetty<sup>8</sup> found it in 3.2% cases of EP. Barnhart *et al.*<sup>20</sup> found that among all the possible risk factors of EP, the strongest evidence is for an association

between previous EP and subsequent EP. As traditional risk factors, history of infertility was found as a major risk factor. Same was found in a study by Mufti *et al.*<sup>7</sup> and Mishra<sup>21</sup> – 8.77 and 9.67% respectively. Previous  $\geq 1$  spontaneous abortion is associated with six times increased risk of EP. Several other studies, e.g., Moini *et al.*<sup>21</sup> and Bouyer *et al.*<sup>22</sup> and our study have shown the association of prior spontaneous abortion with increased risk of EP. With regard to the available evidence, the cause of this relationship is most likely due to infection as shown in Bouyer *et al.*<sup>10,23</sup> hormonal imbalance as shown by Bouyer *et al.*,<sup>10</sup> Doyle *et al.*,<sup>23</sup> Fernandez *et al.*<sup>23</sup>; or immunologic factors as shown by Bouyer *et al.*<sup>10</sup> History of post abortion and puerperal infection is associated with increased risk of EP. This association appears to be due to PID after abortion and delivery. The PID leads to chronic pelvic pain, pain during intercourse, infertility, and a higher risk of EP. Post abortion antibiotic prophylaxis is advised for both induced and spontaneous abortion as found in Montgomery *et al.*<sup>25</sup> The IgG antibody test for *Chlamydia trachomatis* was not available in our institution. Intraoperative findings of EP were available, but could not be compared with that of IUP. So, we were solely dependent on clinical history of PID. Adnexal surgeries, C-section, appendectomy, and tubal surgeries were found to be increased risks for EP. Tubal corrective surgeries performed were recanalization in two cases and peritubal adhesiolysis in one case. 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 metaanalysis by Ankum *et al.*<sup>26</sup> There was no statistically significant relation found between EP and prior tubal surgery in Parashi *et al.*<sup>18</sup> It is uncertain whether the increased risk is arising from a surgical procedure or from the underlying problem. In Cheng Li *et al.*,<sup>16</sup> previous adnexal surgery and previous appendectomy were found to be associated with increased risk. This increased risk is most probably due to formation of adhesion in adnexa, which impairs tubal function. In the current study, we found the increased risk of EP in patients of genital and extragenital TB (OR = 2.803, 95% CI = 0.251–31.23 and OR = 4.378, 95% CI = 1.163–16.47 respectively). In Sharma *et al.*,<sup>27</sup> genital TB was responsible for 13.2% of all cases of EP. We in our study sent the samples of salpingectomy in 132 cases of ruptured EP for histopathological examination, acid fast staining, and DNA polymerase chain reaction (PCR) of *Mycobacterium* TB. We also performed Montoux test on the cases, but we could not do the same in controls. So, we could not compare the data between cases and controls. Contraceptive failure is considered to be an important factor associated with the increased incidence of EP. Due to the national family planning policy and religious and

social practices of people in this region, there may be a difference in the contraception preferences. All methods of contraception can effectively reduce the number of IUPs and EPs. However, from our study, when pregnancies occur as a result of contraceptive failure, the risk of EP is significantly increased in women, who become pregnant after tubal sterilization and LNG EC. In our study, we saw that if pregnancy occurs in women of tubal ligation, there is 2.829 times increased risk of EP. Similar finding was found in study of Patel *et al.*<sup>6</sup> and Mufti *et al.*<sup>7</sup> We did not find any association of past and current user of IUD and EP. The LNG EC use in current cycle shows a 1.993 times increased risk of occurrence of EP as the same was found in the study by Cheng Li<sup>16</sup> and Zhang *et al.*<sup>28</sup> Previous studies indicated that progesterone and its analog, LNG, could effectively inhibit human tubal activities as shown by Wanggren *et al.*<sup>29</sup> and Zhao *et al.*,<sup>30</sup> which have been considered as the main cause of impaired embryotubal retention and implantation, as documented in Shaw *et al.*<sup>31</sup>

## CONCLUSION

Motherhood is the identity of women in India. We can see that the two extremes of her motherhood – infertility and high parity – both are responsible for this dreaded outcome of pregnancy. Factors contributing for the causation of EP in both conditions are different. In cases of high parity, post abortion infection, puerperal infection, increasing age of mother, and contraception exposures appear to be main contributing factor for EP. Tuberculosis has come out as a major risk factor of EP in our study. Being a developing country, we are still fighting with *Mycobacterium* TB, which is a silent moth of the human organ system. Though new, finer diagnostic tools of detection of TB are increasingly available in the form of bacterial cultures and PCR-based diagnostics, suspicion by clinicians remains the main tool for diagnosis of the condition. Hence, doctors need to be properly trained to become more conscious of TB. Active TB infection, especially in adolescent period, should be taken care of aggressively. By identifying risk factors being amenable to modification, such as post abortion and puerperal infection, the effective risk-reduction strategies should be devised and that helps in safe motherhood. Guidelines for adnexal surgeries should be targeted for reduction of postoperative adhesion. Intraoperative and postoperative precautions should be taken to reduce adhesion. Over-the-counter availability of LNG EC should be stopped because irrational and inappropriate use of LNG EC has come out as an important emerging risk factor for EP. Long-time known risk factors like infertility, parity, and PID are inherent aspects of womanhood. We should concentrate on modifiable risk factors like pelvic surgeries, contraception, and TB for the prevention of EP.

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