



ISSN (P): 2522-6614
ISSN (E): 2522-6622
© Gynaecology Journal
www.gynaecologyjournal.com
2020; 4(3): 153-157
Received: 14-03-2020
Accepted: 18-04-2020

Ufaque Muzaffar

Senior Resident, Department of
Obstetrics and Gynaecology, GMC
Srinagar, Jammu and Kashmir,
India

Sabahat Rasool

Lecturer, Department of Obstetrics
and Gynaecology, GMC Srinagar,
Jammu and Kashmir, India

Kaiser Ahmad

Postgraduate, Department of
Obstetrics and Gynaecology, GMC
Srinagar, Jammu and Kashmir,
India

Muzamil Rasool

Postgraduate, Department of
Obstetrics and Gynaecology, GMC
Srinagar, Jammu and Kashmir,
India

Corresponding Author:

Ufaque Muzaffar

Senior Resident, Department of
Obstetrics and Gynaecology, GMC
Srinagar, Jammu and Kashmir,
India

Risk factors for ectopic pregnancy in women: A case control study

Ufaque Muzaffar, Sabahat Rasool, Kaiser Ahmad and Muzamil Rasool

DOI: <https://doi.org/10.33545/gynae.2020.v4.i3c.596>

Abstract

Introduction: Ectopic pregnancy can mimic practically each and every gynaecological disorder as well as many surgical catastrophes. It has always challenged ingenuity of the obstetricians and gynaecologists by its bizarre clinical picture. If it is not diagnosed attended in time, it may lead to maternal morbidity and mortality.

Methodology: This study was conducted on 440 patients at Government Medical College, Srinagar between Jan 2018 and March 2020. All study participants consented in writing. The study was approved by the Institutional Ethics Committee. Study participants were grouped into A and B. 220 ectopic pregnancy cases were designated as Group A and their 220 postnatal controls designated as Group B. The aim of this study was to assess the risk factors of ectopic pregnancy and to determine an association between the studied risk factors and ectopic pregnancy. Both groups were compared for various risk factors for ectopic pregnancy by means of detailed history with focus on socio economic characteristics like education, occupation, smoking status, age, gynaecological history, pelvic inflammatory disease (PID), parity, prior abortions, prior ectopic, surgical histories, use of assisted conception and contraception.

Results: In this study the main risk factors for ectopic pregnancy were Tuberculosis (OR=11.87), history of infertility ($P < 0.001$), abortions ($P=0.01$) and a history of prior ectopic pregnancy (OR=8.129). Other risk factors found to be associated with an increased risk for ectopic pregnancy were PID (OR=2.856) / Chlamydia infection (OR=0.29), endometriosis ($P=5.40$), induced conception cycle (OR=3.142), intrauterine device usage (OR=3.75), prior Caesarean section (OR=3.85) and appendectomy (OR=2.42). On the contrary, barrier methods (OR=0.25) and oral contraceptive use (OR=0.26) were protective from ectopic pregnancy.

Conclusion: PID particularly TB and Chlamydia are major etiological factors for ectopic pregnancy in our setup. Furthermore, prior ectopic pregnancy and infertility may be the result of a PID that might have caused tubal sequelae. As a preventive strategy screening and early treatment for TB and chlamydia in reproductive age group should be done so that tubal damage can be prevented. Advancing maternal age and low socioeconomic status are risk factor for ectopic pregnancy possibly due to increased chances of exposure to sexually transmitted infections (STIs) and PID. Patients with risk factors like pelvic surgeries, endometriosis, induced conception cycle, intrauterine contraception device (IUCD) users should be counselled about the possible risk of ectopic pregnancy once they conceive. So that they are kept under surveillance for early detection.

Keywords: Ectopic pregnancy, PID, Chlamydia, TB, IUCD

Introduction

Detection of ectopic pregnancy in early gestation has been achieved mainly due to enhanced diagnostic capability. Despite all the notable successes in diagnostics and detection techniques ectopic pregnancy remains a source of serious maternal morbidity and mortality worldwide especially in countries with poor prenatal care. Ectopic pregnancy was the 4th most common cause of maternal death in the most recent confidential enquiry into maternal deaths (CEMD) in UK 2000 – 2002, accounting for 73% of early pregnancy deaths [1, 2, 3]. Furthermore, it is still the most common cause of maternal deaths in the 1st trimester.

Ectopic pregnancy is 10 and 50 times as dangerous as vaginal delivery and induced abortion respectively and an important cause of maternal mortality [4]. The vast majority of ectopic pregnancies implant in the fallopian tube (95-98%). Pregnancies can grow in the fimbrial end (5%), the ampullary section (80%), the isthmus (12%) and the cornual and interstitial part of the tube (2%) [5]. A review published in 2010 concludes that tubal ectopic pregnancy is caused by a combination of retention of the embryo within the fallopian tube due to impaired embryo-tubal

transport and alterations in the tubal environment allowing early implantation to occur.

Remaining of ectopic pregnancies occur in the ovary, cervix, abdomen (primary or secondary), rudimentary horn of bicornuate uterus, caesarean scar [6]. Other very rare types of ectopic pregnancy are heterotopic pregnancy, multiple ectopic pregnancy [7] and ectopic after hysterectomy [8]. Rarely, ectopic pregnancy is reported retroperitoneally and in liver [9, 10]. John Bard of New York City performed the 1st abdominal surgery for ectopic pregnancy [11].

Tubal pregnancy presents as a chronic or an acute illness or as an acute on chronic illness. The former is much more common but the acute picture is so dramatic that it tends to receive more attention. Signs and symptoms include classical triad of amenorrhea (5-9 weeks), pain and vaginal bleeding, acute abdominal pain (dull, cramps or colicky pain). There is evidence of hemodynamic instability (hypotension, collapse, signs and symptoms of shock), adnexal mass (with or without tenderness), signs of peritoneal irritation and absence of gestational sac in uterus on ultrasound with a BHCG of 2500 mIU/ml. The diagnosis is based on the classical clinical triad with positive pregnancy test (50%), TVS with empty uterus, thickened endometrium, pseudo gestational sac and extra uterine findings of live tubal pregnancy, complex adnexal mass, fluid in POD or ring of fire on colour Doppler and HCG levels in discriminatory zone. A laparoscopic confirmation of diagnosis is useful at times [6].

During the past two decades, incidence of ectopic pregnancy has doubled to tripled in many parts of the world¹² and as per Centre for Disease Control USA, incidence has quadrupled from 1970 to 1983, 21 from 4.5% to 16.18% per 1000 pregnancies [13, 14]. However, the fatality rates have decreased by 90%. As per American College of Obstetricians and Gynaecologists (2008), 2% of all 1st trimester pregnancies in United States are ectopic and accounts for 6% of all pregnancy related deaths¹⁵. In a multicentric case control study in India the incidence was 3.12/1000 pregnancies [16].

Methodology

This study was conducted on 220 ectopic pregnancy cases designated as Group A and their 220 postnatal controls designated as Group B, in Government Medical College Srinagar. The aim of this study was to assess the frequency of risk factors of ectopic pregnancy and to determine an association between the studied risk factors and ectopic pregnancy. Both cases and controls were compared for various risk factors for ectopic pregnancy by means of detailed history on socio economic characteristics like education, occupation, smoking status, age, gynaecological history, PID, parity, prior abortions, prior ectopic, surgical histories, use of assisted conception and contraception.

Results

Table 1: Socio demographic, gynaecological and surgical histories

Risk Factors	Group A (%)	Group B (%)	Results
Age >30 years	60.4%	40.2%	P=0.011
Low Socioeconomic Status	54.6%	6.9%	P< 0.001
TB	8.1%	0.79%	OR=11.87
Smoking	4.0%	1.5%	OR=2.45
Chlamydia	15.8%	2.9%	OR=5.29
Parity >1	67.3%	52.5%	P=0.007
Endometriosis	12.3%	1.5%	P=0.041
Abortions	24.5%	9.8%	P=0.01
Infertility	22.6%	2.9%	P< 0.001
PID	23.6%	8.9%	OR=2.856
Ovulation Induction	14.3%	4.8%	OR=3.142
Barrier Contraception	4.5%	18.1%	OR=0.25
Post Coital Pill	2.5%	0%	P=0.233
Oral Contraceptive Pills (OCPs)	3.6%	12.4%	OR=0.26
IUCD	12.9%	3.4%	OR=3.75
Cesarean Section	24.6%	8.2%	OR=3.85
Appendectomy	21.4%	10.6%	OR=2.42
Myomectomy	4.8%	1.1%	OR=4.097
Ovarian Surgery	6.1%	0.8%	OR=4.121
Previous Ectopic	12.7%	1.5%	OR=8.129

Following results were drawn from the study

1. The risk of ectopic pregnancy statistically significantly increased with age (p=0.011).
2. Ectopic pregnancy occurred more in lower socioeconomic status as compared to controls with (p< 0.001) which is statistically highly significant. 54.6% of Group A belonged to lower socioeconomic classes compared to only 6.9% of Group B.
3. 4% Group A and 1.5% of Group B patients were smokers in our study with OR 2.45. the risk of ectopic pregnancy is 2.45 times higher in smokers, indicating that smoking is a risk factor for ectopic pregnancy.
4. 24.5% of Group A and 9.8% of Group B had prior abortion (spontaneous/induced). This association was found statistically significant (p=0.01) suggesting that prior abortions is a risk factor of ectopic pregnancy.
5. 67.3% of Group A were multipara whereas 52.5% of Group B were primiparas. Increasing parity increases the risk of ectopic pregnancy (p=0.007).
6. 23.6% of Group A and 8.9% of Group B had history of PID. Odds Ratio was found to be 2.856, making PID a risk factor for ectopic pregnancy.
7. Among 220 patients in group A 8.1% and out of 220 patients in group B only 0.79% had history of TB with an OR of 11.87. TB was a very strong risk factor for ectopic pregnancy in our study.
8. IgG anti Chlamydia antibody testing using ELISA kits was done in all 220 patients in group A and 220 patients in

group B, out of them 15.8% and 2.9% were positive, respectively. Chlamydia infection was found to be strongly associated with ectopic pregnancy in our study with an OR of 5.29.

9. Out of 220 patients in group A, 12.3% had endometriosis and out of 220 patients in group B 1.5% had endometriosis. Endometriosis is found to increase risk of ectopic pregnancy.
10. Of 220 patients in group A, 22.6% were treated for primary infertility whereas of 220 patients in group B studies, only 2.9% had history of primary infertility This association was statistically found to be significant (p value <0.001)
11. Out of 220 patients in group A 14.3% and out of 220 patients in group B only 4.8% had undergone OI for the present pregnancy. Ovulation induction predisposes to ectopics with an OR of 3.142.
12. 4.5% patients in group A had history of use of barrier contraception whereas 18.1% of patients in group B had history of use of Barrier contraception. Barrier contraception was found to be protective for ectopic pregnancy with an OR of 0.25
13. 3.6% had history of OCP use whereas of 220 controls studied, 12.4% had similar history. As per this study the rate of ectopic pregnancy among pill users was lower than non users with OR =0.28
14. 24.6% and 8.2% respectively had previous caesarean sections in Groups A and B.
15. In present study 21.4% of patients in group A and 10.6% of patients in group B had history of Appendectomy with OR of 2.42.
16. 4.8% of patients in group A and 1.1% of patients in group B gave history of myomectomy with OR of 4.097.
17. Out of 220 patients in group A 6.1%, 0.8% had history of ovarian Surgery with OR = 4.121
18. In this study 12.7% of Group A and 1.5% of Group B participants had prior ectopic pregnancy with an OR of 8.129.

Our study demonstrates that in 35% of ectopic pregnancies had no identifiable known risk factor. In remaining cases, the predominant risk factors were history of TB (OR=11.87), infertility (p=0.001), abortions (p=0.01) and prior ectopic pregnancy (OR=8.129). Other risk factors found to be associated with an increased risk for ectopic pregnancy are PID / Chlamydia infection (OR=2.856), endometriosis (P=0.041), induced conception cycle (OR=3.142), intrauterine device usage (OR=3.75), prior Caesarean section (OR=3.85) and Appendectomy (2.42). Barrier contraception and OCPs were protective from ectopic pregnancy with ORs of 0.25 and 0.26, respectively.

Discussion

Age: In our study, we found a significant relationship between age and ectopic pregnancy. The risk of ectopic pregnancy increased with increasing age and it remained statistically significant (p=0.012) as observed by Coste J, *et al.* Duncan WC *et al.* and Archibong EI *et al.* in their studies [17, 18, 19].

Socio economic status: Our study concluded that ectopic pregnancy occurred more frequently in lower socioeconomic status as also observed by, Kim YJ *et al.* Aboyegi AP, and Banerjee B *et al.* in their studies [20, 21, 22].

Smoking: In our study smoking had an OR of 2.45 for ectopic

pregnancy. Similar observations were made by Davis F *et al.* Lucantoni Vat el, Saraiya M, *et al.* and Coste J *et al.* in their studies [23, 24, 25, 26].

Abortions: In our study, the association of prior abortion was found statistically significant as a risk factor for ectopic pregnancy. (p 0.01). This observation was similar to those made by Jobspira N *et al.*, Bouyer J *et al.* and Parazzini F *et al.* [27, 17, 28].

Prior deliveries: Our study concluded that ectopic pregnancy increased with increasing parity. These observations were similar to those by Alswadi H *et al.* R.C Karki *et al.* [29, 39].

PID: In our study out of 220 cases and their equal number of controls, 23.6% of cases and 8.9% of controls had evidence of PID. OR was found to be 2.856. These observations were similar to the Observations made by Van der Veen F *et al.*, Coste J *et al.* and Karaer A *et al.* [31, 32, 17].

TB: In our study of 220 cases 8.1% had confirmed TB and out of 220 controls only 0.79% had TB. OR was 11.87. These observations were similar to Chowdhury JR Khan NH and Nabang W *et al.* in their studies [33, 34, 35].

Chlamydia: In the our study IgG anti chlamydial antibody testing using ELISA kits was done and 15.8% of ectopic pregnancies and 2.9% postnatal patients were positive with and OR of 5.29. These observations were comparable to the observations made by W.J. Ankum W M *et al.*, Omo Aghoja L *et al.* and Treqoning SK, *et al.* [31, 36, 37].

Endometriosis: In our study, out of 220 cases, 12.3% had endometriosis and out of 220 controls 1.5%) had endometriosis. This correlation was similar to observation made by other authors Collect P, *et al.* (1993), Malak M, *et al.* (2011), Vercellini P, *et al.* (2012) in their study [38, 39, 40].

Infertility: 22.6% of ectopic pregnancies had history of primary infertility compared to 2.9% postnatals. This association was statistically significant (pvalue <0.001). This result was similar to Bouyer J *et al.* Malak M *et al.* Ankum WM *et al.* [17, 39, 41].

Ovulation induction: 14.3% in Group A versus 4.85 in Group B had conceived the present pregnancy after ovulation induction, with OR of 3.142. Following observations were similar to ones made by Avsar FA *et al.* Coste J *et al.* Marchbanks PA *et al.* [32, 42, 43].

Barrier contraception: barrier contraception was found to be protective against ectopic gestations with an OR of 0.25. These observations matched those made by Oluwole A *et al.* Avsar FA, R.C Karki in their studies [44, 32, 30].

Postcoital pill: In our study only 2.5% of Group A took postcoital pill of levonorgestrel in index pregnancy whereas none of the controls gave such a history. Possible association of levonorgestrel with ectopic pregnancy has been supported by Candelier C, Jain S H *et al.* and Jian Z *et al.* [45, 45, 47].

Oral contraceptive pills: 3.6% of ectopic pregnancies group had history of OCP use compared to 12.4% postnatals. As per this study the rate of ectopic pregnancy among pill users was lower than non users with OR =0.26. These observations

matched with the observations made by Bouyer J, *et al.* Mol BWJ *et al.*, Wong MT *et al.* and Franks AL *et al.* [17, 48].

IUCD: 12.9% of Group A patients and 3.5% of Group B patients had history of IUCD usage with an OR of 3.75. These observations matched similarly with the observations made by Oluwole A *et al.*, Avsar FA *et al.* [42, 44].

LSCS: In our study of 220 cases, 24.6% had previous history of LSCS and of 220 controls, 8.2% had previous history of LSCS. this study shows 2 to 3 fold rise of ectopic pregnancy with previous LSCS. OR was 3.85. These observations matched with the observations of Avsar FA, *et al.* (2006), Lucantoni Vet *et al.* (1998) in their study [32, 51].

Appendectomy: In our study 21.6% of ectopic pregnancies cases and 8.2% of controls gave history of Appendectomy with OR of 2.42. These observations matched with the observations made by Job-Spira *et al.* (1991) Minaretzis D. *et al.* (1992) in their study [49].

Myomectomy: In our study 4.8% of cases and 1.1% of controls gave history of myomectomy with OR of 4.097. So as per this study ectopic pregnancy occurs 4 fold more in women with myomectomy than those with no such history. These observations matched with the observations made by Tawfeeq T *et al.* (2011) Thorburn Jet *et al.* (1999) in their study [39, 50].

Ovarian cystectomy: Out of 220 cases 6.1% and 0.8% controls had history of ovarian surgery with OR = 4.121. This study shows that risk of ectopic pregnancy in women with history of ovarian cystectomy is twice than women with no such history. This association was similar to observations made by other authors are Tawfeeq T *et al.* (2011), Szydłowska I *et al.* in their study [39, 51].

Prior Ectopic: In our study 12.7% cases and 1.5% controls had previous history of ectopic pregnancies. OR was 8.129. These observations were consistent with the observations made by Mol BW *et al.* (2006) Egerup P, *et al.* (2012) in their study [41, 52].

Conclusion

PID particularly TB and Chlamydia are major contributing factors for ectopic pregnancy in our setup. Furthermore, prior ectopic pregnancy and infertility also predispose heavily to ectopic gestations. As a preventive strategy, screening and early treatment for TB as well as Chlamydia in reproductive age group should be done so that tubal damage can be prevented.

Advancing maternal age and low socioeconomic status are risk factor for ectopic pregnancy possibly due to increased chances of exposure to STIs and PID.

These women should be targetted while counselling for risk of ectopic pregnancy in their future pregnancies History of previous ectopic pregnancy has a strong association with next pregnancy being ectopic pregnancy. Such women should be kept under surveillance and counselled adequately so that they are picked up early and managed accordingly, thus reducing their morbidity and mortality.

Previous history of abortions either spontaneous or induced are strongly incriminated as an etiological risk for ectopic pregnancy. So importance of effective contraception rather than an abortion for unwanted pregnancy needs to be stressed so that rate of abortions can be reduced and therefore reducing the risk of ectopic pregnancy.

Due to increasing trend towards abdominal delivery, risk of ectopic pregnancy is increasing. Our study depicted an important association between caesareans and ectopic pregnancy. So one of the preventive measures to decrease the risk of ectopic pregnancy is to properly counsel the patients for the future risk before on-demand cesarean sections. Further, patients with risk factors like pelvic surgeries endometriosis, induced conception cycle, post coital pill and IUCD users should be counselled about the possible risk of ectopic pregnancy once they conceive. It goes without saying that medical and conservative methods of ectopic management are suited for patients detected and diagnosed early, thus reducing morbidity and mortality associated with ectopic pregnancy.

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