CHANGING TRENDS IN RISK FACTORS OF ECTOPIC PREGNANCY- A CASE CONTROL STUDY*Sujamol Jacob¹, Aswathy Gopi Nath²*¹*Additional Professor, Department of Obstetrics and Gynaecology, Sree Avittom Thirunal Hospital, Government Medical College, Trivandrum.*²*Junior Resident, Department of Obstetrics and Gynaecology, Sree Avittom Thirunal Hospital, Government Medical College, Trivandrum.*

ABSTRACT

BACKGROUND

Ectopic Pregnancy (EP) is an early pregnancy complication occurring in 1% - 2% of all naturally conceived pregnancies. The overall incidence has increased over the past decades. Although, the risk factors have been analysed in various studies, the exact role and strength of these factors may vary over years. The purpose of this study is to evaluate the changing scenario in the contribution of individual risk factors associated with EP.

MATERIALS AND METHODS

This is a prospective case-control study conducted at Sree Avittom Thirunal Hospital Govt. Medical College, Trivandrum - a major tertiary care referral centre in Kerala, South India. A total of 125 cases of ectopic pregnancy and 125 controls of early intrauterine pregnancy are included in the study. Patients in early pregnancy admitted with abdominal pain or bleeding per vaginum was evaluated and categorised as cases and controls after ultrasound confirmation. Personal interview was conducted using a structured questionnaire regarding the probable risk factors in both cases and controls.

RESULTS

The findings revealed that the case and control groups were similar with regard to socio-demographic profile like education, occupation, socio-economic status and place of residence. But high risk for ectopic was found with advancing age of > 30 years and increasing parity. Prior adverse reproductive outcomes like spontaneous and induced abortions and previous history of ectopic pregnancy showed a significant correlation with occurrence of EP. Patients with history of infertility was a major contributing factor to EP in the present study. But unlike earlier studies, current use of contraception and contraceptive failure and clinically diagnosed pelvic infections accounted for only a small proportion of EP cases.

CONCLUSION

The study identified factors like prior ectopic gestation, tubal sterilisation and history of infertility has 3 major contributors to EP. Increasing public awareness on sexual hygiene and availability of contraceptive measures with significantly low failure rates could account for the declining role of these factors.

KEYWORDS

Ectopic Pregnancy, Risk Factors, Infertility, Contraception.

HOW TO CITE THIS ARTICLE: Jacob S, Nath AG. Changing trends in risk factors of ectopic pregnancy- a case control study. J. Evolution Med. Dent. Sci. 2017;6(11):831-836, DOI: 10.14260/jemds/2017/181

BACKGROUND

Ectopic Pregnancy (EP) is a life-threatening emergency encountered in women of reproductive age group. It remains the leading cause of maternal mortality in the first trimester of pregnancy and accounts for almost 5% of maternal deaths. Numerous studies have attempted to explain the risk factors for ectopic pregnancy.^{1,2} This study is aimed to evaluate the changing scenario in the contribution of risk factors for EP.

Over the past decades, EP has increased as a result of an increased and persistent exposure to its risk factors. The popularity of various contraceptive methods has predisposed its users to EP following contraceptive failure. Studies^{3,4} have shown that OCP, IUD and female sterilisation cause increased risk of EP to different degrees in cases of contraceptive failure.

The association between infertility and EP⁵ is complex, as it can be consequence of infertility as well as a cause. Two principal factors for EP in infertile patients are genital tract infections and tubal surgery. Patients with tubal factor infertility are at increased risk of ectopic pregnancy.

A previous history of EP is considered a major risk factor for subsequent recurrence.^{6,7} After one EP, the patient has a 7 - 13 increased likelihood of another EP. Each successive occurrence significantly increases the risk.

Pelvic inflammatory disease has been implicated in the increased incidence of EP following either natural or assisted conception.⁸ Chlamydia trachomatis infection is the most common STD worldwide that leads to tubal occlusion, EP and infertility.

Financial or Other, Competing Interest: None.

Submission 29-12-2016, Peer Review 22-01-2017,

Acceptance 28-01-2017, Published 06-02-2017.

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DOI: 10.14260/jemds/2017/181

But despite the knowledge of these risk factors, the strength of association between these factors and risk of EP have evolved over time. With advances in assisted reproductive technology and newer methods of contraception, more insights are needed to learn about these factors. Also, the incidence and risk factors vary among population studied. Therefore, this study is designed to identify the changing scenario of potential risk factors among women with EP attending Sree Avittom Thirunal Hospital, Govt. Medical College, Trivandrum - A major tertiary care referral hospital in Kerala, South India. Eventually, this analysis will help in successful implementation of risk reduction counselling programme pre-conceptionally and also aid in early diagnosis of EP in high risk patients, so that optimal management can be implemented before tubal rupture, thereby preserving their future fertility.

MATERIALS AND METHODS

This is prospective case-control study conducted at Sree Avittom Thirunal Hospital, Govt. Medical College, Trivandrum, Kerala. The study protocol was approved by the Institutional Research Committee and State Board of Medical Research Medical College, Trivandrum. Written informed consent was obtained from all participants before interview.

RESULTS

During the study period of 12 months from March 2013 to February 2014, a total of 250 were enrolled in the study; 125 cases were diagnosed as EP by menstrual history, symptoms, physical examination and confirmed by serial beta-HCG and transvaginal ultrasound; 125 women with ultrasound confirmed early intrauterine pregnancy served as control.

Data was collected using a structured questionnaire by personal interview regarding women's prior reproductive history such as previous spontaneous abortions, induced abortions, previous h/o ectopic pregnancies. Detailed h/o infertility evaluation and treatment, current or past use of contraceptive measures like OCP IUD, LNG - IUS, EC pills; sexual history and treatment of PID and STDs and h/o tubal surgeries like sterilisation and recanalisation.

Data was analysed by examining the frequency distribution of each variable in case and control groups. Univariate analysis was done to estimate the Odds Ratio (OR) of each variable and 95% Confidence Intervals (CI). P value of < 0.05 was considered statistically significant. Logistic regression analysis was performed including variables with significant P value. Adjusted odds ratio was calculated, which gave an additional dimension to the study which becomes significant at the community level.

Profile		Ectopic Pregnancy (N = 125)		Intrauterine Pregnancy (N = 125)		OR (95%, CI)	P value
		N	%	N	%		
Age	> 30	32	25.6	9	7.2	4.44 (2.02 - 9.75)	< 0.001
	< 30	93	74.4	116	92.8		
Education	Up to 10 th	44	35.2	47	37.6		0.693
	Plus Two and Higher	81	64.8	78	62.4		
Occupation	Housewife	116	92.8	114	91.2		0.641
	Employed	9	7.2	11	8.8		
SES	Upper Lower/Lower	73	58.4	61	48.8		0.128
	Lower Middle/Upper Middle	52	41.6	64	51.2		
Residence	Rural	83	66.4	94	75.2		0.126
	Urban	42	33.6	31	24.8		

Table 1. Socio-Demographic Profile of Participants

Risk of EP is found to increase with advancing age (> 30 years), which was statistically significant (OR 4.44, 95% CI 2.02 - 9.75, P value < 0.001). There is no significant difference between cases and controls with regard to other socio-demographic characteristics, thereby having a comparable group as control.

		Ectopic Pregnancy		Intrauterine Pregnancy (N = 125)		OR 95%, CI	P Value
		N	%	N	%		
Gravida	Multi	60	48.0	30	24.0	2.92 (1.70 - 5.02)	< 0.001
	Primi	65	52.0	95	76.0		
Previous H/O ectopic		8	6.4	1	0.8	8.48 (1.04 - 68.83)	0.017
Previous spontaneous abortion		10	8.0	2	1.6	5.35 (1.15 - 24.93)	0.018
Previous MTP		10	8.0	2	1.6	5.35 (1.15 - 24.93)	0.018
History of infertility		23	18.4	10	8.0	2.59 (1.18 - 5.71)	1.015
Previous caesarean		23	18.4	16	12.8		0.222
H/O tubal sterilisation		22	17.6	3	2.4	8.69 (2.53 - 29.85)	< 0.001

Table 2. Reproductive History of Participants

Most of the conditions studied under reproductive history showed significant association with ectopic pregnancy. Multiparity is strongly related to risk of EP, though the number of multi's were less in the study group (OR 2.92, 95% CI 1.70 - 5.02, P value < 0.001). Adverse pregnancy outcomes such as spontaneous abortion, induced abortion and previous h/o EP also shows a significant association with a P value < 0.05. This could probably be mediated through sub-clinical pelvic infection, which is often missed due to lack of specific symptoms and signs. However, previous caesarean section does not seem to increase the risk of ectopic in subsequent pregnancies, (P value - 0.222).

Causes	Ectopic Pregnancy (N = 125)		Intrauterine Pregnancy (N = 125)		OR (95% CI)	P Value
	N	%	N	%		
Total infertility	23	18.4	10	8.0	2.59 (1.18 - 5.71)	0.015
Male factor	3	2.4	2	1.6		0.651
PCOS	10	8.0	2	1.6	5.35 (1.15 - 24.93)	0.018
Tuboperitoneal	8	6.4	1	0.8	8.48 (1.04 - 68.83)	0.017
Ovulation induction	6	4.8	2	1.6	3.211 (1.31 - 7.90)	0.151
OI + IUI	14	11.2	5	4.0	3.027 (1.05 - 8.68)	0.032
Unexplained	2	1.6	5	4.0		0.250

Table 3. Relation between Causes of Infertility and Ectopic Pregnancy

History of infertility was associated with the risk of ectopic as per many reports. Our study also showed infertile patients on treatment are at significantly increased risk of ectopic pregnancy (p value - 0.015) compared to women with high fecundity. Women with tuboperitoneal factors like endometriosis and peritubal adhesions (p value 0.017) and those with polycystic ovaries (p value 0.0218) show significant correlation. Ovulation induction with clomiphene citrate alone does not show an increased risk (p value 0.151), while ovulation induction followed by intrauterine insemination seems to significantly increase the risk (p value 0.032).

Contraceptive Method	Ectopic Pregnancy (N = 125)		Intrauterine Pregnancy (N = 125)		OR 95% CI	P Value
	N	%	N	%		
Total	5	4.0	3	2.4		0.472
Natural	1	0.8	0			
Condoms	0	0	2	1.6		
OCPs	0	0	0	0		
IUCD	0	0	0	0		
DMPA	1	0.8	0	0		
EC Pills	3	2.4	1	0.8	3.04 (0.31 - 29.72)	0.313
Sterilisation Failure	22	17.6	3	2.4	8.69 (2.53 - 29.83)	< 0.001

Table 4. Contraception and Ectopic Pregnancy

Earlier studies showed that most forms of contraception can increase the relative incidence of EP by decreasing the number of intrauterine pregnancies. But a meta-analysis case control study by Cheng Li 2014 reported that woman with current use of most contraceptives reduced the risk of both intrauterine and ectopic pregnancies. Our study also did not show a significant correlation between current use of contraception and ectopic pregnancy. In fact, only 5 cases (4%) resulted from contraceptive failure, which was not statistically significant (P - 0.472). There was no case of OCP and IUD failures in the study population. But a correlation was observed between DMPA and emergency contraceptive pill users and occurrence of ectopic, even though it did not reach statistically significant proportions. The slightly increased risk in progesterone only contraceptive preparations may be attributed to its effect in diminishing tubal motility.

Tubal sterilisation failure showed a significant correlation. There were 22 cases of ectopic pregnancies compared to only 3 cases of intrauterine pregnancy among sterilised patients. This is statistically significant. The odds for ectopic following tubal sterilisation is 8, highlighting the need for high index of suspicion for ectopic pregnancy among sterilised patients.

Importance of pelvic infection causing ectopic pregnancy following either natural or assisted conception is well documented in several studies. But the present study showed pelvic infections predisposing to ectopic pregnancy did not reach statistical significance among natural conceptions (P value - 0.151), while tubal factor in infertile subjects was a significant risk factor for ectopic pregnancy (OR 8.48, 95% CI = 1.94 to 68.83, P value 0.017). Other minor factors evaluated were tubal recanalisation and other abdominopelvic surgeries like ovariectomy and appendectomy, but none showed significant correlation probably due to the limited number of cases in the study population.

Table 5 shows the results of the multivariate analysis between the ectopic pregnancy and individual risk factors. In order to build a prediction model and find the most significant risk factors of EP, binary logistic regression was employed. The result of the analysis showed that other than advancing age and parity, the two major factors associated with a significant increase in risk of ectopic in the recent years are tubal sterilisation (AOR - 3.904, 95% CI 0.983 - 15.510, P value 0.053) and history of infertility (AOR 3.410, 95% CI 1.497 - 7.766, P value 0.003).

	OR	B	S.E.	Wald	df	p	Adjusted OR	95% CI for AOR	
								Lower	Upper
Age > 30	4.4	1.019	.437	5.431	1	.020	2.769	1.176	6.523
Multiparity	2.92	.454	.341	1.771	1	.183	1.575	.807	3.074
Tubal sterilisation	8.69	1.362	.704	3.744	1	.053	3.904	.983	15.510
H/O of infertility	2.59	1.227	.420	8.535	1	.003	3.410	1.497	7.766
H/O ectopic	8.48	1.219	1.153	1.118	1	.290	3.385	.353	32.442
H/O spontaneous abortion	5.53	.979	.861	1.295	1	.255	2.663	.493	14.384
H/O induced abortion	5.53	1.250	.854	2.145	1	.143	3.491	.655	18.604
Constant		-14.329	3.562	16.187	1	< 0.001			

Table 5. Binary Logistic Regression predicting Risk Factors of EP

Clinical Outcome of Cases

Majority of patients presented in early pregnancy with abdominal pain (38.4%) or bleeding pre-vaginum (41.6%). Some were diagnosed at routine antenatal ultrasound (18.4%). None of the patients came in a state of circulatory collapse. Majority of cases could be diagnosed in the unruptured phase (79.2%). Only 26 cases (20.8%) came with features of rupture; 28% of cases were successfully managed with methotrexate and 39.2% could be expectantly managed. Surgical treatment was resorted to only one-third (32.8%) of the cases. Increasing awareness of the emerging risk factors and high index of suspicion together with high resolution ultrasound has made the early diagnosis of ectopic pregnancy possible. Also advances in medical and expectant management has helped these patients to preserve their future fertility.

DISCUSSION

In the present study, we demonstrated that the risk of ectopic pregnancy increases in women over 30 years of age. A 4 - 5 fold increase is observed above the age of 30 compared to those below 30. Bouyer et al⁸ in a large case-control study reported significant correlation between age and EP. The slope of the association appeared to be steeper after 35 - 40 years. Kareer et al⁷ also reported similar observations with increase in incidence occurring even before age 40. However, the exact pathological factors of advanced maternal age on ectopic pregnancy risk is unclear. Age related changes in tubal function in the form of progressive loss of myoelectrical activity of the fallopian tube affecting tubal motility might lead to tubal implantation. Coste et al⁹ refers to the possibility of exposure to multiple risk factors with increasing age and parity as the cause for tubal implantation.

Prior spontaneous and induced abortions show significant correlation with the incidence of ectopic pregnancy in our study. But studies on this issue give conflicting results. Bouyer et al⁸ have found a strong relation between spontaneous abortion and risk of ectopic, especially in women with three or more consecutive abortions. But a meta-analysis study by Ankum et al⁵ observed no significant association between spontaneous abortion and ectopic pregnancy. Coste et al⁹ suggested that induced abortion may be a risk factor, whereas other studies report no significant association. The association may be interpreted as the consequence of infection following multiple abortions. Hormonal factors may also play a role acting as a common risk factor for both EP and abortion.

In a followup study by Tuomivaara¹⁰ on 929 infertile couple showed an ectopic rate of 9% indicating very strong association between infertility and ectopic gestation. The two principal risk factors among infertile subjects could be genital

tract infection and tubal surgery. Patients with tubal factor infertility are at significantly increased risk of EP. The prevalence of EP following ART ranges from 2.1 to 8.6% of all pregnancies and it can reach up to 11% with history of tubal factor pathology.¹¹ Another study described that the odds for EP in 900 women following IVF was 8.81 (95% CI 1.68 - 21.21) for those with tubal factor infertility compared to 5.82 (95% CI 3.47 to 9.78) for non-tubal infertility.¹² Even though IVF bypasses the fallopian tube altogether, EPs can occur if the embryo is placed too high in the uterine cavity - giving the embryo greater chance of wandering and implanting in the tube. The alteration in the endocrine milieu in the stimulated cycle following COH may also be a potential risk factor for EP following IVF - ET. Higher circulating concentration of Estradiol could be associated with a reversed migratory process of transferred embryo. The incidence of heterotopic pregnancy is also increased to the rate of 1 in 8000 after ART.^{13,14} However, a 10-year study conducted by Perkins et al in United States from 2001 - 2011 show that the incidence of EP following ART, especially IVF ET has been reported to reduce since 2001.¹⁵ But the present study still show a significant association between infertility and ectopic pregnancy (OR 2.95, 95% CI, 1.18 - 5.71, P value 0.015); 18% of the ectopic pregnancy group gives history of infertility, while only 8% in the control group had infertility treatment. Tubal factor infertility had a highest association with EP (OR 8.48 95% CI 1.04 - 68.83, P value 0.017).

The association between polycystic ovarian syndrome and ectopic pregnancy was studied in patients undergoing controlled ovarian hyper-stimulation. In a study that included 5399 women who had clinical pregnancies after IVF - ET (PCOS - 205 and non-PCOS - 5134). PCOS women are at increased risk of ectopic pregnancy than non-PCOS subjects.¹⁶ There appears to be a lower threshold of hyper-physiological estradiol level, which triggers the occurrence of EP after COH. Fresh and Cryo thawed. ET cycles were analysed separately. In fresh ET cycles in women undergoing COH, women with PCOS had 3.06 times higher risk of EP compared to those without PCOS. But in Cryo thawed cycles without COH, the ectopic rates between women with and without PCOS were similar (OR 0.94).¹⁷ In our study, the odds for ectopic pregnancy in PCOS subjects was 5 compared to non-PCOS subjects, which was similar to the previous subjects. Studies report that IUI per se does not increase the risk of ectopic, but all women having infertility treatment need to be aware of possibility of EP. Present study showed the significant risk of EP when ovarian hyper-stimulation was given prior to intrauterine insemination.

A multi-centre case control study conducted at Shanghai reported that women with current use of most contraceptives reduce the risk of both unwanted intrauterine and ectopic

pregnancy, but a meta-analysis study by Mol et al showed that OCPs, IUDs and female sterilisation could increase the risk of ectopic pregnancy to different degrees in cases of contraceptive failure. But previous use of IUDs was linked to only slightly increased risk (AOR - 1.87) of ectopic pregnancy based on the duration of use. Bouyer et al also reported a decreased risk of ectopic in previous users of OCPs and LNG-IUS. In short the incidence of ectopic due to contraceptive failure is on a declining trend, probably due to increasing contraceptive awareness in choosing the right method at the right time.

Female tubal sterilisation is the most accepted method of contraception in India contributing to roughly 62% of all contraceptive use. But failures can occur even several years after the procedure. In the first year after sterilisation, the estimated failure is 0.1% - 0.8%. A greater proportion of early failures (< 1 year) are mainly due to initial non-occlusion of tube due to improper procedure compared with late failures due to tubal regeneration leading to spontaneous tubal recanalisation or tubo-peritoneal fistula. In a report by NEJM,¹⁸ while EP after tubal sterilisation is not common, it is also not rare. Many EP occur years after the procedure and was more frequent in women aged < 30 years at the time of sterilisation and in those who had inflamed fallopian tubes. Present study also showed a significant correlation (OR - 8.69, 95% CI 2.53 - 29.85, P value < 0.001).

The importance of infectious factors in EP is well documented following either normal or assisted conception.^{19,20} A past history of PID is associated with 7.5 times greater risk of EP. Chlamydia trachomatis is the most common STD worldwide that leads to tubal occlusion, EP and infertility. Despite spontaneous clearance of chlamydial infection, antibodies against this organism (cHSP 60) remain detectable for many years and is associated with poor reproductive outcomes including early pregnancy loss and EP following IVF.²⁰ However, this association was not significant after adjustment for prior PID, as the clinically diagnosed ones is statistically low. But subclinical tubal infection could be the indirect cause of EP associated with spontaneous or induced abortions, IUDs and tubal factor infertility.

CONCLUSION

Ectopic pregnancy is a major medical and emotional problem in a woman's reproductive life. Although several risk factors for ectopic pregnancy are known, the cause for a large proportion of EP still remains to be studied. The social and cultural characteristics in different countries also influence the risk. The present study shows a tight link between infertility and EP. Other major risk factors have shown a shift from traditional factors like pelvic infection and contraceptive failure to common events like tubal sterilisation and h/o of previous ectopic pregnancy. Hence, refocusing your attention to the changing scenario is necessary. The increased awareness and knowledge of emerging risk factors will enable us to make early and accurate diagnosis of EP and thereby optimise management strategy. Resorting to proper medical therapy instead of surgery is pivotal for subsequent fertility and should be our primary aim in managing ectopic pregnancy.

Abbreviations

EP - Ectopic Pregnancy, OCP - Oral Contraceptive Pill, IUD - Intrauterine Device, LNG-IUS - Levonorgestrel Intrauterine System, DMPA - Depot Medroxyprogesterone Acetate, EC Pills - Emergency Contraceptive Pills, PID - Pelvic Inflammatory Disease, STD - Sexually Transmitted Disease, HCG - Human Chorionic Gonadotropin, ART - Assisted Reproduction Technology, COH - Controlled Ovarian Hyperstimulation, PCOS - Polycystic Ovarian Syndrome.

Acknowledgement

The author wish to thank Dr. Aswathy G Nath, Junior Resident, SAT Hospital for her sincere and committed efforts in data collection and helping me with the analysis. Special thanks to Mr. Jayakumar Parmeswaran, Biostatistician for his keen interest in statistical analysis. Also thanking Mrs. Devi V, Computer Assistant in computing the study.

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