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The Risk Factors for Ectopic Pregnancy

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ABSTRACT

BACKGROUND AND OBJECTIVE: Ectopic pregnancy is a common complication and one of the causes of pregnancy-related deaths. Considering the increased prevalence of ectopic pregnancy in recent years and the increased risk factors such as assisted reproductive treatment, the present study was conducted to investigate the risk factors for ectopic pregnancy in Babol, northern Iran.

METHODS: This case-control study was performed on pregnant women who were admitted with suspicion for ectopic pregnancy or acute abdomen within a 6-year period. Patients diagnosed with ectopic pregnancy were selected in the case group and the control group was selected from among the pregnant women's medical record during the same years. Patients were examined in terms of age, parity, history of abortion, type of contraception, history of ectopic pregnancy, history of pelvic infections, history of cesarean section, infertility treatment, history of smoking, marriages within the family, medical history and underlying disease.

FINDINGS: In this study, 201 patients were examined in each group. The mean age for the case group was 29.75±5.6 and for the control group was 28.62±6.4 years. Among the risk factors, assisted reproductive treatment (OR=10.24, p≤0.001), abdominal and pelvic surgery (OR=2.35, p=0.002), infertility (p=6.76, p<0.001), contraceptive pills (OR=0.61, p<0.001) and nulliparity (OR = 1.61, p=0.019) were associated with increased risk of ectopic pregnancy.

CONCLUSION: According to the results of this study, the most important risk factors for ectopic pregnancy are the use of hormonal pills to prevent pregnancy and nulliparity, respectively.

KEYWORDS: *Pregnancy, Ectopic pregnancy, Risk factors, Babol, Infertility.*

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Introduction

An ectopic pregnancy occurs when a fertilized egg implants outside of the uterus or not within the uterine cavity (1), and is a common complication worldwide and is the main cause of maternal mortality during the first trimester of pregnancy and its prevalence varies from country to country (2–5). In the UK, ectopic pregnancy is one of the ten causes of maternal mortality (6). In developed countries, 1–2% of all reported pregnancies are ectopic pregnancy. This figure is higher in developing countries, and from 1972 to 1992, the prevalence of ectopic pregnancy has increased 6 times (7). In a study in Iran, the overall prevalence of ectopic pregnancy was estimated to be 2.6 per 1,000 pregnancies, which increased from 1.5 per 1,000 pregnancies in 2000 to 4.8 per 1,000 pregnancies in 2010 (8). Previous history of ectopic pregnancy and previous history of reproductive system infection are reported as the main factors while having multiple sexual partners, history of infertility, induction of labor for prolonged pregnancy, recent use of IUD, previous history of cesarean section and smoking during fertilization as other factors related to ectopic pregnancy were reported as other factors (9).

The first successful in vitro fertilization (IVF) treatment in humans resulted in ectopic pregnancy. Since then, reproductive technologies have consistently increased the incidence of ectopic pregnancy by 8.6% (10). According to a study by Quinton Katler et al. in 2018, reproductive technologies increased the incidence of ectopic pregnancy by 11% in infertile women undergoing reproductive technologies. In addition, in a study in Iran in 2017, 5.5% of people who underwent IVF had ectopic pregnancy (12).

Among Iranian women, history of previous ectopic pregnancy, history of tubal ligation, use of IUD and previous abdominal and pelvic surgery are the major risk factors for ectopic pregnancy. In addition, ectopic pregnancy among Iranian women is associated with history of ectopic pregnancy, abortion, cesarean section and infertility (13).

Considering the increased prevalence of ectopic pregnancy and the increase in some risk factors such as assisted reproductive therapy in ectopic pregnancy and given the impact of identifying these risk factors in diagnosing and treating the patient appropriately and the lack of new data about ectopic pregnancy and its risk factors in Babol, the present study was conducted to evaluate the risk factors for ectopic pregnancy in Babol, northern Iran.

Methods

This case-control study was approved by the Ethics Committee of Babol University of Medical Sciences, and was conducted among all patients admitted to the gynecological emergency with suspicion for ectopic pregnancy or acute abdomen within a 6-year period from 2011 to 2016 in Ayatollah Rouhani and Yahyanejad hospitals in Babol.

Patients whose medical record was incomplete and did not have the information in the checklist were excluded. Of these records, the records of patients whose ectopic pregnancy was diagnosed through surgery (laparoscopy or laparotomy) and the records of patients whose ectopic pregnancy was diagnosed through Beta HCG (Titration) and vaginal ultrasound were examined (case group). The control group was randomly selected from among the records of pregnant women within the same years (for each ectopic pregnancy record, one normal pregnancy record in the same year was randomly separated). Patients were examined in terms of age, parity, history of abortion, type of contraception, history of ectopic pregnancy, history of pelvic infections, history of cesarean section, infertility treatment, history of smoking, marriages within the family, medical history and underlying disease. The data entered SPSS 18 and analyzed using independent t-test, chi-square and logistic regression. P value<0.05 was considered significant.

Results

In this study, after reviewing the records in the archive and considering the inclusion and exclusion criteria, 201 patients with ectopic pregnancy were included in the case group and then the same number of pregnant women were included in the control group (Fig 1). Within six years of investigation, the number of women in case group was the highest in 2016 and the lowest in 2011 (Fig 2). The mean age for the case group was 29.75±5.6 years and for the control group was 28.62±6.4 years. 46.3% of women in the case group and 34.8% of women in the control group had no previous history of delivery ($p<0.05$), which was significant and indicated that the odds ratio of ectopic pregnancy is higher among nulliparas. History of abortion, ectopic pregnancy, cesarean section, and history of pelvic infection were not significantly correlated between the two groups (Table 1). In this study, history of tubal ligation and abdominal and pelvic surgery were significantly different in the case and control groups

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(p=0.004), (p=0.025). There was no history of smoking in either group.

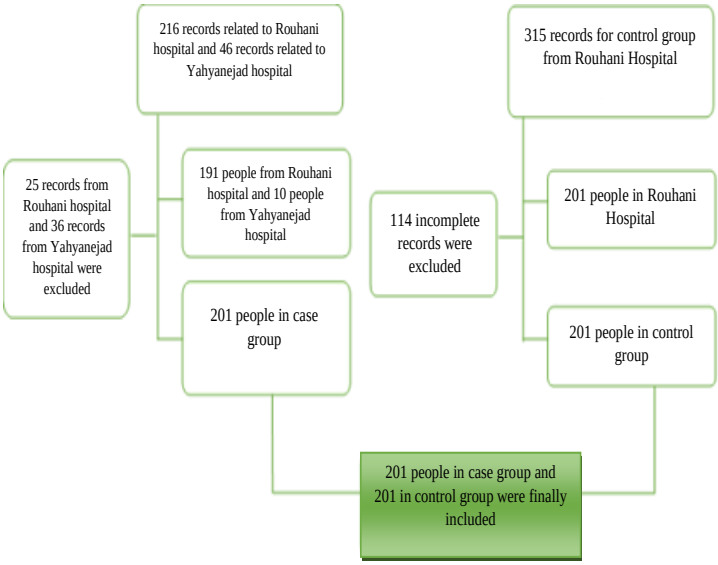

Figure 1. Samples included in the study

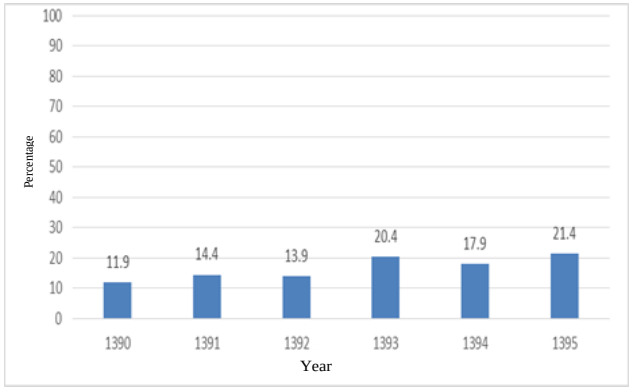

Figure 2. Percentage frequency of ectopic pregnancy during the years 2011 – 2016

Table 1. Characteristics of women with and without ectopic pregnancy

Pregnancy Variable	Ectopic N(%)	Normal N(%)	P-value
History of ectopic pregnancy in the past	8(4)	4(2)	0.241
History of pelvic infection	3(1.5)	0	0.082
Nulliparous	93(46.3)	70(34.8)	0.019
Abortion history	53(26.4)	44(21.9)	0.294
Abdominal and pelvic surgery	38(18.9)	22(10.9)	0.025
History of tubal ligation	8(4)	0(0)	0.004
History of cesarean section	71(35.3)	87(43.3)	0.102
Coitus interruptus	41(20.4)	6(3)	0.00
Assisted reproductive therapy	27(13.4)	3(1.5)	0.00

Different methods of contraception, causes of infertility and IVF treatment as risk factors for ectopic pregnancy showed significant difference between the case and control groups except the IUD method ($p<0.05$). The use of condom and uterine closure were more common in women with ectopic pregnancy than the control group (Table 2). However, coitus interruptus was more common in the control group. 64 women in the case group (31.8%) and 13 women in the control (6.5%) had history of infertility. Of these 64 women in the case group, 28 were male infertility and 30 were female infertility and the risk factor was unknown in other cases (6 women). Furthermore, among those with history of infertility, 34 patients in the case group and 1 patient in the control group received infertility treatment with drug, 19 patients in the case group and 1 patient in the control group had a history of IUI, 12 patients in the case group and 2 patients in the control group had IVF. There was a significant relationship history of infertility ($p<0.001$), male risk factor ($p<0.001$), female risk factor ($p<0.001$), treatment using drug ($p<0.001$), IUI ($p<0.001$)), IVF ($p=0.007$) and in general, reproductive technology and ectopic pregnancy ($p<0.001$) (Table 2).

Table 2. Different contraceptive methods and infertility treatment in women with normal and ectopic pregnancy

Pregnancy Variable	Ectopic N(%)	Normal N(%)	P-value
Contraceptive pill	16(8)	2(1)	0.001
Condom	14(7)	4(2)	0.016
Coitus interruptus	98(48.8)	170(84.6)	<0.001
History of tubal ligation	8(4)	0	0.004
IUD	3(1.5)	0	0.082
Infertility	64(31.8)	13(6.5)	<0.001
Female infertility	30(15)	7(3.5)	<0.001
Male infertility	28(14)	4(2)	<0.001
Drug treatment of infertility	34(16.9)	1(0.5)	<0.001
Intrauterine injection	19(9.5)	1(0.5)	<0.001
Embryo transfer	12(6)	2(1)	0.007

Among infertility treatments, however, none of the women in case and control groups received ICSI, and only one woman in the case group had micro, which had no statistically significant association with ectopic pregnancy. Abdominal and pelvic surgery, and infertility treatment were more common in 2014, while nulliparity, IUI, and IVF were more common in 2016

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(Table 3). The highest odds ratio is associated with reproductive technology risk factors, which increases the probability of ectopic pregnancy by about ten times (Table 4). The interaction effect of the variables was considered in the adjusted odds ratio obtained by multivariate regression, and in this model, the highest odds ratio was related to contraceptive pill, which increased ectopic pregnancy by about ten times. In this study, of 201 women with ectopic pregnancy, 103 women were treated with methotrexate, 12 women underwent laparoscopy and the rest underwent laparotomy.

Table 3. Frequency and factors affecting ectopic pregnancy based on year

Factor	2011 N(%)	2012 N(%)	2013 N(%)	2014 N(%)	2015 N(%)	2016 N(%)
Abdominal and pelvic surgery other than tubal ligation	2(8.3)	5(17.2)	7(25)	11(26.9)	11.6(5)	8(18.6)
Infertility treatment	7(29.2)	5(17.2)	4(14.3)	8(19.5)	6(16.7)	4(9.3)
Embryo transfer	1(2.2)	0(0)	1(3.6)	4(9.8)	1(2.8)	5(11.6)
Intrauterine injection	5(20.8)	1(4.3)	2(7.1)	4(9.8)	2(5.6)	5(11.6)
Nulliparity	10(41.7)	16(55.2)	12(42.9)	18(43.9)	16(44.4)	21(48.8)
Contraceptive pill	0(0)	3(10.3)	4(14.3)	4(9.8)	2(5.6)	3(1.5)
History of tubal ligation	1(4.2)	2(6.9)	1(3.6)	2(4.8)	1(2.8)	1(2.3)
Previous ectopic pregnancy history	0(0)	1(4.3)	2(7.1)	3(7.3)	0(0)	2(4.7)
History of pelvic infection	0	1(4.3)	0	0	0	2(4.7)
History of infertility	10(41.7)	9(31)	6(21.4)	15(36.6)	10(27.8)	14(32.6)

Table 4. Logistic regression model to determine the role of ectopic pregnancy risk factors

Variable	Crude OR(95% CI)	P-value	Adjusted OR(95% CI)	P-value
Age<25	1	-	1	-
Age 25 – 35	1.74(1.07 – 2.83)	0.027	1.97(1.10 – 3.50)	0.022
Age > 35	1.6(0.88 – 3.25)	0.118	1.23(0.55 – 2.74)	0.609
Assisted reproductive techniques	10.24(3.06 – 34.37)	< 0.001	2.18(0.52 – 9.05)	0.284
Abdominal and pelvic surgery and tubal ligation	2.35(1.35 – 4.08)	0.002	2.03(1.01 – 4.07)	0.046
Infertility	6.76(3.58 – 13.76)	< 0.001	4.32(2.00 – 9.33)	< 0.001
Cesarean section	0.72(0.48 – 1.07)	0.102	0.81(0.45 – 1.44)	0.464
Contraceptive pill	8.61(1.95 – 37.94)	0.001	9.15(1.98 – 9.33)	0.005
Ectopic pregnancy history	2.04(0.61 – 6.89)	0.241	0.98(0.24 – 4.07)	0.987
Nulliparity	1.61(1.08 – 2.40)	0.019	1.63(0.88 – 3.04)	0.122
Abortion history	1.28(0.81 – 2.02)	0.294	0.99(0.57 – 1.73)	0.966

Discussion

In the present study, the most important risk factor was hormonal contraception, which increased ectopic pregnancy by nine times with adjusted odds ratio in variables (age, reproductive technology, abdominal and pelvic surgery and tubal ligation, infertility, cesarean section, contraceptive pills, ectopic pregnancy, nulliparity, and history of abortion). However, there was no significant relationship between the use of IUD and ectopic pregnancy. This result contrasts with the results of previous studies, which showed a significant association between ectopic pregnancy and IUD (13–16). The most important reason for this difference in the present study is the lack of providing contraceptive services such as IUD in Iranian health care centers due to the recent policies of the Ministry of Health to increase population. On the other hand, the difference may be associated with the type of contraceptive pill and the dosage of progesterone in the pill, which could not be differentiated based on the existing data and the awareness of the patient. Although the study of Ellaithy et al. about the risk factors of ectopic pregnancy did not find a significant association for IUD like our study, but unlike our study, they found no association for OCP use as a risk factor for ectopic pregnancy (17). This difference may be due to cultural matters in the study of

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Ellaithy et al., since this study was conducted in Saudi Arabia, in which fewer contraceptive methods are used. Some studies have shown that condom use may reduce the risk of ectopic pregnancy due to reduced risk of sexually transmitted diseases (STDs) (9, 18 – 21), whereas our study did not show a significant decline in the incidence of ectopic pregnancy in those who use condom. Perhaps the reason for this discrepancy in the present study is due to the lack of continuous and proper use in people who choose condoms as a contraceptive method.

In this study, the odds of ectopic pregnancy were higher in nulliparous women (1.6 times more than multiparous women). In the studies of Dzhang et al. and Barnhart KT et al., and other studies, the odds of ectopic pregnancy were higher in nulliparous women like our study (22, 23). However, in some studies, people with higher parity were more likely to have ectopic pregnancy (23, 24). This may be due to the fact that people with a history of infertility are more likely to have ectopic pregnancy, but those with higher parity may be less likely to have a tubal damage and have lower odds of ectopic pregnancy, and this may be the reason for higher ectopic pregnancy rate in nulliparous patients, which needs further investigation. Unlike previous studies, according to which previous history of ectopic pregnancy is considered as a risk factor for ectopic pregnancy (25–27) and the odds of having ectopic pregnancy after one previous ectopic pregnancy were 12.5 times and after two previous ectopic pregnancies were 76.6 times (28), in this study, there was no significant relationship between this factor and ectopic pregnancy.

However, because of the low number of people with a previous history of ectopic pregnancy in this study, this assessment does not seem accurate. In the present study, the previous history of abortion was not statistically significant, but in the study of Moini et al. in Tehran, previous history of spontaneous abortion was significant but previous history of induced abortion was not significant (15). In the study of Li et al., unlike surgical abortion, the history of spontaneous abortion was significant and increased the odds of ectopic pregnancy by 1.53 times (16). Perhaps the reason that this risk factor is not significant in the present study is that we considered abortion as a risk factor in general sense and did not separate abortion into spontaneous and induction groups in this study. As in previous studies, the previous history of infertility was associated with ectopic pregnancy in this study (17, 18, 26, 27, 30) so that in the present study, if there was a history of infertility, the probability of ectopic pregnancy was approximately 6 times higher and odds ratio was approximately 4 times higher after changes in variable effect (age, reproductive technology, abdominal and pelvic surgery and TI, infertility, cesarean section, contraceptive pills, history of ectopic pregnancy, nulliparity, and history of abortion).

In the present study, in patients who had a history of ART treatment, this risk factor was significant in univariate analysis, but not in multivariate analysis. In the study of Asnafi et al., the history of treatment with IUI was significant in univariate analysis of this risk factor for ectopic pregnancy, which is consistent with our study (29). In the study of Parashi et al., in subjects with history of reproductive technology treatment, this factor was not significant in multivariate analysis, which is consistent with our study (13). In the present study, it was not possible to perform statistical analysis because of the low number of people who had ectopic pregnancy following recent treatment with reproductive technology. However, previous studies have shown that the number of people who have had their current ectopic pregnancy following a recent treatment with reproductive technology was higher (16, 24).

In the present study, the mean age of women between the two groups was not significant and was similar to the study by Asnafi et al, which was also not statistically significant in their study (29). However, in the study of Jacob et al., the mean age of the two groups was statistically significant (30). These differences appear to be related to the higher age of marriage and fertility in Germany compared with Iran. In this study, contrary to abdominal surgical manipulation, there was no statistically significant association between ectopic pregnancy and history of cesarean section.

In the study of Barnhart, cesarean section was not considered as a risk factor (23), while in the study of Coste et al., the risk of ectopic pregnancy increased by 2.1 times if there was a previous history of cesarean section (9). In another study, a previous history of appendectomy increased the odds of ectopic pregnancy by 1.64 times, but history of cesarean section showed not significant association (24). In a study by Jacob et al., previous history of genital surgery increased the odds of ectopic pregnancy by 2.6 times (30). In the present study, the odds of ectopic pregnancy increased by 2.03 times in case of abdominal and pelvic surgery. This difference may be due to different methods of surgery and its possible complications, which may vary in different groups, or depending on the race and genetics of individuals who are prone to abdominal

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adhesion after surgery. In our study, previous history of pelvic infection had no effect on ectopic pregnancy. In a study by Coste et al., previous pelvic infection increased the odds of ectopic pregnancy by 6.8 times (9). In the study of Islam et al., 22.2% of cases had pelvic infection (25).

The difference in the results of our study compared to other studies may be associated with unreliable information about this factor in the records due to the lack of proper skills to communicate with the patient to obtain accurate history of pelvic infection. However, in the study of Ashraf Moini et al., there was no significant relationship between intrauterine infection and ectopic pregnancy (15). In the study of Bouyer et al., smoking is considered as a major risk factor for ectopic pregnancy (31) and the odds of ectopic pregnancy increase by 3.9 times when the number of cigarettes reaches 20 per day (28). In our study, none of the participants was smoker or denied it because of cultural conditions. Therefore, this factor has not been evaluated. Research limitations included the difficulty of accessing records as a result of incomplete or illegible file information, which led to exclusion. The present study showed that factors such as history of infertility, ART treatment, and history of abdominal and pelvic surgery, as in other studies, have led to increased ectopic pregnancy, while the use of OCP and nulliparity may be considered as important risk factors. Since there are inconsistencies in some of the risk factors for ectopic pregnancy in different studies, we need broader prospective analysis of the different races based on studies with similar methodology.

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