

A Case Control Study Comparing Risk Factors for Ectopic Gestation in Unusual and Tubal Gestations

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ABSTRACT

Aim: To compare risk factors for extratubal gestations with tubal gestations.

Materials and methods: Case control design with retrospective examination of an electronic database to identify ectopic gestations. Ectopic gestations were confirmed through ultrasound examination or serum beta hCG levels. We defined an ectopic gestation as implantation of pregnancy outside uterine cavity; tubal ectopic including implantation in the tube, isthmic, ampullary, or fimbrial and extratubal ectopic including implantation in the ovaries, cervix, abdomen, interstitia or cesarean scar.

Results: Ninety-one (1.1%, 95% CI: 0.9-1.3, 1 in 90 pregnancies) of 8,203 pregnancies during the study period were ectopic gestations including 69 (0.8%, 95% CI: 0.7-1.1, 1 in 120 pregnancies) tubal gestations and 22 (0.3%, 95% CI: 0.2-0.4, 1 in 372 pregnancies) gestations in extratubal locations. Extratubal ectopic gestations were more common in women with advanced maternal age (odds ratio: 7.4, 95% CI: 1.3, 43.9, $p = 0.03$) compared to women with tubal ectopic gestations.

Conclusion: Risk factors for extratubal gestation did not differ from risk factors for tubal gestations except for advanced maternal age. Pregnant women with advanced maternal age have to be additionally counseled on the increased risk for extratubal gestations.

Keywords: Tubal ectopic gestation, Extratubal ectopic gestation, Risk factors, Ectopic pregnancies.

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INTRODUCTION

Ectopic gestation or pregnancy is the leading cause of pregnancy-related maternal deaths during first trimester.¹ Incidence of ectopic gestations is estimated to be between 1 and 2% of all pregnancies, most (upto 95.5%) of which are located in the fallopian tube^{2,3} with 4.5% of ectopics in other extratubal sites of implantation that include the cervix, ovary, previous cesarean scar, interstitial tubal segment and intra-abdominal sites.⁴

Pelvic inflammatory diseases (PID) especially due to chlamydia trachomatis, smoking, previous ectopic pregnancy, previous pelvic surgery, previous cesarean sections and current use of an intrauterine device⁵ are risk factors for ectopic gestations. Other risk factors include history of infertility, history of induction of pregnancy, advanced maternal age, assisted reproduction technology (ART) and induced abortions.

The aim of this study was to determine differences, if any, in the risk factors for tubal and extratubal ectopic gestations.

MATERIALS AND METHODS

We designed a case control study of all ectopic gestations over a period of 2 years, from January 2008 to December 2009, at Fernandez Hospital, a tertiary perinatal center with over 5,000 deliveries per year. Pregnant women booked for antenatal care at Fernandez Hospital, undergo a standardized clinical examination protocol that includes collection of demographic details, personal risk behaviors, previous and current obstetric and medical history, clinical examinations, and trimester-specific ultrasound examinations. The details of the clinical examination are entered and maintained in an electronic database.

We defined an ectopic gestation as implantation of pregnancy outside uterine cavity; tubal ectopic including implantation in the tube, isthmic, ampullary or fimbrial and extratubal ectopic, including implantation in the ovaries, cervix, abdomen, interstitia or cesarean scar. Clinically, an ectopic gestation was suspected if a woman presented with a brief period of amenorrhea indicative of a possible pregnancy and abdominal pain and/or bleeding per vagina or signs and symptoms of shock. The diagnosis of an ectopic gestation was confirmed through an ultrasound (transabdominal and/or transvaginal) examination and serum beta-hCG levels. We retrieved records of women with ectopic gestations from this electronic database for the purpose of this study.

For this study, we defined a case as a pregnant woman with a confirmed extratubal ectopic gestation. The control group comprised pregnant women with a confirmed tubal ectopic gestation. The baseline characteristics of women with tubal and extratubal pregnancies were compared using a one-way analysis of variance (ANOVA) for continuous variables and a chi-square or Fisher's exact test for

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categorical variables. We considered a p-value <0.05 as statistically significant. All statistical analysis was performed using STATA version 9.0 (College Station, Tx, USA).

RESULTS

There were 8,203 pregnancies at the study institute during the years 2008 to 2009. Ninety-one (1.1%, 95% CI: 0.9-1.3, 1 in 90 pregnancies) of these 8,203 pregnancies were ectopic gestations including 69 (0.8%, 95% CI: 0.7-1.1, 1 in 120 pregnancies) tubal gestations and 22 (0.3%, 95% CI: 0.2-0.4, 1 in 372 pregnancies) gestations in extratubal locations. Tubal ectopic gestations (n = 69, 75.8%, 95% CI: 66.3-83.8) accounted for three-fourths of the ectopic gestations. Figure 1 shows the distribution of extratubal ectopic gestations in this series.

A history of pelvic area risk factors was positive for 25 of the 91 (27.4%, 95% CI: 19.1, 37.3) ectopic gestations. The frequency distribution of pelvic area risk factors did not differ significantly by site of ectopic gestations (Table 1). Extratubal ectopic gestations were more common in women with advanced maternal age (odds ratio: 7.4, 95% CI: 1.3, 43.9, p = 0.03) compared to women with tubal ectopic gestations (see Table 2). When we looked at the

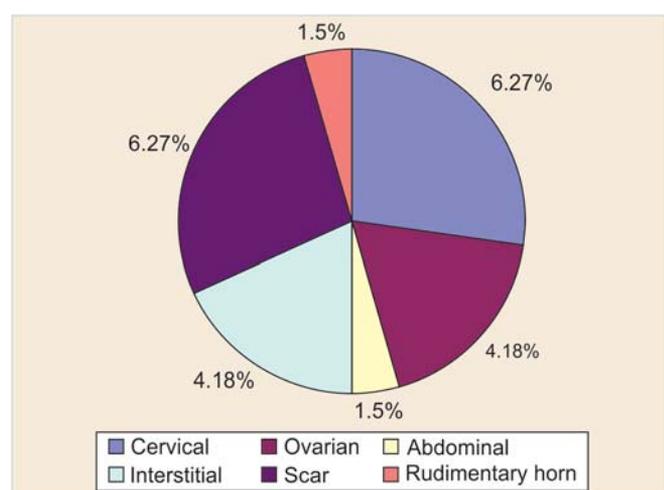


Fig. 1: Types of extratubal ectopic gestations

mode of assisted conception, 11 of the 15 tubal gestations resulted after ovulation induction, three after intrauterine insemination and one after *in vitro* fertilization. The three extratubal ectopic pregnancies following assisted conception were all cervical pregnancies conceived after *in vitro* fertilization. These numbers were very small to do any statistical tests. Of the six cervical pregnancies, three had medical and surgical management, two were managed only with medications and one was on an expectant management strategy. Of the four ovarian pregnancies, two had medical and surgical management, one was managed only with medications and one was managed only through surgery. Two interstitial pregnancies with evidence of rupture were dealt with surgically and the other two were managed medically. The abdominal and rudimentary horn pregnancies were managed surgically. There were six scar pregnancies diagnosed at a mean menstrual age of 8.5 weeks with initial serum beta-hCG values ranging from 1,156 to 16,448 mIU/ml. All these patients presented with amenorrhea and vaginal bleeding. One woman had three previous cesarean sections and the other five had one previous cesarean section each. Two of them had fetal cardiac activity on ultrasound. Four of the women were given medical management and two required surgery subsequently. The other two were directly taken up for surgery. Serum beta hCG normalized in 7 to 8 week's time.

DISCUSSION

Extratubal ectopic gestations accounted for 24.1% of all ectopics in our study as opposed to 6.9% incidence of rare ectopics reported in 1,800 surgically treated ectopics by Bouyer et al.⁴ We have a high prevalence of ectopic, especially extratubal gestations, which is probably associated with the fact that the study institute is an advanced tertiary care referral center. The proportion of different types of rare ectopic pregnancies encountered by us has been compared with other studies in Table 3.⁶⁻¹⁴ Cesarean scar pregnancy is extremely rare, with less than 50 reported cases described in the literature.¹⁵

Table 1: Pelvic area risk factors for tubal and extratubal gestations

Risk factor	Tubal gestation (n = 69)	Extratubal gestation (n = 22)	Student's t-test p-value
Dilatation and curettage (n, %)	5 (26.3%)	0 (0.0%)	0.19
Endometriosis (n, %)	1 (5.3%)	1 (16.7%)	0.39
Fibroids (n, %)	1 (5.3%)	0 (0.0%)	0.57
Intrauterine contraceptive device (n, %)	1 (5.3%)	0 (0.0%)	0.57
Polycystic ovarian disease (n, %)	4 (21.1%)	1 (16.7%)	0.82
Pelvic inflammatory disease (n, %)	1 (5.3%)	1 (16.7%)	0.39
Previous ectopic gestation (n, %)	3 (15.79%)	1 (16.7%)	0.97
Sequel to sterilization (n, %)	1 (5.3%)	0 (0.0%)	0.57
Post-tubal recanalization (n, %)	1 (5.3%)	0 (0.0%)	0.57

Table 2: Comparison of maternal characteristics between women with tubal and extratubal gestations

Characteristics	Tubal ectopic gestations (n = 69)	Extratubal ectopic gestations (n = 22)	Statistical significance
Mean age (SD) in years	27.2 (3.7)	29.3 (5.4)	ANOVA F = 4.48, p = 0.04
Maternal age ≥35 years (n, %)	2 (2.9%)	4 (18.2%)	Fisher's exact test, p = 0.03
Primigravid (n, %)	28 (40.6%)	5 (22.7%)	Fisher's exact test, p = 0.13
Previous ectopic pregnancies (n, %)	5 (7.2%)	3 (13.6%)	Fisher's exact test, p = 0.41
Assisted conception (n, %)	15 (21.7%)	3 (13.6%)	Fisher's exact test, p = 0.41
Presence of at least one risk factor (n,%)	19 (27.5%)	5 (22.7%)	Fisher's exact test, p = 0.66
Mean (SD) gestational age at diagnosis in weeks	6.4 (1.5)	7.1 (2.0)	ANOVA F = 2.93, p = 0.09

Table 3: Comparison of incidence of tubal and rare ectopic gestations

Type of ectopic	Our study % of ectopics (% of all pregnancies)	Bouyer et al ⁴ % of ectopics	Other studies % of ectopics (% of all pregnancies)
All ectopic pregnancies	1.1%	—	1 to 2%
Tubal ectopics	75.8% (0.8%)	93.1%	97.7% (1.95%)
Cervical pregnancy	6.5% (0.07%)	—	(0.01-0.04%) ⁶⁻⁸
Ovarian pregnancy	4.4% (0.05%)	3.2%	1-3% (0.001-0.04%) ⁹
Interstitial pregnancy	4.4% (0.05%)	2.4%	1-3% (0.02-0.06%) ^{10,11}
Abdominal pregnancy	1.1% (0.01%)	1.3%	1.4% (0.03%) ¹²⁻¹⁴
Cesarean scar pregnancy	6.5% (0.07%)	—	—
Rudimentary horn pregnancy	1.1% (0.01%)	—	—

The rarity of ectopic pregnancies in unusual extratubal locations renders the study of management strategies largely observational or based on anecdotal evidence. An understanding of the risk factors for extratubal pregnancy might help to determine appropriate preventive and management strategies besides counseling on potential risk for ectopic gestations. We found advanced maternal age was the only risk factor that was significantly associated with extratubal gestations compared to pregnant women with tubal gestations. Similar findings were also reported in other studies: Median age of 37 years in cervical pregnancies,¹⁶ mean age of 35 years in cesarean scar pregnancies¹⁷ and mean age of 31.2 years in abdominal pregnancies.¹⁸

Highest rates of ectopic pregnancies occurred in women aged 35 to 44 years.¹⁹ Defective embryogenesis may be responsible for ectopic pregnancy in older women.²⁰ The reported increased incidence of tubal pregnancy in perimenopausal women may be related to progressive loss of myoelectrical activity along the fallopian tube which is observed with ageing.²¹

We were unable to find a specific reason for increased incidence of unusual ectopics in women aged above 35 years. Probable contributory factors might be impaired tubouterine transport due to dysperistalsis of the fallopian tubes and uterine myometrium, defective embryos and/or defective endometrial receptivity in these women. This warrants further research.

The potential for bias, especially pertaining to selection of the cases and controls (or assessment of outcome) and assessment of exposures is minimized by the rigorous

documentation and maintenance of an electronic database. Each record identified in the electronic database as that of an ectopic gestation was verified with the individual case records. The completeness of documentation is a major strength of the study. It is, however, possible that there may be differences in the determination of exposures pertaining to risk factors by different clinicians. This is a limitation of a case control design. Given the rarity of extratubal gestations, a prospective cohort study design is not viable. The choice of the control population is also a potential source of limitation in case control designs. However, this is not a limitation for this study as the control population was drawn from pregnant women attending the same institute.

CONCLUSION

Risk factors for extratubal gestation did not differ from risk factors for tubal gestations except for advanced maternal age. The mean age of women with ectopic gestation (tubal or extratubal) in the present study is less than 30 years (contrary to other studies of extratubal pregnancies). Though absolute number of women more than 35 years is significantly more in extratubal group, this can be partly due to significantly more proportion of extratubal pregnancies in the present study as compared to others. Further studies on the distribution and risk factors for ectopic pregnancies will be useful for clinical practice. Pregnant women with advanced maternal age have to be additionally counseled on the increased risk for extratubal gestations.

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