THE INCIDENCE AND ASSOCIATED RISK FACTORS AFFECTING THE RATE OF ECTOPIC PREGNANCY IN PRIME AND MULTIGRAVIDA WOMEN IN SULEIMAN MATERNITY TEACHING HOSPITAL

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ABSTRACT

Background

Ectopic pregnancy (EP) is a potentially life-threatening condition and still the major cause of maternal mortality in the first trimester of pregnancy. It accounts for approximately 10% of maternal deaths. Despite major advances, early diagnosis of EP is still a challenge for clinicians. In the past 20 years, the use of sensitive βhCG tests, high-resolution transvaginal ultrasound, and advances in laparoscopy (LS) have enabled the detection of EP without tubal rupture.

Objectives

The aim of the study is to determine the incidence and associated risk factors for ectopic pregnancy, and to address these risk factors in prime gravid and multigravida.

Patients and Methods

This study was conducted in the period from January the 1st 2015 to the July 1st 2015, all ectopic pregnancy patients admitted to Sulaimani Maternity Hospital were collected. Data from 100 patients recorded, however we didn't have all variables from 7 patients, we analyzed 93 of the cases. Written consent for the study was obtained from all the patients.

Results

Our results show weight and BMI were demographic changes that most significantly affect the results. The higher the weight the higher the risk of ectopic pregnancy. Only (11.8%) has no risk factors, most of patient had multiple risk factors (63.4%) were among multiparas women and (24.7%) had only one risk factors.

Conclusion

We found the main demographic variable was High body weight and BMI. Most of the patient have multiple risk factors and risks higher in multigravida women than prime gravid. The most significant risk factor for increasing the rate was confirmed with previous ectopic pregnancy, combined contraception pills. Pathological vaginal discharge, and previous caesarean section. We found this increase may be due to poor in c/s technique and increase in the rate of caesarean section on request especially in private sector. This study is was unique in the area to address these risk factors for ectopic pregnancy.

Keywords: *Ectopic pregnancy, Risk factors, Previous ectopic pregnancy, Vaginal discharge.*

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INTRODUCTION

Ectopic pregnancy (EP) is a potentially life-threatening condition and still the major cause of maternal mortality in the first trimester of pregnancy. It accounts for approximately 10% of maternal deaths [1]. In most developed countries, the incidence of EP has increased considerably over the last 20 years and now accounts for 1%-2% of all pregnancies [2–5]. Despite major advances, early diagnosis of EP is still a challenge for clinicians [1, 6, and 7]. In the past 20 years, the use of sensitive βhCG tests, high-resolution transvaginal ultrasound, and advances in laparoscopy (LS) have enabled the detection of EP without tubal rupture. In the case of early detection, the possibility and success of noninvasive medical treatment as an alternative to surgical treatment increase [8].

Prior to spontaneous resolution, these pregnancies may cause catastrophic intra-abdominal hemorrhage. Despite advances in diagnostic methods, unexpected tubal rupture with massive hemorrhage still remains a significant source of maternal morbidity and mortality worldwide, especially in countries with poor prenatal care. In the UK, 11 maternal deaths were attributed to ectopic pregnancy in the last triennial CMACE report.

Ectopic pregnancy is a significant cause of maternal morbidity and mortality especially in the sub Saharan Africa (less economically develop counties, LEDC) While mortality from ectopic pregnancy has been on the decrease in the developed countries despite the increase in the incidence, it is not so in the developing countries, where it is major cause of maternal mortality. [9-13].Case fatalities of 27.9 per 1000 [14] and 37 per 1000 [15] had been reported in Accra, Ghana and Lagos, Nigeria respectively.

More than 95% of ectopic pregnancies occur in the Fallopian tube. The other sites include ovaries, cervix, caesarean scar, broad ligament and abdominal cavity [16]. Combined intra-uterine and extra-uterine pregnancy (heterotopic pregnancy) though rare in spontaneous pregnancies (1 in 3000-4000), has been recorded in up to 3% of pregnancies from assisted reproduction [16].

Several factors have been shown to increase the risk of ectopic pregnancy. These risk factors share a common mechanism of action - namely interference with the ciliary functions of fallopian tube [17]. It has been observed that pelvic inflammatory disease is the most common risk factor for ectopic pregnancy and early treatment of the disease does not necessarily prevent tubal damage [17] .The other reported etiological factors include previous ectopic pregnancy, endometriosis, and previous tubal surgery, infertility and infertility treatments, Previous caesarean sections, tubal spasm, congenital defects of the fallopian and psychological and emotional factors have also been implicated [18,19].

Reports show that pregnancies can grow in the fimbria end (5% of all ectopic pregnancies), the ampulla section (80%), the isthmus (12%), and the corneal and interstitial parts of the tube (2%) [20].

Management

Expectant management: About 14% of women will benefit from this type of management, is a useful form of management for ectopic pregnancy in selected cases. It is, however, only acceptable if it involves minimal risks to the woman. Expectant management should only be used for women who are asymptomatic with an ultrasound diagnosis of ectopic pregnancy, with no evidence of blood in the pouch of Douglas and decreasing serum HCG levels that are lower than 1000 iu/l at initial presentation. However medical management is useful in women with an early ectopic pregnancy who are stable, and serum HCG above 1000 iu/l and below 3000 iu/l require treatment with a single intramuscular injection of methotrexate is often successful without recourse to surgery. Fewer than 10% of women treated with this regimen will require surgical intervention [21].

Persistent trophoblastic is detected by the failure of serum HCG levels to fall as expected after initial treatment. It is primarily a problem occurring after salpingeotomy rather than following salpingectomy. Although, even in the presence of persistent trophoblastic, hCG levels may return uneventfully to normal, cases of delayed hemorrhage owing to persistent trophoblastic have been described and this provides the rationale for following women with serial hCG measurements after treatment and administering methotrexate if levels fail to fall as expected.

Earlier diagnosis has made medical management of ectopic pregnancy an option. The potential advantages are the avoidance of surgery and its concomitant hazards, the preservation of tubal patency and function, and a lower cost. Chemical agents that have been investigated include hyperosmolar glucose, [22, 23] urea, cytotoxic agents (e.g., methotrexate [Rheumatrex] and actinomycin), prostaglandins and mifepristone (RU486) [23].

Although the potential for serious toxic effects exists, the low dosages of methotrexate that are used in patients with ectopic pregnancies generally cause only mild,

self-limited reactions. Common side effects include nausea and vomiting, urinary frequency and mild diarrhea. Thus, when the diagnosis is certain and an ectopic mass is less than 3.5 cm in greatest dimension, methotrexate therapy is an option.

The β-hCG level needs to be considered in selecting patients for methotrexate therapy. One study found that β-hCG levels higher than 1,500 mIU per mL are associated with a much higher risk of treatment failure. The same study also showed that patients with 3 -HCG levels higher than 5,000 mIU per mL (5,000 IU per L) usually do not respond to methotrexate therapy. In addition to β-hCG levels, indications for methotrexate include hemodynamic stability, confirmation of ectopic pregnancy by ultrasound examination, significant risk associated with general anesthesia, patient compliance, lack of contraindications to methotrexate therapy, small size of ectopic mass and lack of fetal cardiac motion. [24].

Surgical Managements: A laparoscopic approach to the surgical management of tubal pregnancy, in the aerodynamically stable patient, is preferable to an open approach [25-26]. Laparoscopic surgery has been compared with open surgery in 228 women in three randomized controlled trials (RCTs). Laparoscopic procedures were associated with shorter operation times, less intraoperative blood loss, shorter hospital stays and lower analgesic requirements [27-29]. There was no difference in overall tubal patency rates (RR 0.89, 95% CI 0.74–1.1) between the two approaches. In women who desired future fertility (n = 145), the subsequent intrauterine pregnancy rates were similar (RR 1.2, 95% CI 0.88–1.15) and there was a trend toward lower repeat ectopic pregnancy rates if a laparoscopic approach was used (RR 0.43, 95% CI 0.15–1.2). However, laparoscopic salpingectomy was less successful than an open approach in elimination of the tubal pregnancy (RR 0.90, 95% CI 0.83–0.97), reflected in a trend towards higher rates of persistent trophoblastic (RR 3.6, 95% CI 0.63–21.0).

It is important to note that these three trials only include 228 women, which is insufficient to look at small differences between the two interventions with respect to many of the outcomes examined.

Experienced operators may be able to manage laparoscopic ally women with even a large haemoperitoneum safely [30-31] but the surgical procedure which prevents further blood loss most quickly should be used. In most centers this will be laparotomy. In the presence of a healthy contralateral tube there is no clear evidence that salpingeotomy should be used in preference to salpingectomy. A number of systematic reviews have examined reproductive outcomes following the management of tubal pregnancy with either salpingeotomy or salpingectomy. However, there are no RCTs that specifically compare laparoscopic (or open) salpingeotomy and salpingectomy. These reviews Show that there is not an increased chance of subsequent intrauterine pregnancy after salpingeotomy compared with salpingectomy. However, these data must be interpreted with caution. Included studies are subject to a wide range of biases relating to patient selection, surgical procedures used, length of follow-up and the proportion of patients lost to follow-up. (32-38)

Aim of the Study

Ectopic pregnancy has remained a significant cause of maternal morbidity and mortality especially in the Kurdistan region Suleiman Maternity teaching Hospital. The aim of the study is to determine the incidence and associated risk factors for ectopic pregnancy, and to address these risk factors in prime gravid and multigravida.

PATIENTS AND METHODS

This study is a prospective observational study, carried out at Sulaimani Maternity Teaching Hospital which is the main obstetric & gynecological hospital in the city and serves Sulaimani city (Kurdistan region of Iraq) and its surrounding areas as a tertiary center. The approximate annual rate of childbirth in this hospital is 15000 with (30%) of these delivered by caesarean section.

This study was conducted in the period from January the 1st 2015 till July the 1st 2015, all ectopic pregnancy patients admitted to the Hospital over this period, we collected data from 100 patients, however we don't have all variables from 7 patients, and we analyzed 93 of the cases. Written consent for the study was obtained from all the patients.

These risk factors includes the following: (previous miscarriage , previous ectopic pregnancy, history of IUCD insertion, pathological vaginal discharge, previous caesarean section, previous pelvic and abdominal surgery surgery Fertility treatment using ovulation Induction treatment and relationship to the outcomes of ectopic pregnancy. Appraisal review of affected risk factors as single and multiple risk factors in both primigravida and multigravida available treatment modalities and suggest interventions to reduce its prevalence, morbidity and mortality.

Data collection and analysis

Data collection was performed by direct interview with the participants. Prior to data entry and analysis, the questions of study were coded. The data was entered into a Microsoft Excel Spreadsheet, after data cleaning; the data was transported into SPSS (Statistical Package for the Social Sciences-verstion21.0) package software program for statistical analysis. Descriptive statistics (numbers and percentage) were calculated for all variables, as well as analytical statistics was done to find the relations between variables by using the appropriate statistical tests such as Chi-square. A p-value < 0.05 was considered as significant.

RESULTS

Table 1 showing the significance of demographic changes for both nulliparous and multiparas women. Weight and BMI have a significant effect on the increasing the rate of ectopic pregnancy.

Table 2 shows frequency of ectopic pregnancy between nulliparous and multiparous, also frequency and percentage of related to a single and multiple risk factors, 63.4% had multiple risk factors, while in only 11.8% no risk factors were found.

In figure one you can find that most of multigravie women have multiple risk factors (51.6%) while most of prim gravid women have only one single risk factor (16.1%).

Table 3 showing the significance of sign and symptoms to both nulliparous and multiparous in relation to ectopic pregnancy. None of the following sign and symptom was significant in the diagnosis of ectopic pregnancy.

Table 4 show the significance of individual risk factors to rate of ectopic pregnancy in both nulliparous and multiparas women, contraceptive pills, previous c/s, pathological vaginal and previous ectopic pregnancy has significantly increased the rate.

Table 5 showing the significance of type of treatments in nulliparous and multiparous, and related risk factors as a numbers and as single and multiple risk factors was significant and number of risk factors was significant.

Table 1. Showing the significance of demographic changes for of ectopic pregnancy.

Variables	Parity		P values
	Nulliparous Mean ±S.D	Multiparous Mean ±S.D	
Age	27.3±5.3	30.3±5.9	0.016
Miscarriage	1.6±0.8	1.4±0.9	0.774
Weight	61.0±6.9	69.5±11.1	< 0.001
BMI	24.1±3.3	26.5±3.7	0.003
Duration of contraception use (Months)	9.2±4.8	30.5±24.3	0.093

Table 2. Shows frequency of ectopic pregnancy related to a single and multiple risk factors.

	Frequencies	Percentages
Parity		
Nulliparous	34	36.6
Multiparous	59	63.4
Total	93	100.0
Numbers of risk factors		
No risk factor	11	11.8
Single risk factor	23	24.7
Multiple risk factors	59	63.4
Total	93	100.0

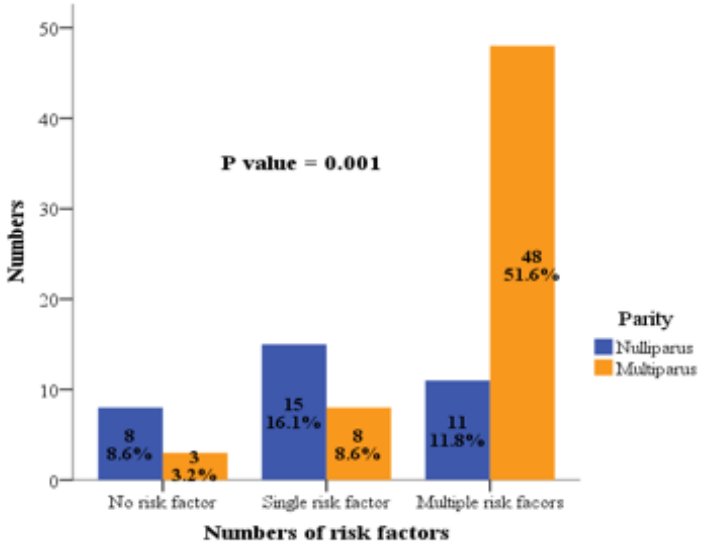

Figure 1. In Figure one you can find the relation of multiple and single risk factors to nulliparus and multiple pregnancy.

Table 3. Showing the significant of sign and symptoms to both Nulliparous and multiparous in relation to ectopic pregnancy.

Sign and symptoms	Parity		P values
	Nulliparous	Multiparous	
	N (%)	N (%)	
Discharge			
Yes	10 (35.7)	18 (64.3)	0.552
No	24 (36.9)	41 (63.1)	
Dyspareunia			
Yes	11 (34.4)	21 (65.6)	0.467
No	23 (37.7)	38 (62.3)	
Pain			
Yes	27 (33.8)	53 (66.3)	0.139
No	7 (53.8)	6 (46.2)	
Bleeding			
Yes	21 (33.9)	41 (66.1)	0.296
No	13 (41.9)	18 (58.1)	

Table 4 Show the significant of individual risk factors to rate of ectopic pregnancy in both nulliparous and multiparas women.

Variables	Parity		P values
	Nulliparous N (%)	Multiparous N (%)	
Combined Contraception Pills Yes No	7(15.9) 27(55.1)	37(84.1) 22(44.9)	<0.001
Intra urine contraceptive device Yes No	3 (21.4) 4)13.3(	11 (78.6) 26 (86.7)	0.392
Progesterone only pills Yes No	0 (0.0) 4 (10.8)	2)100.0(33)89.2(	0.805
Smoking Non-smoker Currently smoker	34 (37.0) 0 (0.0)	58 (63.0) 1 (100.0)	0.634
Previous CS Yes No	0 (0.0) 34 (56.7)	33 (100.0) 26 (43.3)	<0.001
Previous scar in the pelvis Yes No	6 (17.6) 28 (82.3)	15 (71.4) 44 (61.1)	0.275
PID(pathological vaginal discharge) Yes No	10 (40) 24(38)	15(60) 39(61)	0.003
Previous Ectopic Pregnancy Yes No	5(50.0) 29(34.1)	5(50.0) 54(65.1)	0.001
Use of infertility medication Yes No	12 (44.4) 21 (32.3)	15 (55.6) 44 (67.7)	0.193
Miscarriage Yes No	2 (50.0) 9 (40.9)	2 (50.0) 13 (59.1)	0.574

Table 5. Showing the significant of type of treatments and related risk factors.

Variables	Parity		P values
	Nulliparous N (%)	Multiparous N (%)	
Treatment of recent ectopic Medical Surgical Expectant	12 (33.3) 22(42.3) 0 (0.0)	24 (66.7) 30 (57.7) 5 (100.0)	0.151
Numbers of risk factors 0 1 2 3 4 5	8 (72.7) 15 (65.2) 6 (24.0) 2 (9.1) 3) (30.0) 0 (0.0)	3 (27.3) 8 (34.8) 19 (76.0) 20 (90.9) 7 (70.0) 2 (100.0)	< 0.001
Numbers of risk factors No risk factor Single risk factor Multiple risk factors	8 (72.7) 15 (65.2) 11 (18.6)	3 (27.3) 8) (34.8) 48 (81.4)	< 0.001

DISCUSSION

We have shown that the recorded incidence of ectopic pregnancy in Sulaimani region has increased markedly in recent decades reaching a peak incidence by 2015. In the United States, the prevalence of risk factors, for ectopic pregnancy are increasing, accounting, for increasing the incidence of ectopic pregnancy. Further, the increased incidence of ectopic pregnancy may be the result of earlier diagnosis, with the use of sensitive pregnancy tests and transvaginal ultrasound detecting some ectopic pregnancies that in the past may have resolved spontaneously before diagnosis [39].

There are a number of possible explanations for this including both statistical recording of data and an underlying increase in exposure to a causative agent. If the trends are real there is serious cause for concern because of the important immediate and delayed sequelae of ectopic pregnancy. From all demographic changes weight and BMI where the most significantly affect the results. The higher the weight the higher risk of ectopic pregnancy showing in Table 1.

Table 2 showing (36.6%) women have no previous pregnancy experience among multiparas women while (63.4%) where among paras women.

Also evaluated the risk factors affecting the incidence of ectopic pregnancy, (11.8%) has no risk factors, most of patient (63.4%) had multiple risk factors, and (24.7%) had only one risk factors.

Figure 1 showing that multiple risk factors causing ectopic pregnancy in multigravida women (51.6%) more than that in nulliparous women (8.6%), this due to past obstetric history namely previous caesarean section while single risk factor more clearly affect the rate in primigravida 16.1% and 8.6% in multigravida.

Table 3 showing the use sign and symptom of bleeding, pain, discharge and dyspareunia was not help full in predicting ectopic pregnancy in both nulliparous and multiparas women. Table 4 show the effect of each risk factors on the rate of ectopic pregnancy, in both prime and multigravida women. We found that in the general population, pelvic inflammatory disease (generalized fever, Abdominal pain and pelvic pain, and vaginal discharge) is the most common risk factor for ectopic pregnancy. Organisms that preferentially attack the fallopian tubes include Neisseria gonorrhea, Chlamydia trachomatis and mixed aerobes and anaerobes. This was seen in a comprehensive Analysis Based on a Large Case-Control, Population-based Study in France 1993-2000 they found that The main risk factors were infectious history (adjusted attributable risk = 0.33; adjusted odds ratio for previous pelvic infectious disease = 3.4, 95% percent confidence interval [40]. This result was agreed with our study show PID that was diagnosed on the bases of pathological vaginal infection was significant.

Intrauterine devices (IUDs) used for contraception do not increase the risk of ectopic pregnancy, and no evidence suggests that currently available IUDs cause pelvic inflammatory disease. One explanation for the mistaken association of IUDs with ectopic pregnancy may be that when an IUD is present, ectopic pregnancy occurs more often than intrauterine pregnancy [41-44],simply because IUDs are more effective in preventing intrauterine pregnancy than ectopic pregnancy, implantation is more likely to occur in an ectopic location [45-48], IUCD in our study did not increase the risk of ectopic pregnancy and this agreed with above study. In addition we found in our study previous ectopic pregnancy is not increasing the risk, in fact all literature focused on previous ectopic pregnancy becomes a more significant risk factor with each successive occurrence. With one previous ectopic pregnancy treated by linear salpingectomy, the recurrence rate ranges from 15 to 20 percent, depending on the integrity of the contralateral tube [49]. Two previous ectopic pregnancies increase the risk of recurrence to 50 percent, although an intervening intrauterine pregnancy lowers this rate [50]. This result in our study may be due to the fact that most of our patients are treated surgically by salpingectomy rather than salpinotomy.

Because of the small sample size and not allowing an illegal termination in current study previous miscarriage was not statistically significant risk factor for ectopic pregnancy and this contradicting with Japanese study. Their analysis suggests that induced abortion may be one of several risk factors for ectopic pregnancy, particularly for women who have had abortions plus pelvic inflammatory disease or multiple abortions [51].

Endometriosis, tubal surgery and pelvic surgery result in pelvic and tubal adhesions and abnormal tubal function. The fallopian tubes may also be affected by other, less clearly understood causes of infertility, as well as many of the hormones that are administered to aid ovulation and improve fertility [50]. The result of

both previous pelvic surgery and ovulation induction treatment were not significant in our study.

Smoking cigarettes is uncommon among women in our community, therefore it was not a significant risk factor was not significant in both prime and multiparous women. Cigarette smoking has an independent and dose-related effect on the risk of ectopic pregnancy. Cigarette smoking is known to affect ciliary action in the nasopharynx and respiratory tract. A similar effect may occur within the fallopian tubes [52].

We found that one of the important risk factor was previous c/s and combined contraception pills and this agreed with a study done in Georgia on 138 women to determine whether previous cesarean delivery is an independent risk factor for ectopic pregnancy. data collected between October 1988 and August 1990 from a case-control study of ectopic pregnancy among porous, black, non-Hispanic women, 18-44 years old, Adjusted for age, previous caesarean section, parity, marital status, the odds ratio was 0.6 (95% confidence interval 0.4-1.1), indicating significant association [53]. We found this result in our study may be due to poor in c/s technique and increase in the rate of caesarean section on request especially in private sector.

About 36 of ectopic pregnancy is managed by Methotrexate (Mtx) It was determined that the overall success rate was 67.7%. Only the initial serum βhCG level and the diameter of the EP mass were the factors affecting the success of both single- and multiple-dose Mtx treatment. As the serum βhCG measurement was the mainstay of a rapid and early pregnancy diagnosis and an accepted biochemical marker for successful trophoblastic implantation the predictors of success of Mtx in our study were low βhCG values and an adnexal mass diameter of less than 25 mm.

There have been many published studies in the literature about Mtx success rates. In a review article published in 2003, [54] the crude overall success rate in 1327 women was estimated as 88.8% (1181 of 1327). The success rate has been reported to be between 75% and 96% in properly selected patients. The ratio in the present study was lower than the data in the literature. We think that this might be due to the time wasted in referral procedures. However, we have concluded that the medical treatment of EP is a practical treatment.

In the present study 52 women required surgical management; 8 patients were treated with left salpingectomy and 4 with laparoscopic salpingectomy. In 15 patients EP rupture was diagnosed intraoperative. Therefore, one important issue to emphasize is that clinicians must be careful in deciding on an operative treatment for patients. We should consider having pain for a patient who are under MT treatment, could be due to tubal abortion or stretching of the tube by a hematoma.

The laparoscopic surgical treatment was the selected method for patients who had a stable hemodynamic condition. The surgeon's own skills, seemed to have an importance in the selection of surgical method. Lastly, 5 patients were treated by expectant management and those whom only biochemical pregnancy was confirmed/ pregnancy was for unknown location, careful follow up applied.

Conclusion

Although the study duration was 6 months, the rate of birth was around 7500 deliveries and we recruited 100 cases the rate of ectopic pregnancy was 1.3%. We found the main demographic variable was High body weight and BMI. Most of the patient have multiple risk factors and risks higher in multigravida women than prime gravid. The most significant risk factor for increasing the rate was confirmed with previous ectopic pregnancy, combined contraception pills and pathological vaginal discharge, and previous caesarean section. We found this increase may be due to poor in c/s technique and increase in the rate of caesarean section on request specially in private sector and profound use of multiple antibiotic, poor hygiene that increasing the risk of ectopic pregnancy. However intra urine contraceptive device was not statistically increasing the risk of ectopic pregnancy

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