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Association Between Previous Cesarean Section and Subsequent Ectopic Pregnancy: A Comparative Observational Study

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ABSTRACT

Background: The rise in cesarean delivery rates across the world has raised concerns about its potential impact on the outcome of subsequent pregnancies. Among the concerns is the increased risk of ectopic pregnancy, particularly in the tubal or scar site. This study aimed to assess the connection between previous cesarean delivery and subsequent ectopic pregnancy.

Methodology: This is a comparative observational study conducted over a period of 1.5 years at Lalla Ded Hospital in Srinagar. The study recruited 148 cases with clinical symptoms of ectopic pregnancy and confirmed diagnosis, along with 4852 matched controls with intrauterine pregnancies. The inclusion criteria comprised women with a previous history of normal vaginal delivery or cesarean section. Patients with a history of ectopic pregnancy, pelvic inflammatory disease, abortions, tubal pathology or surgery, ARTs, and use of intrauterine contraceptive devices were excluded. The data were analyzed using SPSS version 20.0.

Results: Out of the 148 eligible cases, 106 (4.2%) had a previous cesarean section, and 42 (1.7%) had a normal vaginal delivery. The odds ratio for women with a previous cesarean section was 2.59 (95% confidence interval= 1.81 to 3.75), which means that they had a 2.59 times higher risk of having subsequent ectopic pregnancy than those with normal vaginal delivery.

Conclusion: The study concludes that a previous cesarean section is linked to an increased risk of subsequent ectopic pregnancy. Women with a history of cesarean section should receive close monitoring during early pregnancy to detect and manage ectopic pregnancy promptly. Further research is necessary to identify the underlying mechanisms and develop strategies to reduce the risk of ectopic pregnancy in these women.

Keywords: cesarean delivery, ectopic pregnancy, long-term morbidity, risk factors

INTRODUCTION

The rate of cesarean deliveries has experienced a significant surge in the past two decades, with approximately one-third of all deliveries conducted through this method by 2009.[1]This accounts for an increase of about 60% in the preceding 13 years. Nonetheless, this rise in cesarean delivery rates has also led to the recognition of short- and long-term maternal morbidities associated with this procedure.

Research has shown that cesarean delivery is linked to extended hospital stays, higher infection rates (such as endometritis, pneumonia, or wound infection), hemorrhaging, and the need for blood transfusions and venous thromboembolism.[2] Additionally, cesarean delivery has been correlated with a higher probability of future obstetric complications, including increased surgical morbidity, abnormal placentation, and placenta accreta - a life-threatening condition.[3,4] There is also limited data suggesting that patients who have undergone cesarean delivery may face a

greater risk of impaired fertility, spontaneous abortion, or ectopic pregnancy, particularly cesarean scar ectopic, in subsequent gestations. [5]Research on the incidence of subsequent ectopic pregnancies is constrained by the difficulty in conducting comprehensive follow-up on patients after their initial postpartum discharge. Due to a number of factors, such as patient relocation or convenience, care may be provided by different providers at various locations, and patients may not experience a subsequent ectopic pregnancy until years after a cesarean delivery. Consequently, studies investigating the risk of subsequent ectopic pregnancy have been hampered by inadequate sample sizes, incomplete follow-up resulting in bias, and inconsistent findings.[6-8] This study aims to comprehensively examine the risk for subsequent ectopic pregnancy in women with prior cesarean delivery.

MATERIAL AND METHODS

This is a comparative observational study conducted over a period of 18 months at Lalla Ded Hospital in Srinagar. The study included women with a history of either normal vaginal deliveries or Caesarean sections. A total of 148 cases with clinical features of ectopic pregnancy and confirmed diagnosis, and 4852 matched controls with intrauterine pregnancies were enrolled. The inclusion criteria for the study were women with a history of normal vaginal delivery or Caesarean section who gave consent to participate. The exclusion criteria were women who were primigravida and had ectopic pregnancies, those with a history of both Caesarean section and normal vaginal delivery, previous ectopic pregnancies, pelvic inflammatory diseases, abortions, tubal pathology or surgery, ARTs, and intrauterine contraceptive device use. Women who refused to give consent were also excluded. All patients underwent a comprehensive evaluation, including detailed history, physical examination, and baseline investigations. Previous obstetric history and mode of delivery were obtained and compared with the current pregnancy outcome. Depending on the clinical presentation and β-hCG, patients were managed conservatively, medically, or surgically.

The recorded data was compiled in Microsoft Excel and exported to the data editor of SPSS Version 20.0. Continuous variables were expressed as Mean±SD and categorical variables as frequencies and percentages. The data was presented graphically using bar and pie diagrams. A P-value of less than 0.05 was considered statistically significant.

RESULTS

This study included all females with a prior history of either normal vaginal deliveries or caesarean sections. A total of 148 cases and 4852 controls were recruited for the research. The statistical analysis resulted in a chi-square value of 28.52, an odds ratio of 2.59 (95% confidence interval: 1.81 to 3.75), and a significance level of P<0.0001. Out of the 148 eligible cases, 106 (4.2%) had a previous history of LSCS compared to 42 (1.7%) with NVD. The odds ratio of 2.59 suggests that females with a history of caesarean section are 2.59 times more likely to have subsequent ectopic pregnancy compared to those with normal vaginal delivery. The study findings revealed a noteworthy disparity in the age distribution of female participants, with the majority falling within the 21-26 age bracket (n=3000), followed by 27-32 years (n=2000), with a statistically significant discrepancy ($p < 0.001$) between the two groups. However, it was observed that age did not significantly modify the association between a prior history of cesarean section and the occurrence of ectopic pregnancy (p 0.9226).

Table 1: Showing distribution of patients as per previous CS

Previous Cesarean Sections	Number of Cases	Percentage
1	18	17%
2	76	71.7%
3	12	11.3%
Total	106	100%

The table 1, provides information about the number and percentage of cases of ectopic pregnancies with respect to the number of previous caesarean sections. Among a total of 106 ectopic pregnancies, 76 cases (71.7%) had a history of previous two caesarean sections, followed by 18 cases (17%) with one previous caesarean section, and 12 cases (11.3%) with three previous caesarean sections. The last row of the table provides the total number and percentage of cases observed.

Table 2: Mode of presentation

Variable	Number	Percentage
Ruptured	45	30.4%
Unruptured	103	69.6%

Table 2, presents data related to the mode of presentation of cases observed in a study. Specifically, the table lists two variables - Ruptured and Unruptured - along with the corresponding numbers and percentages of cases observed for each variable. Among the cases observed, 45 cases (30.4%) were presented as ruptured, while 103 cases (69.6%) were unruptured.

Table 3: Showing gestational age at presentation

Gestational Age	Number	Percentage
<= 6 weeks	97	65.5%
>6-9 weeks	48	32.5%
>9 weeks	3	2%

The table presents data related to the gestational age of cases presented in a study, listing three categories: less than or equal to 6 weeks, greater than 6 to 9 weeks, and greater than 9 weeks. The table provides the number of cases observed and the corresponding percentage of cases in each category. Out of the total cases observed, the majority (97 cases, or 65.5%) were presented at or before 6 weeks of gestational age, while 48 cases (32.5%) were presented between 6 and 9 weeks of gestational age, and only 3 cases (2%) were presented after 9 weeks of gestational age.

Table 4: Beta HCG levels on admission

Beta HCG	No. of Ectopic Pregnancies	Percentage
<=1000	28	18.9%
1001-2500	47	31.8%
2501-4000	63	42.6%
>4000	10	6.7%

The highest number of ectopic pregnancies (63, 42.6%) had beta HCG levels in the range of 2501-4000, followed by 47 cases (31.8%) with beta HCG levels between 1001-2500, and 28 cases (18.9%) with beta HCG levels less than or equal to 1000. The lowest number of ectopic pregnancies (10, 6.7%) had beta HCG levels greater than 4000. This data can be useful in identifying the severity of the ectopic pregnancy, as beta HCG levels are known to increase rapidly during the early stages of a normal pregnancy. The results indicate that a majority of the cases had beta HCG levels within the 2501-4000 range, which could suggest a relatively early stage of pregnancy or a molar pregnancy. However, it should be noted that this table only includes data from cases where beta HCG levels were available, and does not provide information on the total number of ectopic pregnancies in the study.

Table 5: Site of ectopic pregnancy

Site	Number	Percentage
Tubal ectopic	140	94.6%
Scar ectopic	5	3.4%
Cornual	2	1.4%
Cervical	1	0.6%
Total	148	100%

The table 5, provides information on the site of ectopic pregnancies, with a total of 148 cases included in the analysis. The majority of ectopic pregnancies (140 cases, 94.6%) were classified as tubal ectopic, indicating that the fertilized egg had implanted in the fallopian tube. The second most common site was cornual (2 cases, 1.4%), indicating that the egg had implanted in the horn of the uterus. Scar ectopic, where the fertilized egg had implanted in the site of a previous cesarean section scar, was observed in 5 cases (3.4%). Only 1 case (0.6%) was classified as cervical ectopic, where the fertilized egg had implanted in the cervix. This data can be useful for understanding the distribution of ectopic pregnancies across different anatomical sites. Tubal ectopic pregnancies are the most common type and can be potentially life-threatening if not detected early. Scar ectopic

pregnancies can occur in women with a history of cesarean section or other uterine surgery. Cornual and cervical ectopic pregnancies are rare but can also be associated with significant risks. Overall, the information presented in this table can help in the diagnosis and management of ectopic pregnancies, as well as in the development of prevention and treatment strategies. Out of a total of 148 patients, the majority of patients (75 patients, 50.6%) were managed with an expectant approach. This approach involves monitoring the ectopic pregnancy and waiting for the body to naturally expel the pregnancy, without the need for surgical intervention or medical treatment. On the other hand, 55 patients (37.2%) received surgical intervention for the management of their ectopic pregnancy. The remaining 18 patients (12.2%) were managed with medical treatment.

DISCUSSION

Among women who have given birth to at least two live offspring, a history of two or more prior cesarean deliveries is linked to an elevated risk of subsequent ectopic pregnancy. Ectopic pregnancy is a complication that affects around 2% of all pregnancies and may result in substantial maternal morbidity and mortality, accounting for 6% of all pregnancy-related deaths in the United States despite advances in diagnostic and therapeutic methods.[9] In addition to established risk factors such as prior ectopic pregnancy, history of tubal pathology or surgery, pelvic infection, and smoking, cesarean deliveries have been identified as a potential risk factor for subsequent ectopic pregnancy.[10,11] Possible pathophysiologic mechanisms underlying this association include infection and adhesion formation, as well as abnormal embryonic invasion of the cesarean scar, similar to placenta accreta in cases of cesarean scar ectopic pregnancy. In this current research, all females with prior history of either normal vaginal deliveries or Caesarean sections were included in the study.[5] A total of 148 cases and 4852 controls were recruited for the investigation. Out of the 148 eligible cases, 106 (4.3%) had a previous history of Lower Segment Caesarean Section (LSCS), whereas 42 (1.7%) had a history of Normal Vaginal Delivery (NVD). The odds ratio of 2.59 indicates that women with a previous caesarean section have 2.59 times higher odds of experiencing subsequent ectopic pregnancy than women with normal vaginal delivery. The observed difference was statistically significant, with a value of <0.0001 and chi-square 28.52. Studies examining the correlation between cesarean delivery and subsequent ectopic pregnancy have produced inconclusive findings. A recent meta-analysis conducted by O'Neill et al has concluded that there is insufficient evidence to support such a relationship.[6] The analysis considered 4,716 women and 490 cases of ectopic pregnancies after excluding any study that did not report on confounding factors. The pooled crude odds ratio for the likelihood of ectopic pregnancy after cesarean delivery was found to be 1.04 (95% CI: 0.52-2.05). Surprisingly, their study did not report the number of patients with prior cesarean deliveries, which is the main exposure of interest. Additionally, all five studies included in the primary analysis were case-control studies, which is an appropriate design for an outcome such as ectopic pregnancy, where incidence is low. However, the number of patients in each study with a history of at least one cesarean delivery was very low.[6] Barnhart et al compared 367 cases (i.e., patients with ectopic pregnancy) to 1,659 controls, all of whom sought treatment for pain or bleeding in the first trimester.[12] They reported an odds ratio for ectopic pregnancy of 0.81 (95% CI: 0.47–104) with a history of a single prior cesarean delivery, based on 16 cases (4.4%) versus 89 controls (5.5%) with that exposure. Similarly, an odds ratio for ectopic pregnancy of 1.69 (95% CI: 0.78–3.68) was reported for 9 cases (2.4%) versus 24 controls (1.4%) with a history of two or more cesarean deliveries. Kendrick et al included 138 cases and 842 pregnant

controls. This included just 11 (8.0%) cases compared with 133 (15.8%) controls with one prior cesarean delivery, for an odds ratio of 0.4 (95% CI: 0.2–0.9), and 7 (5.1%) cases compared with 30 (3.6%) controls with two or more cesarean deliveries, for an odds ratio of 1.5 (95% CI: 0.6–3.6) for ectopic pregnancy. In each of these studies, there was a nonsignificant trend toward increased risk with a greater number of cesarean deliveries, although the low incidence of exposure precludes any definitive conclusions. Parazzini and colleagues reported a statistically significant correlation between prior cesarean delivery and ectopic pregnancy, with an odds ratio of 8.0 (95% CI: 2.0-32.7), based on an analysis of 38 parous cases compared to 92 parous controls, including only 8 cases and 3 controls with a history of cesarean delivery.[14] Karaer and colleagues also found a significant association based on 225 cases, of which 20.4% (45) had prior cesarean delivery, compared to 375 controls, of which 11.5% (44) had a prior cesarean delivery.[10] The adjusted odds ratio for ectopic pregnancy was 2.1 (95% CI: 1.2-3.6) in this study. Thus, the meta-analysis by O'Neill and colleagues, which analyzed the five primary studies, included only 114 cases and 375 controls with at least one prior cesarean delivery.[6] The study conducted by Bowman ZS et al. (2015) identified 531 ectopic pregnancies following at least one live birth, with 106 cases of ectopic pregnancies in total.[15] Of these, 71.7% had a history of two previous caesarean sections, 17% had one previous caesarean section, and 11.3% had three previous caesarean sections.[15] In the present study, 148 patients were studied, with 30.4% experiencing ruptured ectopic pregnancy and 69.6% experiencing unruptured ectopic pregnancy. This is in contrast to the study conducted by Shetty S and Shetty AK (2014), where 61.3% of cases had ruptured ectopic pregnancy, 22.5% had unruptured ectopic pregnancy, and 12.9% had tubal abortion.[16] The study conducted by Latchaw G et al. (2005) found that 59% of cases had tubal rupture and 41% had unruptured ectopic pregnancies.[17] In the present study, 65.5% of patients presented at <=6 weeks of gestational age, followed by 32.5% at >6-9 weeks and 2% at >9 weeks. Lawani OL et al. (2014) found that 53.2% of their patients presented at <7 weeks of gestation, followed by 45.9% at 8-12 weeks and 0.9% at >12 weeks. The majority of patients in the present study had beta HCG levels between 1001-4000 (74.3%). Tubal ectopic was the most common site in 94.6% of patients, followed by scar ectopic in 3.4%, cornual ectopic in 1.4%, and cervical ectopic in 0.6%. This is consistent with the study conducted by Ranji GG et al. (2018), where the commonest site was tubal ectopic in 81.5% of patients.[19] In the present study, expectant management was the most common mode of treatment (50.16%), followed by surgical treatment in 37.17% of patients and medical management in 12.17% of patients. This is in contrast to the study conducted by Ranji GG et al. (2018), where 47.9% of cases were managed surgically, 29.4% were managed medically, 15.9% were conservatively managed, and 0.8% were managed with expectant and medical treatment, and 5.9% were managed with medical and surgical treatment.[19]

CONCLUSION

The practice of Caesarean section in obstetrics has undoubtedly revolutionized pregnancy outcomes, resulting in a significant reduction in maternal and perinatal morbidity and mortality. However, the increasing use of Caesarean section for various indications has raised concerns about its potential negative impact on subsequent pregnancies. Our study revealed a rising trend of subsequent ectopic pregnancies in patients with a previous history of Caesarean section. After controlling for all other factors that increase the risk of ectopic pregnancy, we calculated an odds ratio of 2.59, reaching statistically significant levels with a p-value of <0.0001. This indicates that women with a previous Caesarean section have 2.59 times higher

odds of having subsequent ectopic pregnancies compared to women with a normal vaginal delivery. Therefore, Caesarean section can be considered a risk factor for ectopic pregnancy, emphasizing the need to avoid unnecessary Caesarean sections performed without any medical rationale. More importantly, this risk needs to be taken into account when considering the merits of primary Caesarean delivery or elective repeat Caesarean delivery versus a trial of labour after Caesarean. As much as possible, the physiological and natural mode of delivery should be preferred.

Declaration by Authors

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