ORIGINAL RESEARCH PAPER
Volume - 13 | Issue - 01 | January - 2024 | PRINT ISSN No. 2277 - 8179 | DOI : 10.36106/ijsr
INTERNATIONAL JOURNAL OF SCIENTIFIC RESEARCH

A CORRESPONDING ANALYSIS OF A PERINATAL TERTIARY HOSPITAL DATABASE IN AHMEDABAD, GUJARAT, REVEALED THE RISK OF PLACENTA PREVIA AND PRETERM BIRTH IN PREGNANT WOMEN WITH ENDOMETRIOSIS AND ADENOMYOSIS.

Obstetrics & Gynaecology

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ABSTRACT

In analyzing a significant Indian database, our goal was to look into the associations among endometriosis and adenomyosis and pregnancy challenges. **Methods:** We examined 145,590 singleton pregnancies from the tertiary care facility in hindsight. Adenomyosis or endometriosis-registered pregnant women were referred to as the case group (EA), while propensity-score matching, which was adjusted for age, parity, BMI, smoking history, and the use of assisted reproductive technology, was used to identify the non-EA control group. Preterm birth, hypertensive disorders of pregnancy, and placental malposition were the primary outcomes (HDP). **Results:** A total of 1203 patients were matched and assessed, comprising both the EA and non-EA groups. Compared to the non-EA group, the EA group had substantially higher incidence of low-lying placenta (OR, 2.02; 95% CI, 1.06–3.86), preterm birth (OR, 1.44; 95% CI, 1.13–1.84), and placenta previa (odds ratio [OR], 3.01; 95% confidence interval [CI], 1.84–4.92). On the other hand, the incidence of HDP did not differ significantly (OR, 1.22; 95% CI, 0.90–1.66). **Conclusion:** It was made clear that EA was linked to a higher risk of pregnancy problems, notably placental malposition, which includes placenta previa and low-lying placenta, and preterm birth, but not HDP, by using propensity-score matching to examine a national perinatal database in Japan.

KEYWORDS

Adenomyosis, Endometriosis, Hypertensive Disorder Of Pregnancy, Placenta Previa, Preterm Birth

INTRODUCTION:

Endometriosis and adenomyosis are diseases that present with a variety of symptoms due to the ectopic development of endometrial-gland-like tissues; these ectopic growths are found in the ovaries and pelvis in endometriosis and the myometrium in adenomyosis. The prevalence of both diseases is estimated to be ~1%. [1,2] They exhibit a range of symptoms, such as infertility, chronic pelvic discomfort, dysmenorrhea, and hypermenorrhea. It is thought that the ectopic tissue's aberrant vascular growth and inflammation-mediated processes are responsible for these symptoms. [3]

Patients with these disorders, which are typically diagnosed at reproductive age, are more likely to experience various prenatal problems, according to a number of recent epidemiological studies.

A large-scale database studies have revealed a correlation between perinatal difficulties such placenta previa, preterm birth, and hypertensive disorders of pregnancy (HDP) and the consequences of endo-metriosis. [4,13]

Increased prenatal morbidity, including as HDP, small for gestational age (SGA), premature birth, and stillbirth, has been recorded in instances with adenomyosis, despite the paucity of data on the condition. [4-17] However, for ensuring the caliber of cohort studies, two concerns need to be resolved. The handling of covariates comes first. As people age, the prevalence of adenomyosis and endometriosis rises. [2,18] and when these issues exist, assisted reproductive technology (ART) is frequently needed in order to conceive. [19] Accurate analysis necessitates the calibration of variables like age and the existence of ART because these two variables are also linked to the development of different perinatal problems. The requirement to guarantee a suitable sample size is the second problem. Even though there have been a lot of epidemiological research on endometriosis to date, very few reports have made use of sizable databases with over 1000 positive cases and appropriate calibration for variables including age, parity, and ART. [13,20] Furthermore, there are few large-scale database studies investigating the relationship between adenomyosis and pregnancy problems. [17] Research findings for a range of sample sizes have been published using various covariate treatment strategies. Furthermore, mixed findings have come from the research that has been done thus far, particularly on the link between endometriosis and HDP. More extensive, high-quality research is required to make a more precise risk estimate Herein, we aimed to conduct one of the largest and most comprehensive studies using a high-quality, large database, focusing primarily on south Asian population. to investigate endometriosis and adenomyosis through a cohort study. We used a large nationwide perinatal data- base in India to investigate associations of endometriosis and adenomyosis with perinatal outcomes in a large national perinatal database in India, we evaluated the incidence of perinatal outcomes between patients with propensity-score matching (PSM) for endometriosis/adenomyosis (EA) and non-EA patients. The covariates for PSM were age, parity, ART status, and smoking history. We want to examine the phenotypes of endometriosis and adenomyosis as a group of diseases (EA) despite the fact that they are not easily distinguishable in this database.

METHODS

Study design

This study utilized the comprehensive information on maternal, fetal, and neonatal clinical out- comes from secondary- or tertiary-level perinatal centers in Ahmedabad. Each center submitted standardized reports on all live births and stillbirths that occurred after 22 weeks of pregnancy. The database covered 14689 deliveries after 22 weeks of gestation in 2021, Patient background, pre-pregnancy complications, and delivery outcomes were recorded by obstetricians/gynecologists, midwives, or trained medical clerks after each delivery. The presence or absence of comorbidities related to endometriosis and adenomyosis was registered by obstetricians/gynecologists based on patient information, including the patient's surgical and medical history, imaging findings before and during pregnancy and intra-abdominal findings during cesarean section. The majority of the data were provided by secondary and tertiary delivery facilities, with 88 (22.6%) of the registered facilities being tertiary perinatal centers and 188 (48.3%) being secondary perinatal centers.

Factors that vary

We examined the perinatal outcomes in patients who were registered as having either endometriosis or adenomyosis (EA), as the database does not differentiate between the two conditions. The analysis included the following explanatory variables: parity, age at delivery, use of antiretroviral therapy (ART) or not, and smoking during pregnancy. Placenta previa, low-lying placenta, preterm birth, preterm premature rupture of membranes (PROM), HDP, placental abruption, stillbirth, and fetal growth restriction (FGR) were the objective factors that were analyzed. The patients' self-reports served as the basis for the explanatory variables, while postpartum obstetric diagnoses were used to input the objective variables. Missing values in the data were eliminated from the analysis.

Statistical Analysis

Initially, we compared the background features of the patients in the EA and non-EA groups. For discrete variables, percentages were assessed, while for continuous variables, means and standard deviations (SDs) were used. The chi-square test was used to assess discrete variables and the t-test was used to analyze continuous

variables for group comparisons. In order to account for any confounding variables between patient background factors and EA problems, PSM was also carried out. The logistic regression analysis of each background component for EA complications was used to calculate the propensity scores, and the two groups were matched so that the distribution of background factors was comparable between them. In pairs, the caliper was less than 0.2. The matching package in R (R Foundation for Statistical Computing, version 4.2.0) was used to conduct the analyses. To find out if the variations in each factor's distribution were adjusted for matching, standardized mean differences were computed for each factor. The assumption of balance between the cohorts was deemed to be supported by a normalized difference of less than 0.1. The frequency of perinatal incidents before and after matching was compared using the $\chi 2$ test. The odds ratio and a 95% confidence interval between the two groups were computed for every incident.

RESULTS

4093 individuals with missing data were removed from the study, leaving 6496 participants out of the 4100 patients who had singleton deliveries in 2021 at 22 weeks or later. 561 (13.68%) of them had EA (Figure 1). The background characteristics of the EA and non-EA groups are shown in Table 1 both before and after matching: Patients in the EA group included a higher number of patients who became pregnant with ART (EA: 18.4%, non-EA: 6.7%), were older (EA: 28.87 ± 0.60, non-EA: 25.6 ± 4.5), and smoked less (EA: 1.3%, non-EA: 2.8%). Following PSM, every patient in the EA group was paired with a patient in the non-EA group. Following the matching process, the standardized two groups' differences in each factor were less than 0.1, indicating that the matching was appropriate.

The frequency of each perinatal incident in the EA and non-EA groups is compared before and after matching in Table 2. Before and after matching, the frequencies of placenta previa (OR, 3.91; 95% CI, 3.03–5.05; OR, 3.01; 95% CI, 1.84–4.92) and low-lying placenta (OR, 2.40; 95% CI, 1.64–3.51; OR, 2.02; 95% CI, 1.06–3.86) were both before and after matching, the EA group's was much higher. Both before and after matching, the EA group had a significantly higher rate of preterm delivery (OR, 1.51; 95% CI, 1.29–1.77; OR, 1.44; 95% CI, 1.13–1.84). However, there was no difference observed for preterm PROM (OR, 1.06; 95% CI, 0.75–1.5 before to matching; OR, 0.89; 95% CI, 0.55–1.42 subsequent to matching). Preterm birth was considerably more likely in the EA group before matching in the group without placenta previa or low-lying placenta, but there was no difference after matching (before matching: OR, 1.26; 95% CI, 1.05–1.50; after matching: OR, 1.24; 95% Confidence Interval, 0.96–1.61). Prior to matching, there was a substantial difference for HDP between the two groups, however there was no difference after observed following matching (OR, 1.22; 95% CI, 0.90–1.66); before to matching: 1.33; 95% CI, 1.08–1.64. When comparing the two conditions using HDP typing, there were no discernible differences for preeclampsia (OR, 0.97; 95% CI, 0.60–1.56) and gestational hypertension (OR, 1.33; 95% CI, 1.00–1.76; after matching: OR, 1.43; 95% CI, 0.92–2.21). Before and after matching, the two groups did not exhibit any significant differences in placental abruption, stillbirth, or FGR.

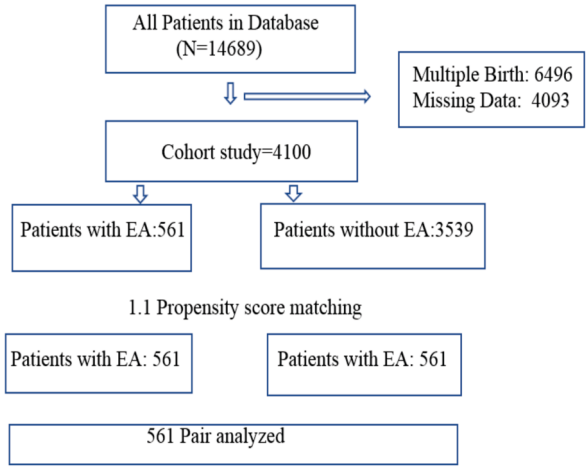

Fig: 1 A diagram showing case and control selection. EA, endometriosis and endomyosis.

Table: 1 Patient characteristics before and after matching.

		Before matching		After matching		
	Non-EA (n=3539)	EA (n=561)	SD	Non-EA (n=561)	EA (n=561)	SD
Age	32.65 ± 5.52	34.89 ± 0.7	0.44	35 ± 4.88	34.89 ± 0.7	—0.02
Parity	0.69 ± 0.88	0.46 ± 3.48	_0.28	0.44 ± 0.66	0.46 ± 3.48	0.03
BMI	21.74 ± 3.92	21.65 ± 0	_0.02	21.67 ± 3.55	21.65 ± 0	_0.01
Smoking	46 (2.8%)	6 (1.3%)	_0.11	19 (1.5%)	16 (1.3%)	_0.02
ART	143 (9.7%)	32 (27.5%)	0.47	312 (25.9%)	332 (27.5%)	0.04
Placenta previa	201 (1.41)	24 (5.32)	3.91 (3.03–5.05) ***	22 (1.82)	64 (5.32)	3.01 (1.84–4.92) ***
Low-lying placenta	147 (0.98)	18 (2.32)	2.4 (1.64–3.51) ***	14 (1.16)	28 (2.32)	2.02 (1.06–3.86) *
Preterm birth Before 32 GW Before 28 GW	1472 (10.22) 485 (3.32) 141 (0.85)	17 (14.71 56 (4.9) 12 (1.41)	1.51 (1.29–1.77) ** 1.65 (1.02–2.67) 1.65 (1.02–2.67)	110 (10.64) 34 (3.32) 14 (1.16)	177 (14.71) 59 (4.9) 17 (1.41)	1.44 (1.13–1.84) ** 1.49 (0.99–2.25) 1.24 (0.96–1.61)
Preterm-birth (normal placenta)	1347 (9.45)	40 (8.63)	1.26 (1.05–1.5) *	115 (9.55)	140 (11.63)	0.89 (0.55–1.42)
Preterm PROM	337 (2.65)	24 (2.82)	1.06 (0.75–1.5)	38 (3.15)	34 (2.82)	
HDP Gestational hypertension	904 (6.29) 461 (3.21)	79 (8.22) 41 (4.23)	1.33 (1.08–1.64) ** 1.33	76 (6.81) 26 (2.99) (1–1.76)	99 (8.22) 51 (4.23)	1.22 (0.9–1.66) 1.43 (0.92–2.21)
Preeclampsia	330 (2.28)	34 (2.82)	1.24 (0.88–1.75)	25 (2.9)	34 (2.82)	0.97 (0.6–1.56)
Placental abruption	178 (1.02)	16 (1.33)	1.3 (0.79–2.14)	12 (0.99)	16 (1.33)	1.33 (0.63–2.84)
Stillbirth	263 (0.38)	8 (0.66)	1.71 (0.84–3.44)	6 (0.49)	8 (0.66)	1.33 (0.46–3.86)
FGR	535 (3.72)	47 (4.73)	1.28 (0.98–1.67)	44 (3.65)	57 (4.73)	1.31 (0.87–1.95)

Note Chi-squared test-based p value: *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$. Abbreviations: CI, confidence interval; EA, endometriosis or adenomyosis; GW, gestational weeks; HDP, hypertensive disorder of pregnancy.

DISCUSSION

In the present study, we used a large statewide database to investigate the relationship between endometriosis/adenomyosis and perinatal problems in detail, controlling for confounding variables such as age, parity, BMI, ART, and smoking using PSM. Preterm birth, low-lying placenta, and placenta previa were all markedly enhanced by EA problems; however, preeclampsia and prenatal hypertension were not linked to HDP. While prior research has been conducted on related subjects, our study stands out for its unparalleled scope and use of a top-notch database overseen by medical experts. We provided distinct data that are unique to South Asian populations and used PSM to account for confounding variables. As a result, although previous research has identified a variety of issues, our study conclusively demonstrated a strong correlation. between EA and an irregular placental location. Furthermore, we found no discernible variation in

our sample for HDP, which has been linked to conflicting outcomes regarding its correlation with EA.

In this study, it was demonstrated that the presence of EA was a risk factor for both placenta previa and low-lying placenta. Endometriosis is also known to be linked to placenta previa. [21] Although there are few reports on placenta previa, endometriosis has been linked to it with an OR of 2.62–3.90.[5,12,20] There is less data on the correlation between the two conditions; one study found an OR of 4.94 (95% CI, 1.70–14.34).[14] The results of earlier research demonstrating the connection between EA and plaque previa are corroborated by the current investigation. Placenta previa is assumed to be pathologically caused by persistent adhesions and inflammation in the rectovaginal region; the risk of placenta previa is known to rise with the severity of endometriosis. [22]

According to reports, the odds ratio (OR) for the correlation between endometriosis and preterm delivery is 1.16–1.67.[6,9,13,23,and24]) Small retrospective studies in adenomyosis found ORs ranging from 2.49 to 3.69.[14,17] We observed results in our study that are consistent with the numerous studies that have linked it to the risk of preterm delivery, even if some publications did not detect any significant differences.[25] Whether the premature delivery is medically indicated due to placenta previa or HDP, or occurs spontaneously, the mechanism behind the increased risk of preterm birth as a result of EA should be explored separately. The rate of placenta previa was higher in the EA group in this study, but there was no difference in the rate of HDP a group. Preterm deliveries in these groups most likely indicated preterm labor medically because of placenta previa. Following matching, there was no statistically significant difference in the percentage of preterm babies between the two groups after eliminating cases of placenta previa. Preterm PROM, which is thought to be the cause of the majority of spontaneous preterm deliveries, did not exhibit any significant differences between the two groups either. In conclusion, the medically indicated preterm births caused by placenta previa may account for the difference in the number of preterm births in the EA group.

Reports varying in strength indicate non-significant [8,24,26] and significant [6,10] correlations between HDP and endometriosis. There are limited publications describing the link between adenomatosis and HDP development, despite a recent meta-analysis suggesting that it may be a risk factor. Recent reports have indicated that pregnant women with diffuse type adenomyosis, in which the adenomyosis lesions are more advanced, have a higher prevalence of preeclampsia. [28] Given that the impact of EA can vary based on its kind and severity, a comprehensive database with thorough clinical information on EA illness state is necessary to analyze the role of EA on the development of HDP and preeclampsia. The divergent findings from the current and earlier investigations could be because there isn't enough large-scale research based on the assessment of suitable HDP illness categories and EA disease condition.

Using a physician-driven, big, well-documented, high-quality database allowed us to perform a detailed analysis of the relationship between rare EAs and pregnancy outcomes, which is one of the study's strengths over earlier publications. Although a number of earlier studies have examined data gathered through insurance claims information [12] or questionnaires [11], the database we employed was gathered nationally by doctors from medical records and was of excellent quality, allowing us to incorporate comprehensive pre-pregnancy data as a correction factor.

This study's adoption of PSM as its statistical methodology—many other researches have relied on logistic regression—is another strength. [5, 9, 11, 12] In this study, a number of clinical outcomes and EA confounded demographic factors, particularly the use or absence of ART. As a result, suitable corrective techniques were needed. We were able to compare presumably similar demographic groupings in order to present the connections in a more comprehensible way using PSM.

We were unable to distinguish between and conduct independent analyses of adenomyosis and endometriosis. But there are numerous similarities between endometriosis and adenomyosis, chiefly ectopic endometrial tissue development, and they frequently coexist in clinical instances such extrinsic adenomyosis and deep infiltrating endometriosis. [29] According to Chapron et al., 50.2% of women with histopathological proven endometriosis also had focal extrinsic adenomyosis. [30] They also noted that it can be difficult to obtain precise pre-surgical diagnostic imaging with MRI, suggesting that classifying a patient as having either endometriosis or adenomyosis may not always be accurate. Consequently, it should be highlighted that earlier research [4–13] on the results of pregnancies in women with endometriosis or adenomyosis has also been limited, possibly because it examined women who had both conditions without mutually exclusive treatment. exclusion, suggesting a significant case overlap. we were unable to conduct an analysis utilizing information about the disease subtypes, severity of endometriosis or adenomyosis, and surgery history due to limitations in the database used for this study. Furthermore, because this study makes use of a database, the precise diagnostic procedure is not provided by the database, and the existence or lack of the disorders was ascertained post-delivery based on information documented. Nonetheless, it is important to take into account the possibility that prenatal problems and the severity of these disorders may be closely correlated. Lastly, there is a lack of information regarding the use of fresh or frozen embryos in ART embryo transfers, and the existence or absence of adenomyosis and endometriosis may have influenced this decision. It is imperative to acknowledge the plausible confounding influence of this variable on the outcomes.

Still, no significant difference was seen when preterm birth cases were analyzed without taking into account those with placenta previa or low-lying placentas. As a result, the role of endometriosis and adenomyosis to spontaneous preterm delivery remains unclear. Furthermore, no correlation was seen with HDP, which includes preeclampsia and gestational hypertension. Notably, earlier study on this topic has produced contradictory results, underscoring the need for more investigation

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