Is endometriosis typology a potentially better classification system for assessing risk of female infertility?

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Objective: To determine whether endometriosis typology, namely ovarian endometriomas (OE), deep infiltrating endometriosis (DIE), or superficial endometriosis (SE), correlates with fertility history.
Design: Prospective cohort.
Setting: One of fourteen surgical centers in Salt Lake City, Utah (n = 5) or San Francisco, California (n = 9).
Patient(s): A total of 473 women (18–44 years) with no prior endometriosis diagnosis, undergoing laparoscopies/laparotomies, irrespective of indication, in Utah or California (2007–2009).
Exposure: Incident endometriosis.
Main Outcome Measure(s): Before surgery, we queried women about time to become pregnant for prior planned pregnancies. Generalized linear models were used to calculate adjusted prevalence ratios (aPR) for association between endometriosis typology and infertility, defined as having ever tried >12 months (>6 months for women ≥35 years) to get pregnant. We also generated fecundability odds ratios (aFOR) to capture time to pregnancy.
Result(s): Twenty-five percent (n = 116) of women were diagnosed with SE only, 5% (n = 23) with OE, 6% (n = 29) with DIE, and 5% (n = 22) with OE + DIE, and 60% (n = 283) with no endometriosis. Compared with women with no endometriosis, women with SE had a 1.58 higher aPR (95% confidence interval [CI], 1.16–2.14), although women with OE and/or DIE had a 2.41 higher aPR for subfertility after adjusting for women's age, body mass index, and site. Compared with women with no endometriosis, women with OE and/or DIE had a 53% lower historic fecundability (aFOR, 0.47; 95% CI, 0.24–0.95); however, no association was found among women with SE (aFOR, 0.81; 95% CI, 0.49–1.33).
Conclusion(s): Specific endometriosis typologies may be associated with fecundability, with OE and/or DIE associated with nearly a 150% higher prevalence of subfertility and over a 50% lower historic fecundability. (F S Rep® 2024;5:394–401. ©2024 by American Society for Reproductive Medicine.)
Key Words: Endometriosis, typology, infertility, fecundability, epidemiology

Infertility, defined as the failure to establish a clinical pregnancy after 12 months of regular sexual intercourse without contraception (>6 months for women aged >35 years) (1, 2), is an increasingly recognized healthcare challenge (3). Currently, one in seven (14.3%) and one in four (25%) couples in western and developing

Received December 29, 2023; revised August 13, 2024; accepted August 14, 2024.
Supported by the Intramural Research Program, Eunice Kennedy Shriver National Institute of Child Health and Human Development, National Institutes of Health, Rockville, Maryland (contracts NO1-DK-63428, NO1-DK-6-3427, and 10001406-02). Research reported in this publication was also supported by the National Heart, Lung, and Blood Institute and National Institute of Aging, National Institutes of Health (award numbers R01HL164715 [to L.F., K.S., and A.P.] and K01AG058781 [to K.S.]) Bethesda, Maryland, and by the Doris Duke Foundation's COVID-19 Fund to Retain Clinical Scientists funded by the American Heart Association, New York City, New York.
Data sharing statement: Data will be made available to the editors of the journal for review or query on request and after appropriate approvals from data steward Eunice Kennedy Shriver National Institute of Child Health and Human Development have been secured.
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F S Rep® Vol. 5, No. 4, December 2024 2666-3341
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https://doi.org/10.1016/j.xfre.2024.08.009

countries, respectively, experience infertility (4–6). Although infertility has many possible etiologic factors, endometriosis is recognized as a major contributor to female infertility (7, 8). The body of epidemiologic research suggests that up to half of infertile women have endometriosis and 30%–50% of women with endometriosis are infertile (8, 9). What remains unknown is whether endometriosis severity or typology is associated with varying risks in female infertility.

The best-known classification system for endometriosis is the revised American Society for Reproductive Medicine (rASRM) system (8). Unfortunately, little correlation has been found between the rASRM staging criteria and meaningful clinical outcomes, including infertility (8, 9). Our own prior research showed nearly a 30% reduction in fecundability or time to pregnancy (TTP) among a cohort of women undergoing laparoscopy/laparotomy regardless of clinical indication but no clear difference in TTP by rASRM stage (10). New staging systems that better correlate with infertility have been proposed, such as the Endometriosis Fertility Index, whose score is determined intraoperatively after surgical intervention describing the function of the tube, fimbria, and ovary on both sides (11). Although the Endometriosis Fertility Index has been found to correlate with infertility, the chief critique is that it may work only because the system includes important clinical variables, including age, years of infertility, and prior pregnancy, that affect fecundability independent of endometriosis (9, 12). Emerging systems that can distinguish between subtypes based on proposed physiologic impact, namely ovarian endometriomas (OE), mass lesions in the ovary; deep infiltrating endometriosis (DIE), with endometrial tissue invading in organs of the pelvis and elsewhere; and superficial endometriosis (SE), involving only surface peritoneal implants of endometrial tissue have also been proposed (13), but their association with infertility has not been fully explored. The objective of this study was to assess whether endometriosis typology is associated with women's infertility, as measured by TTP and seeking infertility treatment, among a cohort of women seeking laparoscopy and/or laparotomy for multiple indications.

MATERIALS AND METHODS

Study population

Data for this secondary data analysis came from the Endometriosis, Natural History, Diagnosis, and Outcomes (ENDO) study, a National Institute of Child Health and Human Development (NICHD) multi-site (California and Utah) cohort study (2007–2009) whose primary objective was to identify environmental and lifestyle factors associated with endometriosis (14). Complete details on study methodology have been previously published (14). In brief, women were eligible to participate if they were currently menstruating, were between the ages of 18 and 44 years, and were scheduled to undergo a diagnostic and/or therapeutic gynecologic laparoscopy or laparotomy, regardless of clinical indication, at any of five participating hospital sites in Salt Lake City, UT, or nine participating clinical centers in San Francisco, CA. Women who had a history of a hysterectomy or cancer (except for nonmelanoma skin cancer), had been breastfeeding within the last 6 months, or had received injectable hormone treatment (LupronDepot, Depot-Provera [depot-medroxyprogesterone acetate] or Depot-Subq 104 in the past 2 years) within the past 2 years were excluded from study participation. In addition, excluded were women with a history of surgically confirmed endometriosis (prevalent cases). This study was approved by the University of Utah and National Institutes of Health Institutional Review Boards for all participating institutions, and all participants gave written informed consent before enrollment and data collection. The ENDO data can be requested from NICHD as part of their NICHD/Division of Population Health Research Biospecimen Repository Access and Data Sharing program. We have a data use agreement form in place from NICHD to conduct our secondary data analysis.

Female infertility and covariate assessment

Participants completed questionnaires on sociodemographic factors, reproductive history, physical characteristics, medical history, and lifestyle information through computer-assisted, in-person interviews approximately 2 months before surgery so that they were not aware of their diagnoses at the time of the interview. Women were asked if they currently consume alcohol or whether they had ever smoked >100 cigarettes in their lifetime. Regarding reproductive history, women provided information about prior pregnancies, their intentions for each pregnancy (planned vs. unplanned pregnancy), TTP or the number of months required to become pregnant, and use of infertility treatment, among other reproductive health characteristics. Women also reported on their age of menarche. Women were asked whether they experienced pain lasting >6 months that was either cyclic (i.e., painful menstrual cramps not relieved by over-the-counter medications) or chronic (i.e., pain located in or near the bladder or vaginal canal not associated with menses) and those answering yes to pain, they were asked about the duration of pain (≥6 months–1 year, >1 year–2 years, or >2 years). Additionally, women were queried about 17 different sources or timing of pain (e.g., pain just before period, deep pain with intercourse, pain with urination, etc.) that they had experienced in the last 6 months (no minimum duration required) and rate the severity of each using an 11-point visual analogue scale, with 0 denoting no pain to 10 denoting the most severe pain imaginable using a standardized questionnaire.

Endometriosis assessment

We used the established clinical gold standard definition for endometriosis or surgically visualized disease (15, 16). All participating surgeons of the ENDO study had surgical training in the diagnosis and staging of endometriosis (14, 17). Before surgery, surgeons indicated one primary reason for surgery, including tubal ligation, pelvic pain, pelvic mass, infertility, fibroids, and menstrual irregularities. Immediately after surgery, surgeons completed the rASRM standardized operative report to capture gynecologic and pelvic pathology, including endometriosis, uterine fibroids, pelvic adhesions, benign ovarian cysts, neoplasms, and congenital müllerian anomalies. An a priori simple random

sample was selected to also undergo pelvic magnetic resonance imaging. Our prior research showed substantial agreement between gynecologic surgeons on endometriosis diagnosis and staging after viewing digital images and after additionally viewing operative reports (17, 18).

Typology was assessed via the rASRM standardized form for women whose rASRM form had information on lesion location and size (n = 180 [95%] out of the 190 women with an endometriosis diagnosis). Women with only superficial lesions on the ovary or peritoneum were considered to have SE, deep lesions (>5 mm invasion) (11), noted in the peritoneum or obliteration of posterior cul-de-sac were considered to be DIE, and deep lesions of any size noted in the ovary were considered to be OE; women who had deep ovarian and peritoneal lesions were considered to have OE + DIE. Women without information on lesion location, size, and depth (n = 10) were assumed to have SE.

Statistical analysis

Demographic, reproductive history, and lifestyle factors were compared by endometriosis typology (no endometriosis or other gynecologic pathology, no endometriosis but other gynecologic pathology, SE, DIE, OE, and DIE + OE) using analysis of variance or nonparametric Wilcoxon–Mann-Whitney U tests for continuous variables and χ^2 or Fisher's exact tests for categorical variables. To visualize overlap between SE, DIE, and OE among women with endometriosis, we created a proportional Venn diagram using eulerAPE (19). We used modified Poisson regression models with robust error variance to estimate unadjusted and adjusted prevalence ratios (aPRs) and 95% confidence intervals (CIs) for the association between ever reporting infertility via time trying (>12 months for women 35 years or younger and >6 months for women aged >35 years and older) and ever reporting infertility treatment. To assess female fecundability as measured by TTP, we restricted our analysis to the 198 women with planned pregnancies for whom TTP was reported for each pregnancy (10). Unadjusted and adjusted survival curves were created with the use of the recurrent survival model with a robust variance estimator. The Kolmogorov-type supremum test was used for checking proportional hazards assumption for all the variables in the recurrent model. Unadjusted and adjusted fecundability odds ratios (FOR) and 95% CI were estimated using a mixed effects shared frailty survival model where its random effect reflected the correlations between multiple pregnancies for the same woman. Time to pregnancy ≥13 months was censored for analysis. Due to limited counts by the six categories, our primary prevalence ratio and FOR models compared women with SE vs. DIE and/or OE vs. no endometriosis (reference group). However, for descriptive purposes, secondary models were run using the six categories.

Factors known to influence women's fertility and endometriosis were considered potential confounders. We fit parsimonious regression models, adjusting for chronological age (categorized <30 years old; 30–39; and ≥ 40.0), body mass index (BMI) (categorized <25.0 kg/m^2 25.0–29.9 kg/m^2; and >30.0 kg/m^2), research site (Utah/California), and smoking (ever smoked ≥100 cigarettes or not). Additional confounders, including age at menarche (years), age at first intercourse (years), presence of pelvic pain (y/n), presence of painful menstrual cramps (y/n), and ever having taken birth control pills (y/n) were evaluated using a purposeful variable selection procedure (20) but did not appreciably alter the estimates in endometriosis typologies. All statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC), and all significance tests are 2-sided with a significance level of 0.05.

RESULTS

Among the ENDO operative cohort, surgical indications for laparoscopy/laparotomy included pelvic pain (n = 206, 42%), pelvic mass (n = 74, 15%), irregular menses (n = 60, 12%), fibroids (n = 49, 10%), tubal ligation (n = 48, 10%), and infertility (n = 35, 7%). The incidence of endometriosis was 40% (190/473 women) in the full cohort and 36% (71/198 women) in the study sample when restricted to women with prior planned pregnancies for whom TTP was reported for each pregnancy (10). Of the 473 women undergoing surgery, 136 (29%) were diagnosed with a normal pelvis, 116 (25%) with SE only, 29 (6%) with DIE, 23 (5%) with OE, 22 (5%) with DIE + OE, and 147 (31%) with no endometriosis but some other type of gynecologic pathology. Among women with endometriosis, a proportional Venn diagram showing overlap between subtypes is shown in Supplemental Figure 1 (available online). Of the 198 women with prior planned pregnancies, 71 (36%) were diagnosed with a normal pelvis, 47 (24%) were diagnosed with SE only, 12 (6%) with DIE, 9 (5%) with OE, 3 (2%) with DIE + OE, and 56 (28%) with no endometriosis but some other type of gynecologic pathology.

Women with endometriosis, notably DIE and or OE, had lower BMI (DIE, 25.6 kg/m^2; OE, 26.9; DIE + OE, 24.2 vs. normal pelvis, 29.2), were more likely to report chronic cyclic pain (DIE, 45%; OE, 52%; DIE + OE, 59% vs. normal pelvis, 33%) and dyspareunia (DIE, 59%; OE, 48%; DIE + OE, 55% vs. normal pelvis, 32%), and had an older age of beginning sexual intercourse (DIE, 19.7; OE, 21.7; DIE + OE, 19.2 vs. normal pelvis, 18.2) than women without endometriosis (Table 1). The percentage of women from Utah with DIE was higher compared with women from California (7% vs. 3%), whereas the percentage of women from Utah with OE was slightly lower than among women from California (5% vs. 7%). The two sites had an equal proportion of women with DIE + OE (5%).

Among the total cohort of women who never achieved pregnancy (n = 155), 67 (43%) reported having ever tried for ≥6 months for pregnancy and 54 (35%) having ever used infertility treatment, with endometriosis most strongly associated with ever having tried for ≥6 months for pregnancy (Supplementary Table 1, available online).

Compared with women with no endometriosis, women with SE had 1.54 times (95% CI, 1.13–2.10) greater aPR forever reporting trying >6 months to get pregnant in multivariable-adjusted models; women with DIEA and/or OE had 2.39 times greater aPR (95% CI, 1.81–3.16) in multivariable-adjusted models (Table 2). We observed similar patterns for history of using fertility treatment. Compared with women without endometriosis, women with SE had

TABLE 1

Population characteristics of Endometriosis, Natural History, Diagnosis, and Outcomes study participants by endometriosis typology (n = 473).

Characteristics	No endometriosis and diagnosed with normal pelvis (n = 136)	No endometriosis but diagnosed with other gynecologic pathology (n = 147)	Superficial (n = 116)	DIE (n = 29)	Endometrioma (n = 23)	Endometrioma/DIE (n = 22)	*P* value
Age (y), mean ± SD	33.8 ± 7.0	33.5 ± 7.2	31.5 ± 7.2	31.1 ± 6.0	34.8 ± 6.1	32.6 ± 5.5	.04
BMI (kg/m^2), mean± SD	29.2 ± 8.8	29.2 ± 8.0	26.8 ± 7.3	25.6 ± 6.7	26.9 ± 9.1	24.2 ± 5.0	.0007
Age at menarche, mean± SD	12.8 ± 1.4	12.8 ± 1.7	12.8 ± 1.8	13.0 ± 1.9	13.1 ± 1.7	13.1 ± 1.9	.98
Chronic pelvic pain	41 (30)	57 (39)	51 (44)	12 (41)	9 (39)	12 (55)	.16
Chronic cyclic pain	45 (33)	45 (31)	56 (48)	13 (45)	12 (52)	13 (59)	.007
Vaginal pain with intercourse	44 (32)	61 (42)	64 (55)	17 (59)	11 (48)	12 (55)	.004
Deep pain with intercourse	42 (31)	56 (38)	64 (55)	17 (59)	7 (30)	13 (59)	.0003
Burning vaginal pain after intercourse	30 (22)	33 (22)	38 (33)	11 (38)	6 (26)	8 (36)	.16
Pelvic pain lasting hours or days after intercourse	29 (21)	35 (24)	39 (34)	12 (41)	4 (17)	6 (27)	.09
Constant burning vaginal pain	12 (9)	12 (8)	14 (12)	5 (17)	4 (17)	3 (14)	.40
Study site							.0001
Salt Lake City, UT	127 (31)	112 (27)	108 (26)	27 (7)	19 (5)	19 (5)	—
San Francisco, CA	9 (15)	35 (57)	8 (13)	2 (3)	4 (7)	3 (5)	—
Ever smoker[a]	52 (38)	56 (39)	38 (33)	4 (14)	5 (22)	6 (27)	.08
Alcohol consumer[b]	100 (74)	108 (74)	79 (68)	19 (66)	16 (70)	16 (73)	.83
Ever hormonal contraception	119 (88)	116 (79)	100 (86)	25 (86)	23 (100)	20 (91)	.08
Age at first intercourse	18.2 ± 3.6	18.4 ± 4.1	18.4 ± 3.5	19.7 ± 3.9	21.7 ± 6.8	19.2 ± 3.4	.05
Surgical indication							< .0001
Pelvic pain	42 (31)	44 (30)	71 (61)	21 (72)	13 (57)	15 (68)	—
Pelvic mass	9 (7)	39 (27)	11 (9)	3 (10)	6 (26)	6 (27)	—
Irregular menses	32 (24)	8 (5)	17 (15)	2 (7)	1 (4)	0 (0)	—
Fibroids	0 (0)	40 (27)	6 (5)	2 (7)	1 (4)	0 (0)	—
Infertility	16 (12)	12 (8)	3 (3)	1 (3)	2 (9)	1 (5)	—
Tubal ligation	36 (27)	4 (3)	8 (7)	0 (0)	0 (0)	0 (0)	—
Ever pregnant	116 (85)	93 (63)	71 (61)	17 (59)	11 (48)	10 (45)	< .0001
Ever tried for ≥6 mo for pregnancy	34 (25)	36 (25)	48 (41)	16 (55)	14 (61)	16 (73)	< .0001
Mean longest attempt (SD) in mo	24.2 ± 23.3	31.5 ± 33.1	30.7 ± 26.3	32.6 ± 59.9	48.9 ± 66.5	30.4 ± 24.1	.52
Ever use infertility treatment[c]	21 (15)	27 (18)	29 (25)	12 (41)	12 (52)	11 (50)	< .0001
Ever had a live birth	111 (82)	71 (48)	63 (54)	12 (41)	8 (35)	4 (18)	< .0001

Note: n (%) unless otherwise noted. Missing: BMI (n = 5), age (n = 1), chronic pelvic pain (n = 1), chronic cyclic pain (n = 2), ever smoked (n = 2), alcohol consumer (n = 2), surgical indication (n = 1), age at first intercourse (n = 67), age at menarche (n = 1), ever tried for ≥6 months for pregnancy (n = 2), and mean longest attempt (n = 1). BMI = body mass index; DIE = deep infiltrating endometriosis.

[a] Using the computer-assisted personal interview, participants reported at baseline whether they currently consume alcohol (yes/no) and drinks per day. For this analysis, we dichotomized to yes/no of being current alcohol consumers.

[b] Using the computer-assisted personal interview, participants reported at baseline whether they had ever smoked >100 cigarettes in their lifetime, and if yes, how many years they smoked, whether they smoked now, and on average how many cigarettes they currently smoke. For this analysis, we dichotomized to yes/no of ever having smoked cigarettes.

[c] Among the 112 women reporting history of infertility treatment (could be >1 type), 78 (70%) had used fertility drugs to stimulate ovulation (clomid, clomiphene citrate, or any other drug in pill form), 21 (19%) had fertility drugs by injection (gonadotropins, human chorionic gonadotropin, drug by injection), 29 (26%) had progesterone by any route, 30 (27%) had intrauterine insemination with their partner's semen, 11 (10%) had intrauterine insemination with a donor semen, and 8 (7%) had in vitro fertilization (IVF) (with 5 having IVF with intracytoplasmic sperm injection).

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TABLE 2

Prevalence ratios for infertility and utilization of infertility treatment by endometriosis typology among all women in the Endometriosis, Natural History, Diagnosis, and Outcomes operative cohort (n = 473).

Prevalence ratios for infertility and utilization of infertility treatment	No endometriosis (n = 283)	Superficial endometriosis (n = 116)	DIE and/or endometrioma (n = 74)
Infertility[a]			
Unadjusted prevalence ratio (95% CI)	1.00 (ref)	1.65 (1.23–2.22)	2.48 (1.89–3.24)
Adjusted prevalence ratio[b] (95% CI)	1.00 (ref)	1.54 (1.13–2.10)	2.39 (1.81–3.16)
Infertility treatment[a]			
Unadjusted prevalence ratio (95% CI)	1.00 (ref)	1.47 (0.98–2.21)	2.79 (1.96–3.97)
Adjusted prevalence ratio[b] (95% CI)	1.00 (ref)	1.36 (0.89–2.09)	2.61 (1.82–3.74)

Note: BMI = body mass index; CI = confidence interval; DIE = deep infiltrating endometriosis; Ref = Reference.

[a] Participants provided information about prior pregnancies, their intentions for each pregnancy (planned vs. unplanned pregnancy), time to pregnancy, and use of infertility treatment. Infertility was defined as ever reporting infertility via time trying (>12 months for women 35 years or younger and >6 months for women aged >35 years and older). Infertility treatment was defined as ever reporting infertility treatment.

[b] Adjusted for age at baseline (<30 years old; 30–39; and ≥40), BMI (<25.0 kg/m^2; 25.0–29.9 kg/m^2; and >30.0 kg/m^2), study site (UT/CA), and having ever smoked cigarettes (yes/no).

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1.36 times (95% CI, 0.89–2.09) greater aPR for using fertility treatment in multivariable-adjusted models and women with DIE and/or OE had 2.61 times (95% CI, 1.82–3.74) greater aPR for using fertility treatment in multivariable-adjusted models.

Figure 1 illustrates the proportion of women not achieving pregnancy over a year of trying by endometriosis typology when adjusting for age, study site, BMI, and cigarette smoking history. A higher proportion of women with no endometriosis or SE became pregnant in all 12 months of trying compared with women with DIE and/or OE. The Kolmogorov-type supremum test showed the adequacy of the proportional assumption. The mean times to pregnancy by disease severity in months for DIE and/or OE was 4.2 months (95% CI, 3.18–5.22); for SE was 3.55 months (95% CI, 2.90–4.20); and for women without endometriosis was 2.85 months (95% CI, 2.49–3.21). In the multivariable shared frailty model, taking into account the within-woman correlations between multiple pregnancies, we found an adjusted FOR (adjusted FOR, 0.83; 95% CI, 0.50–1.37) for SE and (adjusted FOR, 0.49; 95% CI, 0.25–0.97) for DIE and/or OE, compared with women without endometriosis (Table 3). This suggests that compared with women with no endometriosis, women with DIE and/or OE had 51% lower fecundability of achieving pregnancy. This group difference was also evident in Figure 1 showing that the survival curve for DIE and/or OE considerably deviated from the survival curves for SE and no endometriosis, which were mostly identical.

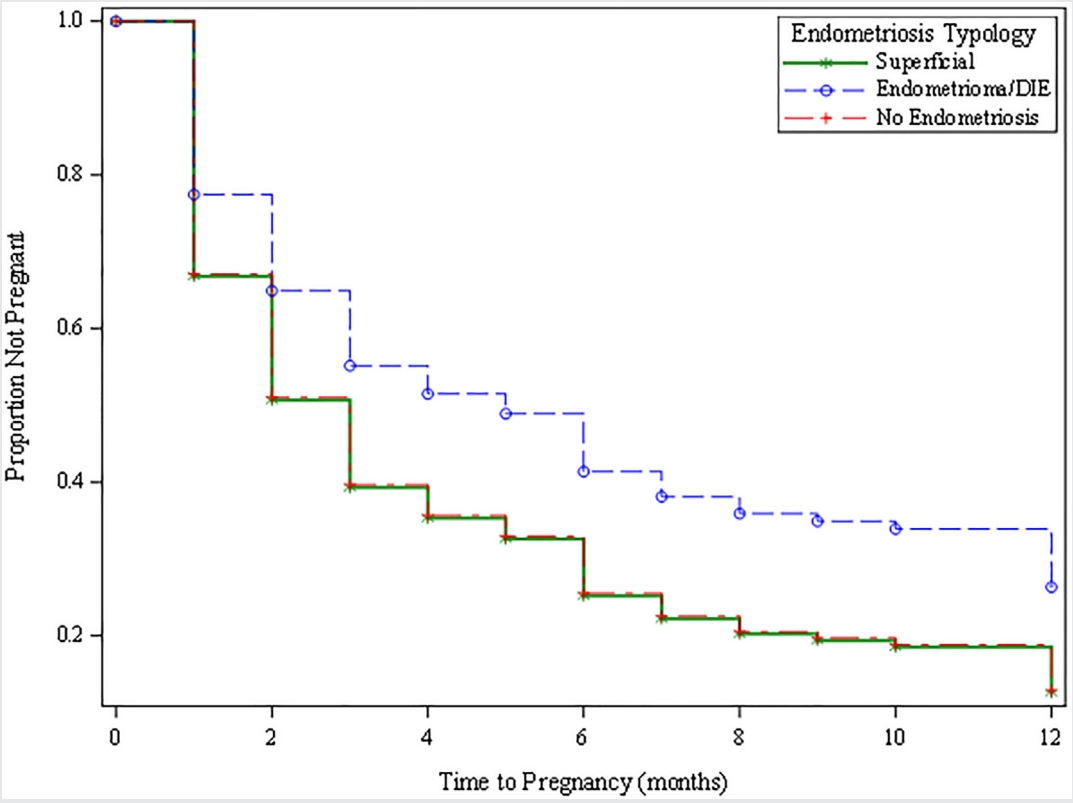
DISCUSSION

To our knowledge, this is the first study to assess reproductive history (intentions and duration of pregnancy attempts) before the diagnosis of incident endometriosis, including endometriosis typology among a diverse sample of women presenting for gynecologic surgery irrespective of indication. This study builds on our prior analysis, where we found that women with endometriosis had a longer TTP than unaffected women but no clear pattern by rASRM disease stage. In this study, we observed that DIE and/or OE were associated with the longest time of pregnancy and separately associated with seeking out fertility treatment as compared with women with SE. All associations of decreased fecundability with DIE and/or OE were held after adjustment for two of the biggest risk factors for women's infertility – age and BMI – suggesting that the role of endometriosis typology is consistent across women of various ages and adiposities. Future studies that can assess predictive value of surgical removal of the different lesion types on subsequent likelihood of postoperative conception in infertile women are essential for improved patient-provider decision-making on effective treatments.

A major strength of the ENDO study is its inclusivity of women, irrespective of surgical indication, from diverse urban clinical sites in Utah and California. The clinical sites chosen for the ENDO study allowed for assessment of infertility outside a fertility clinic setting. Additionally, we had high participant compliance in the study protocol, minimizing missing data bias. Finally, reliance on the clinical gold standard for endometriosis diagnosis and typology, as well as measured rather than self-reported BMI, minimizes misclassification bias. Nevertheless, our study is not without its limitations. Primary surgical indications were pelvic pain and pelvic mass with only 7% listed with infertility as the main reason for surgery, thus, our results may not be generalizable to a non-symptomatic population. Whether known infertility was higher is difficult to discern given that infertility as an indication for gynecologic laparoscopy/laparotomy may not be covered by many of the participant's insurance plans. We had limited power to be able to assess endometriosis subtypes, especially among pregnancy planners, leading to wide confidence intervals. Our study, although prospective in nature, captured reproductive history before endometriosis diagnosis, restricting our ability to make any causal inference. Additionally, prior research has shown that DIE's impact on female infertility is most severe in the presence of adenomyosis (21). Although adenomyosis was captured in our study via magnetic resonance imaging and histopathology reports, we only had nine women with adenomyosis (4 with and 5 without endometriosis) limiting our ability to assess its influence. Finally, our study was predominately non-Hispanic White (75%) limiting generalizability to other racial ethnic groups (14).

The association between endometriosis and the risk of subfertility is well established, with the largest prospective

FIGURE 1



Survival curves for TTP by endometriosis typology. Survival curves for TTP distributions for women with superficial endometriosis (green dashed line and "x"), with deep infiltrating endometriosis (DIE) and/or ovarian endometriomas (purple solid line and "O"), and without endometriosis (red dash line and "+"). Adjusted for age at enrollment, study site, BMI, and ever cigarette smoker. Differences in TTP by endometriosis typology. BMI = body mass index; TTP = time to pregnancy.

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study to date indicating an over 2-fold increased risk (9). A recent systematic review and meta-analysis of 29 studies reported among women undergoing assisted reproductive technology, those with endometriosis had 15% lower odds of achieving pregnancy (95% CI, 0.74–0.98) compared with those without endometriosis (22). This same systematic review reported a 1.30 higher pooled odds ratio (95% CI, 1.25–1.35) for miscarriage among women with endometriosis compared with their counterparts. Disappointingly, pooled estimates by endometriosis subtypes were very limited in this meta-analysis due to sparse research (n = 9 that evaluated OE vs. controls and only 1 evaluating DIE for achieving pregnancy), both reported as null (22).

Whether or not endometriosis causes infertility is still under debate, but multiple mechanisms have been proposed including anatomical distortion, whereby fibrosis and adhesion formation interfere with oocyte pick up and transportation; aberrant uterine contractility interfering with embryo implantation; and inflammatory processes leading to altered oocyte development, sperm motility, uterine receptivity,

TABLE 3

Fecundability odds ratio by endometriosis typology among women in the Endometriosis, Natural History, Diagnosis, and Outcomes study operative cohort who had ever planned and achieved a pregnancy (n = 198).

Fecundability odds ratio	No endometriosis (n = 127)	Superficial (n = 47)	Endometrioma/DIE (n = 24)
Unadjusted fecundability odds ratio (95% CI)	1.00 (ref)	0.85 (0.53–1.36)	0.55 (0.29–1.02)
Adjusted fecundability odds ratio[a] (95% CI)	1.00 (ref)	0.83 (0.50–1.37)	0.49 (0.25–0.97)

Note: CI = confidence interval; DIE = deep infiltrating endometriosis; Ref = Reference.

[a] Adjusted for age at baseline (<30 years old; 30–39; and ≥40.0), BMI (<25.0 kg/m^2; 25.0–29.9 kg/m^2; and >30.0 kg/m^2), study site (UT/CA), and having ever smoked cigarettes (yes/no).

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implantation, and successful maintenance of pregnancy (22, 23). Some inflammatory mediators in peritoneal fluid from women with endometriosis could also lead to sperm DNA damage (24).

The relationship between endometriosis typology and infertility is complex and not fully understood. It is hypothesized that SE, as well as OE and DIE, are responsible for the production of inflammatory mediators in the peritoneal fluid, interfering with ovulation, oocyte uptake, sperm function, gamete fertilization, and embryo migration (25). Ovarian endometriomas is also postulated to lead to follicular loss and intraovarian vascular injury due to the replacement of normal ovarian cortical tissue with fibrous tissue. Deep infiltrating endometriosis may additionally have both a direct and indirect link to infertility. In its direct link, DIE is closely tied to pelvic adhesion formation (26), which can disrupt pelvic anatomy, interfere with oocyte release, or impede oocyte uptake or transport by the fallopian tubes (27, 28). In its indirect link, DIE may be associated with women's infertility via reduced sexual activity among women with dyspareunia (29).

In our primary (exposure grouped into 3 categories) and secondary (exposure grouped into 6 categories) models, we showed that OE and DIE, but not SE alone, were associated with decreased fecundability, as compared with no endometriosis, with DIE having a greater impact on reduced fecundability compared with OE. However, as others have reported (25, 28), it may be the combination of types that produces the greatest adverse impact on female fertility. Finding DIE in isolation is rare, with one prior study showing that among 93 women with DIE, only 6% had isolated DIE, with 61% having concurrent SE, 50% having concurrent OE, and 74% with pelvic adhesions (26). Our prior research in the ENDO study showed that DIE was associated with a 3-fold increased prevalence of miscarriage (>8 weeks) but that neither SE nor OE showed such an association (30). Further research investigating endometriosis subtypes and subsequent female subfertility, that can also evaluate the influence of adenomyosis alone or in combination with endometriosis in larger prospective cohorts is needed before clear mechanisms can be determined. Additionally, given that pelvic adhesions have been directly linked with female infertility (31), further research should also evaluate the influence of pelvic adhesions on infertility risk. Although not the primary objective of this research, our descriptive analysis shows that women with ovary and/or tubal adhesions, regardless of endometriosis status, are approximately twice as likely to report infertility via time trying or infertility treatment compared with women with no ovary or tubal adhesions (Supplementary Table 2). A better understanding of causal mechanisms can inform targeted interventions.

CONCLUSION

In summary, although prior research has reported that rASRM staging criteria for endometriosis correlate poorly with female infertility, we found that endometriosis typology shows clear differences, with DIE and/or OE associated more strongly with infertility than SE. Further, DIE and/or OE, but not SE, were associated with reduced fecundability among women with planned pregnancies compared with women with no endometriosis. Endometriosis classification systems that can better predict the risk of reduced fecundability and potential infertility will be beneficial for both clinicians and their patients in shared decision-making for treatment options associated with endometriosis. Furthermore, biomarkers capable of differentiating DIE or OE from SE may be useful in assessing therapeutic interventions for the different typologies.

CRediT Authorship Contribution Statement

Karen C. Schliep: Writing – review & editing, Writing – original draft, Supervision, Funding acquisition, Formal analysis, Conceptualization. **Anna Z. Pollack:** Writing – review & editing, Writing – original draft, Supervision, Investigation, Conceptualization. **Leslie V. Farland:** Writing – review & editing, Writing – original draft, Supervision, Project administration, Investigation, Conceptualization. **May Shaaban:** Writing – review & editing, Writing – original draft, Formal analysis. **Bin Yan:** Writing – review & editing, Writing – original draft, Visualization, Investigation, Formal analysis. **Jing Wang:** Writing – review & editing, Writing – original draft, Visualization, Supervision, Methodology, Formal analysis, Data curation. **Lina Ghabayen:** Writing – review & editing, Writing – original draft, Visualization, Methodology, Investigation. **Rachael B. Hemmert:** Writing – review & editing, Validation, Supervision, Methodology. **Joseph B. Stanford:** Writing – review & editing, Supervision, Project administration, Methodology, Investigation, Funding acquisition, Data curation, Conceptualization. **C. Matthew Peterson:** Writing – review & editing, Supervision, Resources, Project administration, Methodology, Investigation, Funding acquisition, Data curation, Conceptualization.

Declaration of Interests

K.C.S. has nothing to disclose. A.Z.P. has nothing to disclose. L.V.F. has nothing to disclose. M.S. has nothing to disclose. B.Y. has nothing to disclose. J.W. has nothing to disclose. L.G. has nothing to disclose. R.B.H. has nothing to disclose. J.B.S. has nothing to disclose. C.M.P. has nothing to disclose.

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