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Incidence of endometriosis by study population and diagnostic method: the ENDO Study

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Abstract

Study Objective—To estimate the incidence of endometriosis in an operative cohort of women seeking clinical care and in a matched population cohort to delineate more fully the scope and magnitude of endometriosis in the context of and beyond clinical care.

Design—Matched exposure cohort design.

Setting—Surgical centers in the Salt Lake City, Utah and San Francisco, California areas.

Patients—The operative cohort comprised 495 women undergoing laparoscopy/laparotomy between 2007–2009, while the population cohort comprised 131 women from the surgical centers' catchment areas.

Interventions—None

Main Outcome Measure(s)—Incidence of endometriosis by diagnostic method in the operative cohort and by pelvic magnetic resonance imaged (MRI) disease in the population cohort.

Results—Endometriosis incidence in the operative cohort ranged by two orders of magnitude by diagnostic method: 0.7% for only histology, 7% for only MRI and 41% for visualized disease. Endometriosis staging was skewed toward minimal (58%) and mild disease (15%). The incidence of MRI-diagnosed endometriosis was 11% in the population cohort.

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Conclusions—Endometriosis incidence is dependent upon the diagnostic method and choice of sampling framework. Conservatively, 11% of women have undiagnosed endometriosis at the population level with implications for the design and interpretation of etiologic research.

Keywords

Endometriosis; epidemiology; histology; incidence; laparoscopy; magnetic resonance imaging

Introduction

Endometriosis is frequently described as a clinical enigma reflecting the absence of an established etiology and a multitude of methodologic nuances that challenge understanding at the clinical and population levels. Despite various purported etiologies ranging from congenitally acquired or genetic predisposition to alterations in the endocrine or immune systems (1–4), its etiology remains speculative including the role of endocrine disrupting chemicals (EDCs) (5,6).

Several substantive and methodologic challenges underlie endometriosis research including clinical expertise and diagnostic proficiency, reliance on clinical samples of symptomatic or infertile women, and selection of comparison groups that largely comprise women with other gynecologic conditions (7,8). These limitations may result in misclassification bias on disease status, introduce selection bias, or heighten type II errors, respectively. Despite its importance for research design and clinical interpretation, limited attention has focused on a possible shared etiology for endometriosis with other gynecologic disorders (9).

Our incomplete understanding of endometriosis may also reflect a preponderance of research that has relied upon sampling frameworks comprising symptomatic or infertile women seeking clinical care who undergo laparoscopy, given that surgical visualization is considered the diagnostic gold standard (10,11). However, recent evidence suggests that such women may reflect the “tip of the endometriosis iceberg”. For example, 30% – 50% of women undergoing surgical procedures that fortuitously allow visualization are diagnosed with *incidental* endometriosis - underscoring misclassification of disease status (12–15). Among asymptomatic fertile women undergoing tubal sterilization procedures, incidence ranges from 4% – 43% (16,17). Another pathway for disease misclassification arises from women whose lesions do not progress or spontaneously regress (18,19). This latter group of women may be etiologically informative if some disease truly spontaneously regresses underscoring the importance of inclusive sampling frameworks to minimize exclusion of milder disease and to facilitate conducting sensitivity analyses. A final subgroup of women below the tip of the iceberg include (a)symptomatic women who either do not seek clinical care or who opt out of surgical intervention. The lack of valid and reliable noninvasive biomarkers for endometriosis makes it hard to estimate this group (20). We designed the ENDO (Endometriosis, Natural History, Diagnosis, and Outcomes) Study with two aims: 1) to estimate the scope and magnitude of endometriosis at both the clinical and population level by diagnostic method and choice of comparison group; and 2) to assess the relation of EDCs and risk of gynecologic pathology including endometriosis. This paper focuses on our first aim to estimate incidence above and below the tip of the iceberg so that a more complete understanding of the role of EDCs and endometriosis (second aim) can be achieved.

Materials and Methods

Study Design and Populations

The ENDO Study utilized a matched exposure cohort design with surgery considered the exposure. As such, the exposure (operative) cohort comprises currently menstruating women aged 18–44 years scheduled to undergo a diagnostic and/or therapeutic laparoscopy or laparotomy irrespective of clinical indication at one of 5 participating hospital surgical centers located in Utah between 2007–2009. Women with a history of surgically confirmed endometriosis (prevalent cases) were excluded. Given our interest in endocrine disrupting chemicals, three additional eligibility criteria were required: 1) no breastfeeding for ≥6 months; 2) no injectable hormonal treatment within the past two years; and 3) no cancer history save for non-melanoma skin cancer. The unexposed (population) cohort was matched to the exposed cohort on age and residence within the geographic catchment areas for the participating surgical centers, i.e., ≈50-mile radius that captured approximately 90% of pelvic surgeries based upon residential zipcodes at the time of surgery. The unexposed cohort comprised women who were currently menstruating to ensure they were at risk for developing endometriosis and in receiving a possible diagnosis, given their proximity to the surgical center. Women in both cohorts were restricted to those who could communicate in English or Spanish and without a prior history of laparoscopic confirmed endometriosis to ensure identification of incident disease. *A priori* power calculations were 450 and 95 women in the operative and population cohorts, respectively, to permit detection of significant differences in serum EDC concentrations by endometriosis status. We established a second research site in California with 9 participating clinical centers to recruit 60 operative and 30 population women using the same methodology, but with an added proteomics component. In sum, the matched exposure cohort design utilizes two sampling frameworks: 1) surgical schedules for the exposure cohort and 2) available site-specific population registries (InfoUSA® white pages telephone directory in California and the Utah Population Database in Utah) for the unexposed cohort here after referred to as the operative and population cohorts, respectively.

Data Collection

All women were sent a study packet introducing the study. Research assistants subsequently screened and recruited women by telephone or in-person. Standardized data collection encompassed: a baseline personal interview including pelvic pain and anthropometric assessment; two self-administered screening instruments; operative reports; and collection of biospecimens. The baseline interview with visual prompts was conducted using a computer assisted personal interview administered on laptops that allowed women to directly input sensitive information while ensuring internal consistency of reporting by programmed data quality checks. Women in the operative cohort completed the interview prior to surgery, and women in the population cohort at their earliest convenience. For the anthropometric assessment, height was measured with a portable stadiometer and weight with electronic scales (21). Skinfold and circumference measurements were taken twice; a third measurement was taken if any pairwise measures varied by more than 0.1–0.5 cm for various measurements. The 7-item BDI® FastScreen for Medical Patients was used to screen for depression while the 7-item short version of the International Physical Activity Questionnaires was used to quantify physical activity; both instruments are reported valid and reliable (22,23).

Consistent with the observational design, surgeons were not asked to change their practice in any way, but were encouraged to obtain specimens for histology. Surgeons completed a standardized operative report immediately following surgery to capture gynecologic and pelvic pathology and endometriosis staging using the Revised American Society for

Reproductive Medicine's classification (rASRM) (24). Surgeons were first asked staging using a categorical variable ranging from 1 (minimal) to 4 (severe), and then asked to complete the rASRM form. An algorithm automatically calculated the rASRM weighted point score for comparison with the categorical variable to assess staging reliability.

Blood (≈24 ml) and urine (≈120 ml) specimens were obtained for all women while additional biospecimens were collected from the operative cohort depending upon availability and patient safety as determined by the operating surgeon: endometrial biopsies; peritoneal fluid (≈2–20 ml); omental fat (≈1–5 grams); and endometrial implants representing disease. All biospecimen collection kits were *a priori* determined to be free of the chemicals of interest to the study.

Magnetic Resonance Imaging

An *a priori* simple random sample comprising 96 women (38 with and 58 without preoperative endometriosis) from the operative cohort was selected to also undergo pelvic magnetic resonance imaging (MRI) aimed at identifying endometriosis and other pelvic pathology. In the population cohort, participation required a willingness to undergo a pelvic MRI to identify endometriosis and assess visceral fat distribution. One radiologist conducted and read all MRIs, using either a Siemens Avanto or Espree 1.5 Tesla scanner and a U.S. FDA approved protocol for pelvic imaging, and completed standardized data collection instruments. All images were double read, first by the initial and, subsequently, by a second radiologist.

Human Subjects and Monitoring

Study participants were remunerated for their time and travel. Full human subjects' approval (Committee of Human Research, University of California, San Francisco; Institutional Review Board, University of Utah; Intermountain Healthcare Office of Research, Utah; and the National Institutes of Health Institutional Review Board Reliance) was obtained for the conduct of this study; all women were given informed consents prior to any data collection. Data were de-identified and encrypted prior to being uploaded to the web-based data system. This system was designed to monitor health alerts including any pathology noted on the MRI that required medical follow up, a positive screen for severe depression or suicidal ideation, and chemical exposures with recognized health alerts, i.e., blood lead (≥25 μg/dL), mercury (≥200 μg/L) and/or cadmium (≥10 μg/L) concentrations.

Operational Definitions

Endometriosis diagnoses were derived from one or a combination of three diagnostic approaches. Visualized endometriosis comprised disease observed by operating surgeons, whereas histologically confirmed endometriosis included: endometrial glands and/or stroma, and/or hemosiderin-laden macrophages. MRI visualized endometriosis comprised primarily ovarian endometrioma, but included some other manifestations of disease as well. rASRM staging was categorized as: stage I (scores 1–5), stage II (scores 6–15), stage III (scores 16–40), and stage IV (scores > 40) (24).

Statistical Analysis

To assess the feasibility and utility of using a population based sampling framework, we enumerated the denominators for both cohorts in each site and accounted for all women irrespective of whether they were retained in the numerator. For each cohort, we estimated the incidence of endometriosis as the number of women with newly diagnosed endometriosis identified by a particular diagnostic method divided by the number of eligible women for that particular diagnostic method multiplied by 100. The reliability of

endometriosis staging was estimated by assessing the concordance of the surgeon's categorical (stages 1–4) answer with the categorical algorithm computed score.

Results

Use of an operative sampling framework was successful for establishing the operative cohort, although a large number of women were required in this sampling framework (N=2,962) to achieve enrollment goals (n=495) and to overcome two anticipated methodologic challenges (Table 1). The first challenge was the insufficient time before surgery to screen approximately 31% (n=904) of women. The second challenge was that 69% (n=1,427) of screened women were ineligible despite minimal study eligibility criteria. However, enrollment rates were high (78%) among eligible women. In the population cohort, approximately 9% (n=217) of targeted households were screened resulting in 75% (n=162) of women eligible for participation of which 81% enrolled in the study. The high percentage of eligible and participating women resulted in a large percentage of households categorized as pending further contact. Compliance with the study protocol was excellent with approximately 95% and 98% of women in the operative and population cohorts, respectively, completing the protocol. Blood and urine specimens were collected for all women along with a varying (27% – 89%) percentage of operative biospecimens. Approximately 7% of women in the operative cohort had health alerts compared to 17% in the population cohort. Among women randomized to MRIs, approximately 11% and 14% of women in operative and population cohorts, respectively, had pathology identified requiring clinical follow-up. Approximately 6% and 4% of women in these two cohorts, respectively, screened positive for severe depression or suicidal ideation requiring clinical follow-up. Lastly, despite differences in the sampling frameworks, the two cohorts were relatively similar with the exception of a significantly higher percentage of older and married women in the operative compared to the population cohort; mean ages were comparable (Table 2). Leading reasons for surgery were pelvic pain (42%), pelvic mass (15%) and menstrual irregularities (12%). No significant difference was observed between site and preoperative diagnosis of endometriosis (data not shown).

The incidence of surgically visualized endometriosis for the operative cohort was 41% and varied by an order of two depending upon the diagnostic method (0.7% for histology only, 75 for MRI only and 41% for visualized disease) as presented in Table 3. Among the subgroup of women having all three diagnostic methods available, 34% had endometriosis diagnosed by visualization, histology and MRI. In the population cohort, the overall incidence of MRI visualized endometriosis was 11%.

The majority of women with endometriosis were reported to have minimal disease (stage 1). Table 4 presents staging as measured by physician response to a categorical (stage 1–4) variable and by the automated point based algorithm. The concordance of staging for the overall operative cohort is: 98% for stage 0 or no endometriosis; 70% for stage 1; 37% for stage 2; 61% for stage 3; and 43% for stage 4. Five women with 0 scores in the algorithm staging were recorded as stage 1 by surgeons' ratings. The discordant scores irrespective of stage reflected both under- and over- staging of disease.

Discussion

To our knowledge, this is the first study to employ a matched exposure cohort design to estimate the incidence of endometriosis in two well-defined populations to shed insight into endometriosis that may reside below the tip of the iceberg that we define as women who seek clinical care. This is an important first step when attempting to understand endometriosis at the population level. The similarity of women across study cohorts may

simply reflect the characteristics of women who participate in gynecologic research irrespective of sampling framework. If corroborated, this similarity may enhance the external validity of clinically based research.

Despite an inclusive operative cohort, only 41% of women had visualized disease with staging skewed to minimal or mild (73%) disease, though incidence varied (0.7%–47%) by diagnostic method. Approximately 34% of eligible women had endometriosis diagnosed by all three methods. All histologic confirmed disease was surgically visualized except for one woman. Since surgeons were not required to remove biopsies for all women, the high concordance for histologic-visual confirmation may reflect selective clinical practices. A more complete interpretation will require randomized trials or the requirement that all diagnostic approaches are utilized for all women. The concordance for physician and algorithm staging was 60% for all stages with bi-directional differences noted suggestive of both under- and over-staging of disease. This observation may have implications when assessing potential etiologic exposures for dose dependency relations. However, concordance increased (84%) when dichotomizing staging as minimal/mild verse moderate/severe.

The 11% incident rate in the population cohort is consistent with more endometriosis below the tip of the iceberg or clinical threshold, as does the relatively sizeable percentage of women with MRI visualized pelvic pathology requiring clinical follow up in both the operative (11%) and population (14%) cohorts. The similar percentages argue against the population cohort comprising women with health concerns that may have prompted their participation in the study. Another key finding is the smaller but still notable percentage (≈5%) of women in each cohort who screened positive for severe depression or suicidal ideation requiring clinical follow-up that suggests considerable co-morbidity for women in the operative cohort and untreated disease in the population cohort. This figure is comparable to the 8% of U.S. adults reported to screen positive for depression (25).

Our findings have important study design considerations for all endometriosis investigators including the potential for limited representativeness of study findings for targeted populations when based on a case series design or convenience based sampling, particularly when attempting to study endometriosis beyond the tip of the iceberg. Our findings also underscore the importance of a large operative sampling framework for ensuring a sufficient number of women with incident endometriosis and, particularly, if heterogeneity in staging is desired. As important, our findings demonstrate that population matched cohorts can be obtained relatively easily even with requiring an MRI. The high degree of compliance with this rather intensive study protocol on the part of women and clinicians supports ambitious and trans-disciplinary research approaches to delineating the etiology of endometriosis.

Two recent papers have estimated the annual incidence of pelvic endometriosis (0.25%–0.1%) in women undergoing surgery in two geographically defined populations (26,27). In the former study, approximately 4% of asymptomatic women aged 25–34 years and 33% of women aged ≥45 years were *incidentally* diagnosed intra-operatively. The comparable incidence estimates for operative cohorts contrast sharply with the wide ranges reported for prevalent disease, which recently was attributed to tremendous heterogeneities in prevalence estimates (28).

The incidence of endometriosis among women at risk for the disease but who do not seek care remains a critical data gap. Our finding that at least 11% of women in the population cohort had endometriosis is an attempt to estimate this number, though it is likely an underestimate in that the sensitivity and specificity of MRI for detecting endometriosis in clinical samples varies by the presence of classical implants or atypical lesions and severity.

Unfortunately, we are unable to assess the potential for low specificity in the population cohort, given the absence of staging data. Stratton and colleagues (29) reported MRI sensitivity and specificity relative to histologically confirmed disease to be 69% and 75%, respectively, though higher for moderate and severe disease. Still other authors have reported good (95%) agreement between MRI and AFS staging (30).

In sum, successful completion of The ENDO Study supports continued research efforts aimed at elucidating the etiology of endometriosis from both clinical and population perspectives. A more complete capture of endometriosis and understanding of its possible misclassification may help address the many equivocal findings published to date and to demystify its natural history.

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Table 1

Comparison of sampling frameworks by site and cohort, ENDO Study, 2007–2009 (n=626).

Sampling Framework	California – Operative (n=63) # (%)	Utah – Operative (n=432) # (%)	California – Population (n=36) # (%)	Utah – Population (n=95) # (%)
# Women scheduled for surgery reviewed	614	2,348	--	--
# Surgical women not screened	205 (33) (insufficient time; 21% unable to contact 15%)	699 (30) (unable to contact; 24% insufficient time 22%)	--	--
# Surgical women screened	409 (67)	1,649 (70)	--	--
# Households contacted	--	--	750	1,686
# Households not screened (leading reason)	--	--	692 (92) (reached enrollment; 82%)	1,528 (91) (reached enrollment; 81%)
# Women screened	409 (67)	1,649 (70)	58 (7)	159 (9)
# Not eligible	324 (79) (age; 72%)	1,103 (67) (age; 67%)	10 (17) (age; 30%)	45 (28) (prior Hx; 27%)
# Eligible	85 (21)	546 (33)	48 (83)	114 (72)
# Refusals	22 (26) (too busy; 45%)	114 (21) (other reasons; 19%)	12 (25) (other; 42%)	19 (17) (too busy; 63%)
# Enrolled	63 (74)	432 (79)	36 (75)	95 (83)
# Withdrawals	2 (3) (OR canceled 50%;)	20 (5) (OR canceled; 95%)	1 (3)	--
# Biospecimens Collected				
Blood	63 (100)	432 (100)	36 (100)	95 (100)
Urine	63 (100)	431 (100)	36 (100)	95 (100)
Fat	34 (54)	311 (72)	--	--
Peritoneal fluid	39 (62)	341 (79)	--	--
Endometrial implant	13 (21)	126 (29)	--	--
Endometrial biopsy	47 (75)	387 (90)	--	--
Health alerts:				
No	59 (94)	402 (93)	31 (86)	76 (80)
Yes; specify (not mutually exclusive):	4 (6)	30 (7)	5 (14)	19 (20)
Blood metal concentrations	--	--	--	--
MRI based disease; specify Endometriosis	1 (10)	7 (8)	3 (9)	11 (12)
Ovarian cysts	--	3 (3)	1 (3)	5 (5)
Screen positive severe depression	1 (2)	3 (<0)	--	--
Screen positive suicidal ideation	4 (6)	20 (5)	1 (3)	4 (4)

NOTE: Women were recruited between July 2007 and June 2009. One included woman from the Utah operative cohort provided all data and biospecimens, but did not complete the baseline questionnaire. Key reasons why women were ineligible, not enrolled or withdrew from the study are listed in parentheses below the relevant cell count and percentage.

Table 2

Comparison of study participants by cohort, ENDO Study (n=626).

Characteristic	Operative Cohort (n=495) n (%)	Population Cohort (n=131) n (%)
Age (in years):		
<30	169 (34)	52 (40)
≥30	325 (66)	79 (60)[a]
Mean (±SD)	33 (±7)	32 (±8)
Race/ethnicity:		
Hispanic	68 (14)	14 (11)
Nonhispanic white	369 (75)	106 (81)
Hispanic black	8 (2)	2 (2)
Asian/Islander/Native	29 (6)	5 (4)
Other/multi-racial	21 (4)	4 (3)
Marital status:		
Married/living as married	371 (76)	78 (60)
Other	119 (24)	53 (41)[b]
Household income:[c]		
Below poverty line	55 (11)	16 (12)
Within 180% of poverty	58 (12)	17 (13)
Above poverty	374 (77)	97 (75)
Gravidity (# pregnancies):		
Nulligravida	162 (33)	52 (40)
Gravid	331 (67)	79 (60)
Mean (±SD)	2 (±2)	2 (±2)
Parity (# live births):		
Nulliparous	211 (43)	64 (49)
Parous	284 (57)	67 (51)
Mean (±SD)	1 (±2)	1 (±2)
Primary reason for surgery:		
Pelvic pain	206 (42)	--
Pelvic mass	74 (15)	--
Menstrual irregularities	60 (12)	--
Fibroids	49 (10)	--
Tubal ligation	48 (10)	--
Infertility	35 (7)	--

[a] p<0.05;

[b] p= 0.001. SD, denotes standard deviation

[c] Based upon the 2007 HHS Poverty Guidelines accounting for the numbers of persons in the household for the 48 contiguous states and District of Columbia.

[--], population cohort did not undergo surgery.

Table 3

Incidence of endometriosis by diagnostic method, cohort and site, ENDO Study, 2007–2009 (n=473).

Cohort and Diagnostic Method	California Incidence Rate (%)	Utah Incidence Rate (%)	Total Incidence Rate (%)
Operative cohort			
Any surgical visualization	17/61=28	175/412=42	192/473=41
Histologically confirmed visualized endometriosis	6/26=23	61/117=52	67/143=47
Histologically confirmed only – no surgical visualization	0/26=0	1/117=0.9	1/143=0.7
Magnetic resonance imaging (MRI) only	1/10=10	6/86=7	7/96=7
Any surgical visualization + MRI diagnosis	1/10=10	18/90=20	19/100=19
Any surgical visualization + MRI + histologically confirmed diagnosis	0/2=0	11/30=37	11/32=34
Population cohort			
Magnetic resonance imaging only	3/33=9	11/94=12	14/127=11

NOTE: Denominators for estimating incidence vary depending upon the number of women undergoing surgery and/or specimens sent to histopathology and by MRI randomization status. Excludes 22 women (2 in California and 20 in Utah) whose surgeries were canceled.

Table 4

Distribution of endometriosis severity by method of staging and site, ENDO Study, 2007–2009 (n=473).

Revised American Society of Reproductive Medicine Staging	California n (%)	Utah n (%)	Total n (%)
Operative Report			
No endometriosis	44 (72)	239 (58)	283 (60)
Yes endometriosis; staging	17 (28)	173 (42)	190 (40)
1	8 (47)	87 (50)	95 (50)
2	4 (24)	35 (20)	39 (21)
3	5 (29)	30 (17)	35 (18)
4	--	21 (12)	21 (11)
Subtotal	17 (100)	173 (100)	190 (100)
Algorithm			
No endometriosis	44 (72)	244 (59)	288 (61)
Yes endometriosis; staging	17 (28)	168 (41)	185 (39)
1	9 (53)	98 (58)	107 (58)
2	1 (6)	26 (15)	27 (15)
3	6 (35)	17 (10)	23 (12)
4	1 (6)	27 (16)	28 (15)
Subtotal	17 (100)	168 (100)	185 (100)

NOTE: Excludes 22 women (2 in California and 20 in Utah) whose surgeries were canceled. Staging based upon the Revised American Society for Reproductive Medicine (rASRM) classification for endometriosis (24).