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ASSISTED REPRODUCTION TECHNOLOGIES

A higher prevalence of endometriosis among Asian women does not contribute to poorer IVF outcomes

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Abstract
Purpose The purpose of the study was to determine whether diagnosis of endometriosis or endometriosis with endometrioma influences in vitro fertilization (IVF) outcomes in an ethnically diverse population.
Methods Women undergoing a first IVF cycle (n = 717) between January 1, 2008 and December 31, 2009, at a university-affiliated infertility clinic, were retrospectively assessed for an endometriosis diagnosis. Differences in prevalence of endometriosis by ethnicity were determined, as well as differences in IVF success by ethnicity, with a focus on country of origin for Asian women. A multivariate model was generated to assess the relative contributions of country of origin and endometriosis to chance of clinical pregnancy with IVF.
Results Endometriosis was diagnosed in 9.5% of participants; 3.5% also received a diagnosis of endometrioma. Endometriosis prevalence in Asian women was significantly greater than in Caucasians (15.7 vs. 5.8%, $p < 0.01$). Women of Filipino ($p < 0.01$), Indian ($p < 0.01$), Japanese ($p < 0.01$), and Korean ($p < 0.05$) origin specifically were more likely to have endometriosis than Caucasian women, although there was no difference in endometrioma presence by race/ethnicity. Oocyte quantity, embryo quality, and fertilization rates did not relate to endometriosis. Clinical pregnancy rates were significantly lower for Asian women, specifically in Indian ($p < 0.05$), Japanese ($p < 0.05$), and Korean ($p < 0.05$) women, compared to Caucasian women, even after controlling for endometriosis status.
Conclusions The prevalence of endometriosis appears to be higher in Filipino, Indian, Japanese, and Korean women presenting for IVF treatment than for Caucasian women; however, the discrepancy in IVF outcomes was conditionally independent of the presence of endometriosis. Future research should focus on improving pregnancy outcomes for Asian populations whether or not they are affected by endometriosis, specifically in the form of longitudinal studies where exposures can be captured prior to endometriosis diagnoses and infertility treatment.

Keywords Endometriosis · Endometrioma · In vitro fertilization · Race · Ethnicity

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Introduction

Endometriosis is a common, benign gynecologic condition characterized by the presence of endometrial-like lesions in areas outside of the uterus. It affects approximately 10% of the general population of reproductive-age women and about

20% of infertile women [1]. However, most endometriosis studies are based on highly selected groups of patients with surgically confirmed diagnoses, as reviewed by Eskenazi et al. [1]. Endometriosis is also the third leading cause of gynecologic hospitalizations in the USA after pelvic inflammatory disease and benign ovarian cysts [2]. Although it is a significant cause of pelvic pain and infertility in premenopausal women, the etiology and pathogenesis for this condition remain enigmatic. Several studies have demonstrated decreased in vitro fertilization (IVF) success rates in women with endometriosis [3, 4], although others suggest this is true only of the more severe stages of disease [5].

In more extensive disease, endometriosis can directly involve ovarian tissue, leading to formation of one or more endometriomas, or "chocolate cysts" inside the ovaries [6]. An ovarian endometrioma greater than 1 cm meets criteria for, at a minimum, moderate severity endometriosis (Stage III) [7]. However, unlike pelvic and most other non-ovarian endometriosis lesions, endometriomas can be detected on transvaginal ultrasounds and so confirmatory diagnosis is feasible without the use of the invasive gold standard laparoscopy [8]. In infertility patients, the question of whether or not the removal of endometriomas and endometriosis implants can lead to improved fertility outcomes is also controversial [9].

Asian women appear to have a higher endometriosis prevalence than Caucasians and African Americans, although medical utilization may account in part for the difference [10, 11]. Two studies reported that Asians compared to non-Asians had a higher prevalence of endometriosis [12, 13], although another study of laparoscopically confirmed cases did not [14], and few studies to date have examined the prevalence of endometriosis among the various Asian ethnicities [11–13]. One study reported that Japanese women had the highest hospital admittance rate for endometriosis compared to non-Japanese Asian and non-Asian races, and that Asians in general had a higher endometriosis admittance rate compared to non-Asians [11]. Furthermore, other studies indicated that outcomes for IVF are poorer among Asian patients compared to Caucasians [15–17]. As of yet, only a handful of studies have focused on ethnic differences in the prevalence of endometriosis among Asian women, and none have studied whether differences in IVF outcomes among Asian women of different ethnicities can be attributed to a difference in the prevalence of endometriosis.

Given the pending data gaps, we conducted a retrospective cohort study using data obtained from electronic medical records of patients undergoing IVF at one infertility clinic in northern California. The primary objectives of this study were to characterize the prevalence of endometriosis among Asian ethnicities and among non-Asians and to assess ethnicity and race-based disparities in IVF outcomes among endometriosis patients. As a secondary objective, we explored the impact of endometriomas on IVF outcomes.

Materials and methods

Data abstraction

We conducted a retrospective chart review of all patients (n = 1011) at the University of California, San Francisco (UCSF) Center for Reproductive Health undergoing IVF cycles between January 1, 2008 and December 31, 2009. The cohort was further restricted to fresh embryo transfers (n = 976), the first cycle for each patient to prevent within-patient confounding (n = 745), and to patients who were not missing race or endometriosis status (n = 717) (Fig. 1). Prior approval of the study protocol was obtained from the UCSF Committee for Human Research. Data were abstracted from the electronic medical record (EMR). Demographics including race/ethnicity, age, and country of birth, and clinical characteristics including past and current medical history, body mass index (BMI; kg/m^2), tobacco use (ever/never), number of pregnancies with and without a live birth ("pregnancy history"), infertility history, and gynecological surgical history were recorded at the time of the initial clinical infertility consultation. IVF cycle data including the presence and description of cysts found on ultrasound, the number of oocytes retrieved and fertilized, embryo quality and whether an embryo was transferred, serum human chorionic gonadotropin

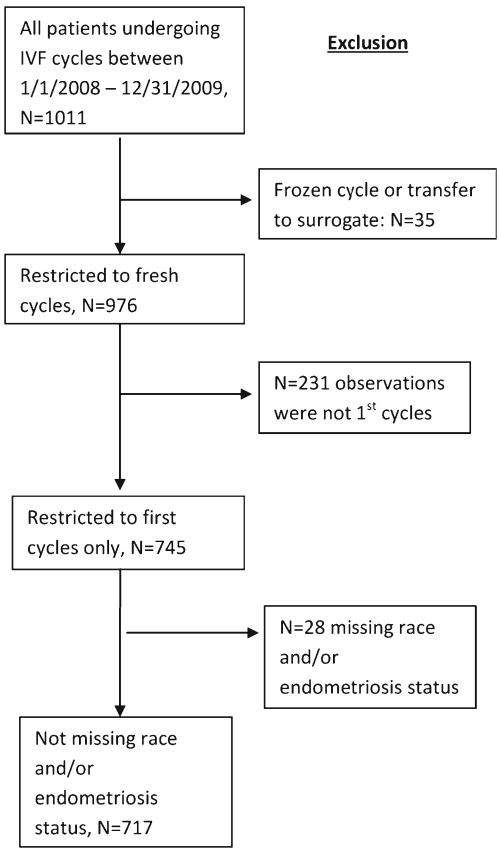

Fig. 1 Sample selection. *IVF* in vitro fertilization

test results 2 weeks post-transfer indicative of successful implantation, and ultrasound results indicative of clinical pregnancy were also abstracted from the EMR.

Endometriosis case ascertainment and outcome definition

Patients with EMR documentation of endometriosis, endometrioma, cyst on ultrasound with characteristics consistent with endometrioma, laparoscopic confirmation for endometriosis, or oophorectomy for endometriomas were carefully recorded and considered as probable endometriosis patients. A patient's electronic charts containing the key words "endometrioma," "endometrial cysts in the ovaries," or "chocolate-like cysts in the ovaries" were considered as probable endometrioma cases. Each patient's chart was reviewed by the first author to eliminate false negatives (AY) and the diagnosis was confirmed by the second author (EBJ), a board-certified obstetrician and gynecologist, reproductive endocrinologist, and infertility specialist. We included both laparoscopically confirmed endometriosis cases and those without laparoscopic confirmation, to maximize the statistical power available to detect modest effects. The primary study outcome was clinical pregnancy, defined as the presence of an intrauterine gestational sac on ultrasound at 6–8 weeks after embryo transfer. The number of cancelled cycles, mean number of oocytes retrieved per woman, the percent of oocytes fertilized per woman, embryo quality assessed as embryo transfer, and implantation were considered to be secondary study outcomes.

Statistical analysis

Normal distributions for continuous variables were assessed using the Kolmogorov-Smirnov test. For continuous variables, including age and BMI, we assessed differences between women with and without endometriosis or endometrioma using Student's t test or the Mann-Whitney U test as appropriate. Chi-square and Fisher's exact tests were used to assess for differences in endometriosis/endometrioma prevalence by race and ethnicity, other categorical covariates, and for evaluating the unadjusted relationship with clinical pregnancy and secondary study outcomes. Multivariate logistic regression was performed to assess the joint roles of race and ethnicity and endometriosis in predicting clinical pregnancy, adjusting for potential confounding by age at IVF cycle start, pregnancy history, BMI, and tobacco use. To assess the impact of endometriosis on the effects of race and ethnicity on IVF outcomes, we further performed multivariate logistic regression analyses stratified by endometriosis status. We also repeated models in a sensitivity analysis limited to women with laparoscopic confirmed diagnoses. Data analyses were performed using SAS v.9.2 (SAS Institute, Inc. Cary, NC, USA) and statistical significance was defined as $p < 0.05$ for a two-tailed test.

Results

The study population is described in Table 1. The prevalence of endometriosis was 9.5% (n = 68); 82.4% (n = 56) were laparoscopically confirmed. Women with endometriosis were younger ($p < 0.01$), more likely to be of an Asian descent ($p < 0.01$), specifically Indian ($p < 0.01$) and Japanese ($p < 0.01$), more likely to have a cyst on their transvaginal ultrasound ($p < 0.01$), and more likely to have a family history of endometriosis ($p < 0.0001$) and infertility ($p = 0.02$). Among n = 68 diagnosed with endometriosis, 25 (36.76%) patients had a cyst that appeared to be an endometrioma on transvaginal ultrasound at the start of the IVF cycle. Fifty-six (82.35%) endometriosis cases were confirmed by laparoscopy. There were no statistically significant differences in the number of cycles cancelled, the mean number of oocytes retrieved per woman, the mean proportion of fertilized oocytes per woman, the number of embryos transferred, the number of implantations, and the number of clinical pregnancies between those with endometriosis vs. those without, respectively (Table 2). There were no statistically significant differences in IVF outcomes or racial/ethnic prevalence for those with endometriomas compared to those without endometriomas (data not shown).

Univariate baseline and IVF outcome analyses were also performed comparing Asians to Caucasians (data not shown). Asian women were younger ($p = 0.02$), with a lower BMI ($p = 0.01$), and less likely to have had a previous pregnancy leading to a live birth compared to their Caucasian counterparts ($p < 0.01$). Asian women were also more likely than Caucasians to have had any endometriosis diagnosis ($p < 0.01$) and to have laparoscopically confirmed endometriosis ($p < 0.01$). With regard to IVF outcomes, there were no differences in whether or not an embryo transfer was done and the average number of oocytes retrieved or fertilized; however, Asians (41.5%) were significantly less likely to have a clinical pregnancy ($p < 0.01$) than Caucasians (54.4%).

As depicted in Table 3, in a multivariate logistic regression model adjusting for age, BMI, pregnancy history, and tobacco use, Asian women had 2.96 times the odds of an endometriosis diagnosis compared to Caucasians (95% CI 1.65, 5.31; $p = 0.0003$). Black, Hispanic, and other races/ethnicities did not differ significantly compared to Caucasians. When individual Asian nationalities were assessed separately (Table 4), Filipino (OR = 4.51; 95% CI 1.52, 13.36; $p = 0.01$), Indian (OR = 3.84; 95% CI 1.56, 9.46; $p = 0.003$), Japanese (OR = 5.52; 95% CI 2.05, 14.82; $p = 0.001$), and Korean (OR = 4.67; 95% CI 1.38, 15.76; $p = 0.01$) women had statistically significantly increased odds of having endometriosis relative to Caucasian women. Results were similar when adjusting for age only. As shown by Tables 3 and 4, these race/ethnicity disparities persisted in a sensitivity analysis using a case definition of laparoscopically confirmed endometriosis (n = 56).

Table 1 Baseline characteristics of in vitro fertilization patients

	All women, *n* (%)	Endometriosis[a], *n* (%)	No endometriosis, *n* (%)
Total patients	717	68 (9.48)	649 (90.52)
Race (% of total)			
Caucasian (%)‡	394 (54.95)	23 (33.82)	371 (57.16)
Asian (%)‡	235 (32.78)	37 (54.41)	198 (30.51)
Chinese (%)	99 (13.81)	10 (14.71)	89 (13.71)
Indian (%)††	49 (6.83)	10 (14.71)	39 (6.01)
Japanese (%)††	28 (3.91)	7 (10.29)	21 (3.24)
Filipino (%)	25 (3.49)	5 (7.35)	20 (3.08)
Korean (%)	19 (2.65)	4 (5.88)	15 (2.31)
Other Asians (%)	15 (2.09)	1 (1.47)	14 (2.16)
Hispanic (%)	38 (5.30)	4 (5.88)	34 (5.24)
Other races	31 (4.32)	3 (4.41)	28 (4.31)
African American/African (%)	19 (2.65)	1 (1.47)	18 (2.77)
Mean age ± SD (years)††	36.87 ± 4.09	35.79 ± 3.70	36.98 ± 4.11
Mean BMI ± SD (kg/m^2)	24.07 ± 4.51	23.13 ± 3.44	24.17 ± 4.60
Cyst on ultrasound‡	55 (7.67)	29 (42.65)	26 (4.01)
Pregnancy history			
Never pregnant	369 (51.68)	42 (61.76)	327 (50.62)
Pregnant but no live birth	236 (33.05)	19 (27.94)	217 (33.59)
Pregnant with live birth	109 (15.27)	7 (10.29)	102 (15.79)
Ever smoker (%)	48 (6.73)	6 (8.96)	42 (6.50)
Family history of endometriosis‡	32 (6.37)	9 (23.68)	23 (4.96)
Family history of infertility†	50 (9.77)	8 (20.51)	42 (8.88)

SD standard deviation, *BMI* body mass index

† $p < 0.05$; †† $p < 0.01$; ‡ $p < 0.001$; comparing endometriosis vs. no endometriosis

[a] Any endometriosis diagnosis in patients' electronic medical records

Overall, Asians further had a 45% (OR = 0.55; 95% CI 0.38, 0.80; $p = 0.002$) significantly decreased odds of clinical pregnancy compared to Caucasian women (Table 5). The results were similar when further stratifying according to laparoscopically confirmed endometriosis (Supplemental Table). In separate models to evaluate specific Asian nationalities (Table 6), the odds of clinical pregnancy were significantly lower for Indian (OR = 0.49; 95% CI 0.25, 0.97; $p = 0.04$), Japanese (OR = 0.34; 95% CI 0.13, 0.88; $p = 0.03$), and Korean (OR = 0.25; 95% CI 0.07, 0.92; $p = 0.04$) women compared to Caucasians, after controlling for endometriosis diagnosis and other confounding variables. While the effect for Indian ethnicity was not statistically significant in the unadjusted model, all race and ethnicity-based differences persisted in the models when adjusting for endometriosis diagnosis and other confounding variables. Effect estimates were also similar, although less precise, when we stratified the multivariable logistic regression models by endometriosis diagnosis.

Table 2 Diagnosis of endometriosis and in vitro fertilization (IVF) outcomes

	Endometriosis[a] ($n = 68$)	No endometriosis ($n = 649$)
Embryo transfer	58 (85.29)	569 (87.67)
Mean no. of oocytes retrieved (%)	11.87 ± 6.29	12.71 ± 7.33
Mean 2PN fertilized (%)	6.21 ± 4.27	7.08 ± 4.83
Pregnant (%)	23 (38.33)	288 (50.70)
Cancelled cycles	5 (7.35)	52 (8.06)

No statistically significant differences ($p \geq 0.05$) between women with endometriosis and women with no endometriosis

2PN oocyte with two pronuclei indicating successful fertilization

[a] Any endometriosis diagnosis in patients' electronic medical records

Table 3 Odds ratios (95% confidence intervals) for endometriosis by race/ethnicity (n = 717)

	All endometriosis cases (n = 68)				Laparoscopically confirmed endometriosis cases (n = 56)			
	Age-adjusted	P value	Confounder-adjusted[a]	P value	Age-adjusted	P value	Confounder-adjusted[a]	P value
Caucasian	Reference	–	Reference	–	Reference	–	Reference	–
Asian	*3.13 (1.78, 5.51)*	*<0.0001*	*2.96 (1.65, 5.31)*	*0.0003*	*2.35 (1.27, 4.35)*	*0.01*	*2.19 (1.16, 4.14)*	*0.02*
Black	0.99 (0.13, 7.77)	0.99	1.43 (0.17, 12.06)	0.74	1.11 (0.14, 8.79)	0.92	1.59 (0.18, 13.78)	0.67
Hispanic	2.08 (0.68, 6.44)	0.20	2.34 (0.75, 7.38)	0.15	2.34 (0.75, 7.33)	0.14	2.58 (0.81, 8.24)	0.10
Other races	1.81 (0.50, 6.52)	0.36	1.80 (0.50, 6.54)	0.37	1.93 (0.53, 7.05)	0.32	1.86 (0.50, 6.89)	0.36
Age	0.95 (0.89, 1.004)	0.07	0.95 (0.89, 1.01)	0.11	*0.92 (0.86, 0.98)*	*0.01*	*0.92 (0.86, 0.99)*	*0.02*
BMI	–	–	0.97 (0.90, 1.04)	0.37	–	–	0.98 (0.90, 1.05)	0.54
Smoking	–	–	1.52 (0.60, 3.83)	0.38	–	–	1.91 (0.75, 4.83)	0.17
Never pregnant	–	–	Reference	–	–	–	Reference	–
Pregnant but no live birth	–	–	0.75 (0.41, 1.36)	0.78	–	–	0.61 (0.31, 1.20)	0.66
Pregnant with live birth	–	–	0.68 (0.27. 1.72)	0.60	–	–	0.53 (0.18, 1.58)	0.48

$p < 0.05$ in italics

BMI body mass index

[a] Multivariable model adjusts for age, BMI, smoking, and pregnancy history

Discussion

This study is the first, to our knowledge, to assess whether a higher prevalence of endometriosis may account in part for the lower IVF pregnancy rates previously described among Asian women than among Caucasians [15, 16]. We demonstrated a higher prevalence of endometriosis in Filipino, Indian, Japanese, and Korean women than in Caucasian women, yet the lower chances of pregnancy persisted in Indian, Japanese, and Korean women after adjustment for the effect of endometriosis. Although we were not able to detect any significant difference in the number of oocytes retrieved or fertilized or whether or not an embryo transfer was done for Asian patients vs. Caucasians, our overall findings are consistent with some studies [18] and inconsistent [19] with others.

Table 4 Odds ratios (95% confidence intervals) for endometriosis by Asian ethnicity (n = 629)

	All endometriosis cases (n = 60)				Laparoscopically confirmed endometriosis cases (n = 48)			
	Age-adjusted	P value	Confounder-adjusted[a]	P value	Age-adjusted	P value	Confounder-adjusted[a]	P value
Caucasian	Reference	–	Reference	–	Reference	–	Reference	–
Chinese	1.95 (0.89, 4.29)	0.10	1.72 (0.76, 3.87)	0.19	1.23 (0.48, 3.17)	0.67	1.06 (0.4, 2.80)	0.91
Filipino	*4.28 (1.46, 12.55)*	*0.01*	*4.51 (1.52, 13.36)*	*0.01*	*4.69 (1.58, 13.94)*	*0.01*	*5.14 (1.71, 15.49)*	*0.004*
Indian	*3.99 (1.69, 9.44)*	*0.002*	*3.84 (1.56, 9.46)*	*0.003*	*3.07 (1.21, 7.78)*	*0.02*	*2.87 (1.07, 7.68)*	*0.04*
Japanese	*5.87 (2.27, 15.70)*	*0.0003*	*5.52 (2.05, 14.82)*	*0.001*	2.46 (0.68, 8.96)	0.17	2.15 (0.58, 8.01)	0.25
Korean	*4.78 (1.45, 15.75)*	*0.01*	*4.67 (1.38, 15.76)*	*0.01*	*5.48 (1.65, 18.27)*	*0.01*	*4.96 (1.44, 17.14)*	*0.01*
Other Asians	1.22 (0.15, 9.75)	0.85	1.11 (0.14, 8.92)	0.92	1.34 (0.17, 10.79)	0.78	1.30 (0.16, 10.62)	0.81
Age	0.97 (0.91, 1.04)	0.40	0.98 (0.91, 1.05)	0.50	0.95 (0.88, 1.02)	0.14	0.96 (0.88, 1.03)	0.24
BMI	–	–	0.92 (0.84, 1.01)	0.08	–	–	0.92 (0.83, 1.02)	0.11
Smoking	–	–	0.94 (0.30, 2.92)	0.91	–	–	1.22 (0.38, 3.86)	0.74
Never pregnant	–	–	Reference	–	–	–	Reference	–
Pregnant but no live birth	–	–	0.99 (0.53, 1.87)	0.68	–	–	0.81 (0.4, 1.65)	0.85
Pregnant with live birth	–	–	0.74 (0.28, 1.93)	0.53	–	–	0.56 (0.18, 1.73)	0.40

$p < 0.05$ in italics

BMI body mass index

[a] Multivariable model adjusts for age, BMI, smoking, and pregnancy history

Table 5 Odds ratios (95% confidence intervals) for pregnancy following in vitro fertilization by race/ethnicity, stratified by endometriosis (any endometriosis diagnosis in patients' electronic medical records) (n = 717)

	Unstratified				Stratified by endometriosis			
	Unadjusted	P value	Confounder-adjusted[a]	P value	Confounder-adjusted (n = 68 with endometriosis)[a]	P value	Confounder-adjusted (n = 649 with no endometriosis)[a]	P value
Caucasian	Reference	–	–	–	Reference	–	Reference	–
Asian	*0.60 (0.42, 0.85)*	*0.04*	*0.55 (0.38, 0.80)*	*0.002*	0.30 (0.07, 1.28)	0.10	*0.58 (0.39, 0.86)*	*0.01*
Black	0.85 (0.31, 2.31)	0.74	0.99 (0.35, 2.85)	0.99	-[b]	0.99	0.83 (0.28, 2.49)	0.74
Hispanic	0.96 (0.46, 1.98)	0.91	0.92 (0.43, 1.95)	0.83	0.09 (0.01, 1.56)	0.10	1.07 (0.48, 2.40)	0.87
Other races	0.55 (0.25, 1.20)	0.13	0.46 (0.20, 1.05)	0.07	0.66 (0.02, 21.52)	0.82	*0.39 (0.16, 0.96)*	*0.04*
Age	–	–	*0.93 (0.89, 0.97)*	*0.0004*	*0.82 (0.68, 1.00)*	*0.05*	*0.93 (0.89, 0.97)*	*0.001*
BMI	–	–	0.99 (0.96, 1.03)	0.77	1.02 (0.83, 1.26)	0.86	0.99 (0.96, 1.03)	0.77
Endometriosis in medical record	–	–	0.63 (0.35, 1.13)	0.12	–	–	–	–
Smoking	–	–	0.77 (0.40, 1.48)	0.44	0.13 (0.01, 2.00)	0.14	0.85 (0.43, 1.69)	0.65
Pregnancy history	–	–	–	–	–	–	–	–
Never pregnant	–	–	Reference	–	Reference	–	Reference	–
Pregnant but no live birth	–	–	1.00 (0.69, 1.44)	0.14	0.25 (0.05, 1.12)	0.60	1.10 (0.75, 1.61)	0.25
Pregnant with live birth	–	–	0.70 (0.42, 1.15)	0.77	0.15 (0.01, 1.79)	0.34	0.78 (0.46, 1.30)	0.22

$p < 0.05$ in italics

BMI body mass index

[a] Multivariable model adjusts for age, BMI, smoking, and pregnancy history

[b] Inestimable effect (n = 1)

Table 6 Odds ratios (95% confidence intervals) for pregnancy following in vitro fertilization by Asian ethnicity and other risk factors, stratified by endometriosis (any endometriosis diagnosis in patients' electronic medical records)

	Unstratified				Stratified by endometriosis			
	Unadjusted OR (95% CI)	*P* value	Confounder-adjusted[a]	*P* value	Confounder-adjusted (n = 60 with endometriosis)[a]	*P* value	Confounder-adjusted (n = 569 with no endometriosis)[a]	*P* value
Caucasian	Reference	–	Reference	–	Reference	–	Reference	–
Chinese	0.85 (0.53, 1.36)	0.12	0.78 (0.47, 1.29)	0.34	0.30 (0.04, 2.42)	0.26	0.89 (0.52, 1.50)	0.65
Filipino	0.54 (0.20, 1.42)	0.49	0.50 (0.19, 1.35)	0.17	0.32 (0.02, 5.76)	0.44	0.50 (0.17, 1.45)	0.20
Indian	0.65 (0.35, 1.21)	0.21	*0.49* (*0.25*, *0.97*)	*0.04*	0.44 (0.07, 2.98)	0.40	*0.44* (*0.21*, *0.93*)	*0.03*
Japanese	*0.28* (*0.11*, *0.73*)	*0.01*	*0.34* (*0.13*, *0.88*)	*0.03*	0.29 (0.03, 3.43)	0.33	0.37 (0.127, 1.09)	0.07
Korean	*0.21* (*0.06*, *0.76*)	0.02	*0.25* (*0.07*, *0.92*)	*0.04*	0.34 (0.02, 5.57)	0.45	*0.20* (*0.04*, *0.94*)	*0.04*
Other Asians	0.53 (0.17, 1.65)	0.27	0.50 (0.16, 1.59)	0.24	-[b]	0.99	0.55 (0.17, 1.81)	0.32
Age	–	–	*0.93* (*0.95*, *0.98*)	*0.003*	0.85 (0.69, 1.04)	0.11	*0.93* (*0.89*, *0.98*)	*0.005*
BMI	–	–	0.99 (0.95, 1.04)	0.74	1.02 (0.81, 1.28)	0.89	0.99 (0.95, 1.04)	0.79
Endometriosis in medical record	–	–	0.64 (0.33, 1.21)	0.17	–	–	–	–
Smoking	–	–	0.74 (0.36, 1.50)	0.40	0.32 (0.02, 5.50)	0.43	0.74 (0.35, 1.56)	0.42
Never pregnant	Reference	–	Reference	–	Reference	–	Reference	–
Pregnant but no live birth	–	–	1.11 (0.75, 1.65)	0.22	0.32 (0.07, 1.52)	0.71	1.26 (0.84, 1.91)	0.13
Pregnant with live birth	–	–	0.75 (0.44, 1.27)	0.18	0.19 (0.02, 2.45)	0.39	0.84 (0.49, 1.45)	0.27

$p < 0.05$ in italics

BMI body mass index

[a] Multivariable model adjusts for age, BMI, smoking, pregnancy history

[b] Inestimable effect (n = 1)

In this study, we observed an increased prevalence of endometriosis among Asian women, compared to Caucasians. These differences were statistically significant despite small numbers of cases per ethnicity. The trend we found among Japanese women is consistent with previous findings of Japanese women and other Asian ethnicities having a greater prevalence of endometriosis [11–13, 20]. If ethnic differences do in fact exist, genetic factors may play a role in this phenomenon. Other investigators have found associations between genetic polymorphisms and endometriosis in Asian ethnicities; however, findings have been inconsistent [21–25]. Our data further suggest that family history of endometriosis and infertility are significant predictors of endometriosis, consistent with the previous studies that found a genetic predisposition to endometriosis may increase one's risk [26–28]. More recently, investigators reported a higher risk for endometriosis among women with higher early life soy exposure [29]. However, we did not collect dietary data and so were unable to evaluate the impact.

While within our study population BMI was not a significant independent predictor of endometriosis, we found BMI to be lower in Asian women compared to Caucasian women. This is consistent with previous studies that found BMI to be inversely associated with endometriosis risk [14, 30–36]. Several studies from the prospective Nurses' Health Study II found that validated self-reported birth weight and body size at ages 5, 10, and 20 were inversely associated with endometriosis risk [37, 38]; thus, if BMI is a significant contributor to endometriosis risk, then risk may be determined at a younger age. However, most of these studies were conducted in Caucasian women; the relationship between low BMI in childhood and early adulthood and endometriosis is yet to be established in Asian women.

Having an endometrioma at baseline did not seem to affect pregnancy rates or IVF outcomes substantially in our study. Yet, pregnancy rates appeared to be reduced significantly in those with a cyst on ultrasound, consistent with but not diagnostic of endometrioma, at baseline compared to those without (54% decreased odds); however, controlling for endometriosis status removed this association, and so an independent endometrioma effect appears unlikely. Other authors have reported that endometrial cysts contribute to worse IVF outcomes [39–41], but the evidence remains inconsistent [42, 43]. Consistent with our results, a recent meta-analysis of 33 individual studies reported no difference for pregnancy following IVF/ICSI in women with and without endometrioma [44].

Our detection of worse IVF outcomes among Asians was not surprising, given that similar results have been reported elsewhere [15, 16]. The authors of these previous studies speculated that the disparities could be attributed to a multitude of differences, including genetic, social, behavioral, and cultural factors, as well as environmental and dietary exposures. However, the etiology of poorer IVF outcomes in Asian women remains unclear.

There are several limitations to note in this study. Our retrospective study design provides a measure of prevalence, and so we cannot distinguish the impact of ethnicity on incidence of endometriosis from duration of the disease. Although the associations we found were strong and were adjusted for key confounders, we cannot rule out the possibility of unmeasured confounding in an observational study. While stratifying by Asian ethnicities allowed us to understand the effects in the subgroups, the small cell sizes limited statistical power to detect modest effects and so the results should be confirmed in a larger investigation. Furthermore, the relatively low prevalence of endometriosis and endometriomas in our small study group limited our statistical power to detect significant differences in clinical pregnancy rates and produced imprecise effect estimates. In our study population, endometriosis was defined as endometriosis diagnosis anywhere in the patients' medical records to conserve statistical power; hence, a limitation of this study is the potential for inaccurate case counts. One matched exposure cohort study found that endometriosis incidence was dependent on diagnostic method and sampling framework, especially when comparing surgical, histological, and MRI diagnosis [45]; thus, we cautiously reviewed and recorded information from the medical records in order to minimize this bias. Among the cases, 56 of 68 (82.4%) were laparoscopically diagnosed. Among the patients without laparoscopically confirmed diagnoses, nine (75%) had thorough transvaginal ultrasound records that were confirmed as ovarian endometriomas by a clinician (EBJ) and two (16.7%) were diagnosed while undergoing other surgeries and were later confirmed by the authors (EBJ and AY). Further, transvaginal ultrasounds are considered to be the primary diagnostic method for ovarian endometriomas [46]. Several validation studies have indicated that transvaginal ultrasounds are very reliable in predicting ovarian endometriomas and deep infiltrating endometriosis and can accurately distinguish between endometriomas and other ovarian masses [46–48]. Unfortunately, we were unable to assess the duration of endometriosis prior to the IVF cycle, which could have led to exposure misclassification if disease-free at the time of IVF. Since our study population was limited to women undergoing IVF from an infertility clinic, these findings may not be relevant to infertile women that do not seek treatment or to women from IVF clinics with different selection factors, and so these results should be generalized with caution [49, 50]. An advantage of restricting to women presenting at an infertility clinic is that heterogeneity is less of a concern; in other words, risk factors that lead to endometriosis with concurrent infertility as opposed to without concurrent infertility are likely to be similar among these women [36].

Our study focused on differences in endometriosis prevalence and their relationship to IVF outcomes in Asian ethnicities, as both higher the prevalence of endometriosis among Asians [11–13] and the lower pregnancy rates with IVF than

for Caucasians [15, 16] have been studied by other investigators. In conclusion, this study provides additional evidence that endometriosis is more prevalent among Asian women. However, this does not appear to be the sole cause of lower clinical pregnancy rates found in multiple Asian ethnicities compared to Caucasians. Larger, prospective studies are needed to further delineate the degree to which endometriosis contributes to the lower IVF pregnancy rate seen in Asian women and to identify important contributors to the widely reported disparity so that effective clinical interventions can be designed.

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Compliance with ethical standards Prior approval of the study protocol was obtained from the UCSF Committee for Human Research.

Conflict of interest The authors declare that they have no competing interests.

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