Impact of endometriosis on in vitro fertilization outcomes: an evaluation of the Society for Assisted Reproductive Technologies Database

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Objective: To assess the impact of endometriosis, alone or in combination with other infertility diagnoses, on IVF outcomes.
Design: Population-based retrospective cohort study of cycles from the Society for Assisted Reproductive Technology Clinic Outcome Reporting System database.
Setting: Not applicable.
Patient(s): A total of 347,185 autologous fresh and frozen assisted reproductive technology cycles from the period 2008–2010.
Intervention(s): None.
Main Outcome Measure(s): Oocyte yield, implantation rate, live birth rate.
Result(s): Although cycles of patients with endometriosis constituted 11% of the study sample, the majority (64%) reported a concomitant diagnosis, with male factor (42%), tubal factor (29%), and diminished ovarian reserve (22%) being the most common. Endometriosis, when isolated or with concomitant diagnoses, was associated with lower oocyte yield compared with those with unexplained infertility, tubal factor, and all other infertility diagnoses combined. Women with isolated endometriosis had similar or higher live birth rates compared with those in other diagnostic groups. However, women with endometriosis with concomitant diagnoses had lower implantation rates and live birth rates compared with unexplained infertility, tubal factor, and all other diagnostic groups.
Conclusion(s): Endometriosis is associated with lower oocyte yield, lower implantation rates, and lower pregnancy rates after IVF. However, the association of endometriosis and IVF outcomes is confounded by other infertility diagnoses. Endometriosis, when associated with other alterations in the reproductive tract, has the lowest chance of live birth. In contrast, for the minority of women who have endometriosis in isolation, the live birth rate is similar or slightly higher compared with other infertility diagnoses. (Fertil Steril® 2016;■: ■–■. ©2016 by American Society for Reproductive Medicine.)
Key Words: Endometriosis, implantation rate, IVF, live birth rate, SART

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Endometriosis is a chronic benign gynecologic disease that affects 10% of women and is a major cause of chronic pelvic pain and infertility (1, 2). Anatomic distortion leading to tubal occlusion, poor oocyte quality, impaired implantation, and P resistance have all been implicated; however, the mechanisms of endometriosis-associated infertility remain incompletely understood. A number of observational studies have sought to determine the effects of endometriosis on pregnancy rates, with some reporting negative associations and others noting no association. A meta-analysis of the available observational data in 2002 suggested that patients with endometriosis-associated infertility undergoing IVF had an absolute pregnancy rate (detection of serum hCG) almost half that of other

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diagnostic groups, with similar trends in other surrogate markers of IVF success, including oocyte yield, fertilization rate, and implantation rate (3). However, more recent analyses have suggested that a diagnosis of endometriosis may be associated with comparable pregnancy outcomes compared with other infertility diagnostic groups. In a retrospective analysis of linked cycles from the Society for Assisted Reproductive Technology (SART) database over a 7-year period, live birth rates were similar to other IVF diagnostic groups in both fresh and frozen cycles (4). However, this particular analysis reported on endometriosis as a single diagnosis. Because it is more typical for endometriosis to present in conjunction with other diagnoses than in isolation, this can complicate counseling patients regarding IVF outcomes.

To reconcile this controversy, the proposed study sought to assess the relationship between a diagnosis of endometriosis, either in isolation or in combination with other infertility diagnoses, and IVF outcomes using population-level data from the SART Database, with the hypothesis that endometriosis would be associated with lower live birth rates compared with other diagnostic groups, particularly in endometriosis with concomitant infertility diagnoses.

MATERIALS AND METHODS

This is a population-based retrospective study of subjects from SART's national database from 2008–2010 representing the IVF cycles from >85% of infertility clinics in the United States. This study proposal was reviewed by the Institutional Review Board at the University of Pennsylvania and was deemed appropriate for full institutional review board review exemption owing to use of de-identified data. Cycles were analyzed according to reported infertility diagnosis, with endometriosis as the exposure of interest. Cycles were categorized as those having an isolated diagnosis of endometriosis ("Endometriosis Only"), endometriosis plus at least one other concomitant diagnosis ("Endometriosis Plus"), an isolated diagnosis of tubal factor infertility ("Tubal Factor"), or an isolated diagnosis unexplained infertility ("Unexplained"). Patients for whom the reason for infertility was a diagnosis other than endometriosis, tubal factor, or unexplained infertility (including those listed as "Other," or "Other Noninfertile" with additional explanatory comments that excluded endometriosis or tubal factor) were classified as "All Other Diagnoses." All donor, gestational carrier, and banking cycles were excluded.

The primary outcome of interest was live birth rate, defined as delivering a live-born infant after 22 weeks' gestation. Secondary outcomes included oocyte yield, fertilization rate (number of embryos/oocyte yield), proportion of cycles resulting in blastocyst transfer, implantation rate (number of fetal hearts with detectable activity/number of embryos transferred), and early pregnancy loss rate (biochemical pregnancy, ectopic pregnancy, or miscarriage—[clinical intrauterine gestation resulting in pregnancy loss or abortion]). Analyses of oocyte yield were restricted to fresh cycles, and analyses of fertilization rate were restricted to fresh cycles with an oocyte yield ≥ 1. All other analyses were restricted to those cycles in which an ET was performed to reduce bias from canceled cycles due to inadequate response.

Baseline and demographic characteristics were analyzed with analysis of variance and Pearson χ^2 testing as appropriate. Generalized linear regression models were used for multivariable modeling, whereas analysis of count data and implantation rate was performed using Poisson regression (5). Comparisons of oocyte yield and fertilization rate were performed using negative binomial regression modeling to account for excess variability (over dispersion) in the rates. All other outcomes were analyzed with logistic regression modeling using backwards elimination.

Models of proportion of blastocyst transfer, implantation rate, and pregnancy outcomes evaluated the potential for effect modification by cycle type (fresh vs. frozen) with adjustment for significant confounders. Mixed cycles (those with both fresh and frozen embryos transferred) were excluded. Maternal age, body mass index (BMI), race, smoking history, number of prior treatment cycles, maximum FSH level, prior parity, use of intracytoplasmic sperm injection (ICSI), assisted hatching, and year of treatment were considered as potential confounders in the relationships between infertility diagnosis and the outcomes of interest as appropriate. Missing data were given separate categorical indicators within each covariate for analysis to account for the effects of missing data. An a priori subanalysis of first IVF cycles was considered to address the influence of multiple or prior treatment cycles. To account for the influence of multiple comparisons and the impact of a large number of observations in this dataset, a P value $<.001$ was considered statistically significant. All data were analyzed using STATA version 12.0 (StataCorp).

RESULTS

Of the 400,059 cycles reported during 2008–2010, 347,185 were included in the analyses after excluding all donor, gestational carrier, and banking cycles. There were 39,356 initiated cycles of patients with endometriosis, which constituted 11% of the study sample. Of these, 14,053 cycles (4%) were in women who had an isolated diagnosis of endometriosis (Endometriosis Only), whereas 25,303 cycles (7%) were in women who had a diagnosis of endometriosis and at least one additional diagnosis (Endometriosis Plus). Isolated tubal factor infertility (Tubal Factor) was representative of 25,906 cycles (7%), and 44,200 cycles (12.7%) were classified as unexplained infertility (Unexplained). Table 1 summarizes the characteristics of each diagnostic group. Notable differences include that women with isolated endometriosis were younger than those in other diagnostic groups. Those with tubal factor infertility had a higher BMI and were more likely to report African American race. Women with endometriosis in combination with another diagnosis (Endometriosis Plus) were more likely to have undergone a flare protocol for ovarian stimulation, ICSI, assisted hatching, and were more likely to have had at least one prior IVF cycle.

Of women with Endometriosis Plus, 65% had a single additional infertility diagnosis, 28% had two additional diagnoses, 6% had three additional diagnoses, and the remaining 1% had four or more diagnoses reported. The

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TABLE 1

Demographic characteristics by diagnostic group.

Characteristic	Endometriosis only (n = 14,053) (%)	Endometriosis plus (n = 25,303) (%)	Unexplained (n = 44,200) (%)	Tubal factor (n = 25,906) (%)	All other diagnoses (n = 237,723) (%)	*P* Value
	Total initiated cycles (n = 347,185)					
Age (y), mean (SD)[a]	34.6 (4.1)	35.3 (4.4)	35.7 (4.1)	35.3 (4.3)	36.0 (4.9)	<.0001
BMI (kg/m^2)						<.0001
<18.5	3.1	2.8	2.8	1.7	2.5	
18.5–25	53.7	48.7	53.4	38.6	44.7	
25–30	16.8	19.5	16.4	22.9	18.6	
30–35	5.9	7.9	6.1	11.3	9.0	
35–40	2.0	3.2	2.8	4.8	4.3	
>40	0.8	1.3	1.2	2.2	2.3	
Missing	17.7	16.6	17.3	18.5	18.6	
Race						<.0001
White	49.7	50.8	43.5	39.0	46.6	
African American	2.5	4.0	2.5	11.2	4.9	
Mixed/other	7.7	8.1	8.8	7.4	8.4	
Missing	40.1	37.1	45.2	42.4	40.1	
Full-term birth history						<.0001
No prior full-term birth	53.9	53.3	54.4	46.4	51.8	
At least 1 full-term birth	25.6	26.6	26.5	43.0	28.7	
Missing	20.5	20.1	19.1	10.6	19.5	
Preterm birth history						<.0001
No prior preterm birth	75.8	75.6	77.6	83.3	75.9	
At least 1 preterm birth	3.4	4.2	3.1	5.7	3.9	
Missing	20.8	20.2	19.3	11.0	20.2	
Miscarriage history						<.0001
No prior miscarriages	52.4	48.8	49.7	50.4	48.5	
At least 1 prior miscarriage	27.0	31.1	31.2	38.9	31.9	
Missing	20.6	20.1	19.1	10.7	19.6	
Tobacco use						<.0001
No	78.1	82.1	79.4	77.2	79.9	
Yes	4.5	5.1	3.6	7.3	5.0	
Missing	17.4	12.8	17.0	15.5	15.1	
ICSI (some/all)	41.2	50.8	42.7	35.9	54.3	<.0001
Assisted hatching						<.0001
No assisted hatching	55.9	49.9	54.6	55.7	50.4	
Assisted hatching (some/all)	35.9	39.1	37.5	36.4	38.7	
Missing	8.2	11.0	7.9	8.0	10.9	
Protocol (fresh cycles only)						
Agonist	53.0	45.0	48.9	52.3	39.7	<.0001
Antagonist	32.9	36.4	36.3	32.7	30.7	
Flare	11.1	14.4	9.8	10.5	10.8	
Missing	3.0	4.2	5.0	4.5	18.8	
Year of treatment						<.0001
2008	28.8	37.6	27.1	28.9	34.3	
2009	36.3	30.6	35.7	36.4	32.6	
2010	34.9	31.8	37.2	34.7	33.1	

Note: Values are percentages unless otherwise noted.

[a] Differences in mean maternal age assessed with analysis of variance; χ^2 test used for all other covariates.

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distribution of concomitant diagnoses associated with endometriosis is presented in Supplemental Table 1 (available online).

A total of 291,244 ET cycles were analyzed, of which 11.5% had endometriosis: 4.2% (12,335) had an isolated endometriosis diagnosis (Endometriosis Only), and 7.3% (21,223) had endometriosis in combination with other diagnoses (Endometriosis Plus). Women with endometriosis and concomitant diagnoses were significantly more likely to have a canceled cycle (11.3%) in comparison with women with isolated endometriosis, tubal factor, or unexplained infertility (8.5%, 8.3%, and 8.1%, respectively, $P<.0001$). Ovarian stimulation and pregnancy outcomes for women, based on diagnosis, are reported in Table 2. Overall, women

TABLE 2

Ovarian stimulation and pregnancy outcomes after IVF, according to diagnosis.

Cycle	Endometriosis only (n = 12,335)	Endometriosis plus (n = 21,123)	Unexplained (n = 38,713)	Tubal factor (n = 22,778)	All other diagnoses (n = 196,295)
All ET cycles					
Blastocyst transfer[a]	36.0	35.9	33.8	37.6	35.4
Implantation rate[b]	31.1 [30.5–31.8]	24.6 [24.1–25.1]	29.3 [28.9–29.7]	28.8 [28.3–29.3]	25.7 [25.5–25.8]
Biochemical	8.0	9.2	8.2	7.2	8.9
Ectopic pregnancy	0.80	0.94	0.86	0.86	0.74
Miscarriage	7.1	7.7	7.6	7.8	8.2
Live birth	42.5	33.4	39.6	38.7	34.4
Fresh embryo transfer cycles					
Oocyte yield[c]	12.1 (6.9)	11.5 (7.0)	12.7 (7.0)	12.6 (7.2)	12.3 (7.6)
Fertilization rate[b]	59.0 [58.5–59.5]	58.0 [57.7–58.4]	59.1 [58.8–59.3]	60.3 [59.9–60.6]	56.8 [56.6–56.9]
Blastocyst transfer[a]	30.3	28.9	28.7	31.2	29.2
Implantation rate[b]	32.6 [31.9–33.4]	25.2 [24.6–25.8]	30.3 [29.9–30.7]	30.0 [29.5–30.6]	26.2 [26.0–26.4]
Biochemical	7.5	8.7	7.5	6.8	8.3
Ectopic pregnancy	0.95	1.05	0.94	0.95	0.83
Miscarriage	6.7	7.5	7.5	7.7	8.1
Live birth	44.7	34.6	41.1	40.4	35.3
Frozen embryo transfer cycles					
Blastocyst transfer[a]	54.2	58.2	53.4	56.4	55.9
Implantation rate[b]	26.3 [25.0–27.6]	22.8 [21.8–23.8]	25.7 [24.9–26.4]	25.0 [24.1–26.0]	24.0 [23.7–24.3]
Biochemical	9.7	10.7	10.7	8.7	11.0
Ectopic pregnancy	0.37	0.62	0.54	0.60	0.44
Miscarriage	8.2	8.4	8.1	8.1	8.5
Live birth	35.4	29.8	33.7	33.6	31.3

Note: Values are percentages.
[a] Percentage of transfer cycles resulting in blastocyst transfer.
[b] Geometric mean [95% confidence interval].
[c] Mean (SD).

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with a diagnosis of endometriosis (either isolated endometriosis or concomitant with another diagnosis) had a reduction in oocyte yield (risk ratio [RR] 0.91 [95% confidence interval (CI) 0.91–0.92]), implantation rate (RR 0.94 [0.93–0.96]), proportion of blastocyst transfer (RR 0.96 [0.93–0.99]), and a 6% reduction in in live birth rate compared with women without endometriosis in adjusted analyses of fresh cycles (RR 0.94 [0.91–0.97]). Fertilization rate was similar (RR 1.00 [1.00–1.01]). Implantation rate and live birth rate followed similar trends of poorer outcomes in endometriosis compared with those without endometriosis in frozen/thawed transfer cycles.

We further examined the outcomes of women with isolated endometriosis (Endometriosis Only) and those with a concomitant infertility diagnosis (Endometriosis Plus) separately to test our a priori hypothesis that outcomes may differ in each subgroup and thus explain the differences in the findings of prior studies. These data are presented in Tables 3 and 4. Table 3 presents the IVF outcomes of women with isolated endometriosis compared with women with other diagnoses. Although not found in all comparisons with all subgroups, an isolated diagnosis of endometriosis (Endometriosis Only) was generally associated with a decrease in oocyte yield and a slightly lower or similar fertilization rate, blastocyst transfer rate, and pregnancy loss rate. However, women with isolated endometriosis were found to have a similar or higher liver birth rate compared with those with other infertility diagnoses. These findings were similar in fresh and frozen embryo transfer cycles.

Table 4 presents the IVF outcomes of women with endometriosis and at least one other concomitant diagnosis (Endometriosis Plus) in comparison with other diagnostic groups. This subgroup was noted to have significantly poorer IVF outcomes compared with women with other infertility diagnoses. Oocyte yield was consistently 7%–9% lower compared with unexplained, tubal factor, and all other diagnostic groups. Despite similar fertilization rates and blastocyst transfer rates, there was an 11%–17% reduction in implantation rates in Endometriosis Plus compared with unexplained infertility, tubal factor, and all other diagnostic groups combined. Live birth rates were reduced by 19%–26% in fresh cycles. Trends were similar in frozen cycles, noting a 12%–18% reduction in live birth rates. A restricted analysis of first cycles demonstrated no significant difference in reported trends in oocyte yield, implantation rate, or live birth rate.

Subanalyses of mechanisms of early pregnancy loss demonstrated no differences in incidence of ectopic pregnancy, biochemical pregnancy, or miscarriage among women with Endometriosis Only compared with tubal factor and unexplained infertility in fresh and frozen cycles ($P>.05$ for all comparisons). Interestingly, among those with a positive pregnancy test, those with Endometriosis Plus were significantly more likely to have a biochemical pregnancy or miscarriage compared with those with Unexplained Infertility and Tubal Factor Infertility in fresh cycles (RR 1.26 [1.16–1.37], $P<.0001$ and RR 1.19 [1.08–1.31], $P<.0001$, respectively).

TABLE 3

Adjusted and unadjusted RRs for IVF outcomes in women with isolated endometriosis compared with women without endometriosis.

Cycles	Endometriosis only vs. unexplained: Unadjusted RR [95% CI] *P* value	Endometriosis only vs. unexplained: Adjusted RR [95% CI] *P* value	Endometriosis only vs. tubal factor: Unadjusted RR [95% CI] *P* value	Endometriosis only vs. tubal factor: Adjusted RR [95% CI] *P* value	Endometriosis only vs. all other diagnoses: Unadjusted RR [95% CI] *P* value	Endometriosis only vs. all other diagnoses: Adjusted RR [95% CI] *P* value
Fresh embryo transfer cycles						
Oocyte yield[a]	0.95 [0.94–0.96] .0001	0.92 [0.91–0.93] .0001	0.95 [0.94–0.97] .0001	0.93 [0.92–0.95] .0001	0.99 [0.97–1.01] .34	0.90 [0.88–0.92] .0001
Fertilization rate[b]	0.99 [0.99–1.01] .45	0.99 [0.98–1.00] .17	0.97 [0.96–0.98] .0001	0.97 [0.96–0.98] .0001	1.02 [1.01–1.03] .0001	1.00 [0.99–1.01] .43
Blastocyst transfer[c]	1.08 [1.03–1.14] .002	0.99 [0.94–1.05] .74	0.94 [0.90–1.00] .06	0.88 [0.83–0.94] .0001	1.05 [1.01–1.10] .02	0.91 [0.87–0.96] .0001
Implantation rate	1.11 [1.08–1.14] .0001	0.99 [0.96–1.01] .33	1.10 [1.07–1.14] .0001	1.04 [1.01–1.07] .02	1.25 [1.22–1.28] .0001	1.04 [1.01–1.06] .007
Early pregnancy loss	0.94 [0.88–1.00] .05	0.97 [0.91–1.04] .44	0.98 [0.91–1.05] .57	1.01 [0.94–1.09] .70	0.88 [0.83–0.93] .0001	0.91 [0.87–0.97] .005
Live birth	1.16 [1.10–1.21] .0001	1.02 [0.97–1.07] .41	1.19 [1.13–1.25] .0001	1.11 [1.05–1.17] .0001	1.40 [1.34–1.45] .0001	1.13 [1.08–1.18] .0001
Frozen embryo transfer cycles						
Blastocyst transfer[c]	1.04 [0.95–1.13] .40	1.03 [0.94–1.12] .56	0.91 [0.84–1.00] .05	0.89 [0.81–0.98] .02	0.95 [0.88–1.02] .16	0.91 [0.84–0.98] .01
Implantation rate	1.02 [0.96–1.08] .52	0.99 [0.96–1.02] .40	1.03 [0.97–1.10] .29	1.04 [1.01–1.08] .02	1.08 [1.02–1.13] .007	1.03 [1.01–1.06] .004
Early pregnancy loss	0.94 [0.84–1.05] .25	0.95 [0.85–1.06] .36	1.07 [0.95–1.20] .27	1.07 [0.95–1.20] .29	0.92 [0.84–1.01] .09	0.94 [0.85–1.03] .19
Live birth	1.08 [0.99–1.18] .10	1.04 [0.95–1.14] .38	1.08 [0.99–1.19] .09	1.04 [0.95–1.15] .41	1.17 [1.09–1.27] .0001	1.10 [1.02–1.19] .02

[a] Oocyte yield adjusted for maternal age, BMI, race, smoking history, prior parity, number of prior cycles, year of treatment, maximum serum FSH level.
[b] Fertilization rate adjusted for maternal age, BMI, race, smoking history, prior parity, number of prior cycles, year of treatment, maximum serum FSH level, and ICSI.
[c] Percentage of transfer cycles resulting in blastocyst transfer.

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DISCUSSION

The impact of endometriosis on fecundity and IVF outcomes continues to be debated. This study confirms that endometriosis is associated with lower live birth rates than other infertility diagnoses, and specifically compared with tubal factor and unexplained infertility. As previously noted, this difference is more apparent after adjusted, rather than crude, analysis of the data (3). This may explain the discrepancy between these findings and the Clinic Summary Report of SART. However, the association of endometriosis and IVF outcomes is confounded by other infertility diagnoses. The majority of couples with a diagnosis of endometriosis presenting for IVF will have at least one other infertility diagnosis, which contributes to the clinical challenge of assessing the impact of a sole diagnosis on IVF outcomes. In fact, our analysis demonstrates that when endometriosis was seen in isolation, it was associated with a similar or even higher live birth rate compared with all other diagnoses in fresh autologous cycles, despite lower oocyte yield. These patients may represent a milder phenotype of endometriosis and thus may have a more favorable response to the specific benefits that IVF avails, including optimizing oocyte–sperm interaction outside the inflammatory peritoneal environment, and P supplementation to overcome relative P resistance. Importantly, this only applies to a minority of all patients presenting with endometriosis. Endometriosis more commonly presents in conjunction with at least one other fertility diagnosis, and as this larger subgroup of patients has poorer prognoses overall, as evidenced by the higher likelihood of prior IVF cycles and more aggressive (flare) stimulation protocols.

The mechanism of endometriosis-related infertility, or its impact on IVF, has not been fully established (6). Because endometriosis is a chronic and often progressive disease, it possible that as the disease advances it will result in alterations that will be categorized as other infertility-related diagnoses. Thus, it is possible that women with isolated endometriosis represent a subgroup of women with "mild" disease. If so, these results are similar to previous findings (3) and those of a recent meta-analysis (7). In the latter, a 21% reduction in both implantation and clinical pregnancy rates in those with stage III–IV endometriosis was noted (RR 0.79 [95% CI 0.67–0.93], $P=.0006$ and RR 0.79 [0.65–0.91], $P=.0008$, respectively), but no difference in live birth rates in stage I–II or stage III–IV endometriosis was observed (RR 0.92 [0.83–1.02], $P=.10$ and RR 0.86 [0.68–1.08], $P=.19$, respectively) (7). Similarly, a large single-center cohort study spanning a 20-year period of autologous GnRH agonist cycles in Norway noted that cycles with endometriosis were associated with similar cumulative live birth rates compared with tubal factor infertility (stage I–II 73% [95% CI 58%–75%]; stage III-IV 58% [22%–94%]; tubal factor 66% [58%–75%]), demonstrating clear heterogeneity within the population of those with endometriosis by stage (8).

A possible mechanism of lower live birth rates among those with endometriosis seems to be linked to oocyte quality,

TABLE 4

Adjusted and unadjusted RRs for IVF outcomes in women with endometriosis and other concomitant infertility diagnoses compared with women without endometriosis.

	Endometriosis plus vs. unexplained		Endometriosis plus vs. tubal factor		Endometriosis plus vs. all other diagnoses	
Cycles	Unadjusted RR [95% CI] *P* value	Adjusted RR [95% CI] *P* value	Unadjusted RR [95% CI] *P* value	Adjusted RR [95% CI] *P* value	Unadjusted RR [95% CI] *P* value	Adjusted RR [95% CI] *P* value
Fresh embryo transfer cycles						
Oocyte yield[a]	0.90 [0.90–0.91] .0001	0.91 [0.90–0.92] .0001	0.91 [0.90–0.92] .0001	0.93 [0.92–0.94] .0001	0.93 [0.92–0.94] .0001	0.92 [0.91–0.92] .0001
Fertilization rate[b]	0.99 [0.98–0.99] .0001	0.99 [0.99–1.00] .41	0.96 [0.95–0.97] .0001	0.98 [0.97–0.99] .0001	1.01 [1.00–1.04] .06	1.01 [1.00–1.01] .02
Blastocyst transfer[c]	1.01 [0.97–1.05] .62	1.06 [1.01–1.11] .01	0.88 [0.84–0.93] .0001	0.96 [0.91–1.01] .14	0.98 [0.95–1.02] .32	0.99 [0.95–1.03] .56
Implantation rate	0.85 [0.83–0.87] .0001	0.84 [0.82–0.86] .0001	0.84 [0.82–0.86] .0001	0.89 [0.86–0.91] .0001	0.95 [0.93–0.97] .0001	0.88 [0.87–0.90] .0001
Early pregnancy loss	1.09 [1.03–1.15] .001	1.11 [1.05–1.17] .001	1.14 [1.08–1.21] .0001	1.14 [1.07–1.21] .0001	1.02 [0.98–1.07] .33	1.05 [1.00–1.09] .04
Live birth	0.76 [0.73–0.79] .0001	0.74 [0.71–0.78] .0001	0.78 [0.74–0.81] .0001	0.81 [0.77–0.85] .0001	0.91 [0.88–0.95] .0001	0.84 [0.81–0.87] .0001
Frozen embryo transfer cycles						
Blastocyst transfer[c]	1.21 [1.13–1.30] .0001	1.28 [1.18–1.38] .0001	1.07 [0.99–1.15] .09	1.09 [1.01–1.19] .03	1.11 [1.05–1.18] .001	1.10 [1.03–1.16] .003
Implantation rate	0.89 [0.85–0.94] .0001	0.83 [0.81–0.86] .0001	0.90 [0.85–0.96] .0001	0.88 [0.85–0.91] .0001	0.94 [0.90–0.98] .005	0.88 [0.86–0.90] .0001
Early pregnancy loss	1.03 [0.94–1.12] .57	1.03 [0.94–1.13] .49	1.17 [1.06–1.29] .002	1.16 [1.05–1.29] .004	1.01 [0.94–1.08] .85	1.02 [0.95–1.09] .66
Live birth	0.83 [0.77–0.90] .0001	0.83 [0.76–0.90] .0001	0.84 [0.77–0.91] .0001	0.82 [0.75–0.89] .0001	0.91 [0.85–0.97] .002	0.88 [0.83–0.94] .0001

[a] Oocyte yield adjusted for maternal age, BMI, race, smoking history, prior parity, number of prior cycles, year of treatment, maximum serum FSH level.
[b] Fertilization rate adjusted for maternal age, BMI, race, smoking history, prior parity, number of prior cycles, year of treatment, maximum serum FSH level, and ICSI.
[c] Percentage of transfer cycles resulting in blastocyst transfer.

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as reflected by lower oocyte yield, as well as impaired implantation. Diminished ovarian reserve was a highly prevalent concomitant diagnosis in the Endometriosis Plus group. These women had a higher rate of cancellation compared with those with tubal factor and unexplained infertility, confirming poorer prognosis for this subgroup overall. The link between diminished ovarian reserve and endometriosis has been suggested by studies noting lower serum markers of ovarian reserve in patients with endometriosis compared with tubal factor infertility (9, 10).

In a retrospective cohort study of autologous and donor oocyte cycles in patients with endometriosis compared with other diagnoses, endometriosis was similarly associated with a lower pregnancy rate per transfer ($P<.0004$) and implantation rate ($P<.0003$) compared with tubal factor infertility (11). Furthermore, when analyzing the impact of endometriosis on uterine environment in oocyte donation cycles, there was a lower implantation rate after transfer of embryos from endometriotic ovaries into women without endometriosis, whereas there was no difference in pregnancy rates between women with endometriosis and tubal factor receiving donor oocytes, suggesting that oocyte quality and not the uterine environment is the main contributor to lower pregnancy rates (11). These findings were later corroborated by a case–control analysis from the same group (12); however, these studies did not differentiate the contribution of the oocyte from the embryo.

Our data do not suggest that endometriosis has a large impact on embryo progression to blastocyst as a surrogate of embryo quality. We noted that the rate of blastocyst transfer were similar if not higher in the Endometriosis Plus group compared with other diagnostic groups, despite lower oocyte yield. However, the embryo–endometrial interaction, and subsequent impact on implantation rate, may be associated with a reduction in live birth rate noted. Possible mechanisms for this finding may include altered HOXA10 gene expression (13, 14), altered endometrial receptivity (15–17), and/or P resistance (18–21).

We note that the frozen embryo transfer cycles resulted in a lower pregnancy rate across all diagnostic subgroups compared with fresh cycles and did not differ in those with endometriosis compared with those without endometriosis overall. However, the majority of the cycles included in this analysis were fresh cycles; as such, caution should be taken in extrapolating these results to suggest inherent differences in fresh and frozen cycles, because the retrospective nature of this analyses is most certainly subject to selection bias with respect to cycle type (fresh vs. frozen). These observations are likely due to the routine practice of selecting the best-quality embryos for fresh transfer and cryopreserving supernumerary embryos, with high frozen blastocyst transfer rates reflecting selective blastocyst cryopreservation. As such, the impact of peri-implantation environment would be better ascertained in a prospective, controlled study.

This study used the SART Database to capture infertility diagnosis and outcome data at a population level, given that the more than 345,000 cycles included represent the majority of IVF practices in the United States over a 3-year period. Although the size of this study strengthens the conclusions drawn, and using a national database lends generalizability, we acknowledge that the findings may still be affected by confounding and bias. By accounting for relevant confounders, including age, prior parity, FSH, prior cycles, micromanipulation, and year of treatment, this study design and analysis allowed for a conservative method of analyzing this population-based data to reduce the risk of overstating conclusions.

We acknowledge that this study is limited by information bias, and the abstracted data did not have identifiers for linking cycles within an individual. Because patients in the Endometriosis Plus group were more likely to have had prior cycles represented within the dataset, this may have resulted in bias of the reported results away from the null. However, Kalra et al. (22) were able to link data from multiple cycles per woman and estimated the within-woman correlation of multiple cycles to be nearly zero (Sarah Ratcliffe, personal communication); given that the majority of women contributed one cycle (59% in their study; 47% reported no prior cycles in the present study), we believe the impact of linking multiple cycles would have a negligible effect on our conclusions.

Because stage of endometriosis, the presence or absence of endometriomas, and prior interventions for endometriosis is not universally reported, the impact of disease severity and endometriosis treatment on IVF outcomes cannot be completely ascertained from this analysis.

There is theoretical risk of diagnostic misclassification with respect to the endometriosis only and tubal factor only groups when using administrative data (21). However, IVF centers are able to report multiple SART diagnoses (as seen by 29% of the Endometriosis Plus group reporting concomitant tubal factor). Thus any misclassification is likely nondifferential, resulting in a bias toward the null. Of note, there is the possibility of diagnostic misclassification such that some of those with unexplained infertility may have undiagnosed endometriosis given the shift in clinical care away from routine diagnostic laparoscopy for all infertility patients. As such, misclassification could be differential, or unidirectional. It is unknown whether correct diagnostic classification would result in bias toward the null or perhaps an even more dramatic reduction in the live birth rates observed.

In conclusion, endometriosis is a heterogeneous disease with respect to presentation and outcomes in those with infertility. In vitro fertilization undeniably remains one of the most effective treatments for women with endometriosis-associated infertility; yet there are nuances of this complex disease process that are important for counseling patients with respect to expected IVF outcomes. In general, endometriosis is associated with lower oocyte yield, lower implantation rates, and lower pregnancy rates. Endometriosis, when associated with other alterations in the reproductive tract (either as a result of progression or by chance) has the lowest chance of live birth. In contrast, for the minority of women who have endometriosis in isolation, the live birth rate is similar or slightly higher compared with other diagnostic groups. Further studies are needed to assess the role of periimplantation environment and endometrial receptivity, to understand the mechanism(s) of endometriosis-associated infertility and how it may be overcome.

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SUPPLEMENTAL TABLE 1

Distribution of concomitant diagnoses associated with endometriosis.

Endometriosis + male factor	10,569 (41.8)
Endometriosis + tubal factor	7,401 (29.3)
Endometriosis + diminished ovarian reserve	5,558 (22.0)
Endometriosis + PCOS or ovulation disorder	3,686 (14.6)
Endometriosis + uterine factor	2,748 (10.9)
Endometriosis + noninfertile	632 (0.3)
Endometriosis + PGD	53 (0.2)
Endometriosis + other	6,115 (24.2)

Note: Values are number (percentage). PCOS = polycystic ovary disorder; preimplantation genetic diagnosis.

[a]Total percentages >100% owing to overlapping diagnoses.

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