

IMPACT OF ENDOMETRIOSIS ON FERTILITY AND ASSISTED REPRODUCTIVE TECHNOLOGY OUTCOMES: A SYSTEMATIC REVIEW AND META-ANALYSIS

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Abstract

Background: The effect of endometriosis on ovarian response and reproductive success is not always clear, and its effect on assisted reproductive technology (ART) outcomes is unclear.

Objective: To assess the effect of endometriosis on fertility and ART outcomes.

Methods: Comparative original studies of women with endometriosis and non-endometriosis controls were included. 21 reports from 20 independent parent studies were retained. Random effects models with restricted maximum likelihood estimation and Hartung–Knapp confidence intervals were used to pool risk ratios (RRs) and mean differences (MDs). Outcomes were separated according to their definitions and denominators.

Results: Four to nine studies were included in individual analyses. Endometriosis was associated with lower cumulative live birth (RR 0.84, 95% CI 0.73–0.95; $I^2=0.0\%$) and cumulative clinical pregnancy (RR 0.81, 95% CI 0.72–0.91; $I^2=0.0\%$). Women with endometriosis also had fewer retrieved oocytes (MD -1.61 , 95% CI -2.44 to -0.78 ; $I^2=77.7\%$). Differences were not statistically conclusive for live birth per treatment attempt or transfer (RR 0.86, 95% CI 0.68–1.08), clinical pregnancy (RR 0.91, 95% CI 0.81–1.03), pregnancy loss (RR 0.96, 95% CI 0.47–1.94), mature oocytes (MD -0.92 , 95% CI -1.88 to 0.04), or fertilized oocytes (MD -0.28 , 95% CI -0.60 to 0.05).

Conclusions: The cumulative reproductive success and the yield of oocytes were reduced in endometriosis, but there was no definitive effect on individual-attempt outcomes. Caution should be used when interpreting the results due to heterogeneity and the small number of studies.

Introduction

Endometriosis is a chronic, estrogen-dependent inflammatory disease in which endometrial tissue is found outside the uterine cavity. It is present in women at any age of their reproductive life and is linked to pelvic pain, dysmenorrhea, dyspareunia, decreased quality of life and infertility [5,11,36,40]. The clinical picture and the severity of the disease is very

variable, but one of the most important clinical features is the impairment of fertility. There is also some population-level evidence that surgically confirmed endometriosis is linked to decreased fertility throughout the reproductive lifespan, and decreased likelihood of a first birth [37].

The mechanisms of endometriosis-associated infertility are complex and likely not due to a

single anatomical or biological abnormality. Distorted tubo-ovarian anatomy and pelvic adhesions may affect the release of the oocytes, tubal transport and fertilization. Furthermore, chronic inflammation, oxidative stress, changes in the composition of follicular fluid, dysfunction of steroidogenesis and ovarian function can have a negative impact on ovarian reserve and on the competence of the oocytes [7,15,22]. There has also been some evidence of embryo development and endometrial receptivity changes in women with endometriosis, but the clinical significance of these changes is not consistent [12,16,19]. The relative importance of each mechanism could vary depending on the disease phenotype, severity, ovarian involvement, previous surgery, age and coexisting reproductive disorders.

Treatment of endometriosis-associated infertility may involve expectant management, surgery, ovulation induction, intrauterine insemination or assisted reproductive technology (ART), depending on the age of the patient, ovarian reserve, severity of the disease, and length of infertility [5,34]. Some anatomical problems with endometriosis can be overcome with in vitro fertilization or intracytoplasmic sperm injection, but the same cannot be said for poor ovarian response or poor oocyte competence. The use of surgery prior to ART is also controversial. Surgery for ovarian endometrioma can also lead to a decrease in ovarian reserve and functional ovarian tissue, and may not always result in an improvement in live birth rates [3,9].

There have been conflicting results from clinical trials on the outcomes of ART in women with endometriosis. Some studies have reported decreased numbers of retrieved or matured oocytes, decreased ovarian response and decreased availability of viable embryos [8,23,28,39]. Others have reported similar results for pregnancy and live-birth rates following embryo transfer compared to women without endometriosis, even when embryo quality is monitored by transferring euploid blastocysts [6]. Other studies that have focused on women with diminished ovarian reserve, early-stage disease or certain endometriosis phenotypes have yielded inconsistent results for oocyte yield, fertilization, clinical pregnancy and

live birth [13,17,21,27]. Such differences may be due to differences in the definition of the disease, stage of disease, comparator populations, stimulation protocols, embryo-transfer practices and previous surgical treatment.

Another significant source of variation is the denominator used to determine reproductive outcomes. Live birth can be reported per woman, per treatment cycle started, per oocyte retrieval or per embryo transfer, while cumulative live birth includes fresh and frozen embryo transfers from one or more treatment cycles. Therefore, the outcomes per transfer might seem relatively well preserved even if there is a reduction in the number of oocytes or embryos available throughout the entire treatment. In recent cohort studies, therefore, cumulative pregnancy and live-birth outcomes have been focused on, instead of the outcome of a single transfer [1,2,25,31]. Frozen embryo-transfer populations also indicate that endometriosis may interact with other factors of infertility and adenomyosis, and that these should be considered separately [33,38].

These uncertainties have not been completely addressed by previous systematic reviews and meta-analyses. Previous studies indicated that endometriosis might have a negative impact on the process of fertilization and implantation, and more recent syntheses indicated either a smaller effect or an effect specific to the type of outcome [4,24,26]. Other factors such as differences between fresh and frozen embryo transfer, previous surgery, disease phenotype and the use of autologous or donated oocytes can further influence reproductive outcomes [10,29]. Pooled estimates can also be misleading if incompatible denominators are used or if multiple studies are conducted on the same population but with different time periods.

A full synthesis that differentiates between single-attempt outcomes and cumulative outcomes, and separates reproductive events by the correct denominator is therefore needed. The aim of this systematic review and meta-analysis was to assess the effects of endometriosis on fertility and ART outcomes, such as live birth, cumulative live birth, clinical pregnancy, cumulative clinical pregnancy, pregnancy loss, oocyte yield, mature oocyte yield and

fertilization. The review was also designed to assess if there was variation in disease phenotype or in the population and outcome denominator across the available evidence that could account for this.

Methods

Study Design and Reporting

This systematic review and meta-analysis was performed following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA 2020) guidelines [30]. The review focused on the impact of endometriosis on natural fertility and assisted reproductive technology (ART) outcomes.

Search Strategy

The databases PubMed/MEDLINE, Embase, Scopus, Web of Science and the Cochrane Central Register of Controlled Trials were searched since their inception until 29 August 2026. The eligible studies and relevant reviews were subjected to backward and forward citation searching and Google Scholar was used for supplementary searching. The search included the use of controlled vocabulary and free text terms for the following: “endometriosis”, “ovarian endometrioma”, “deep infiltrating endometriosis”, “infertility”, “subfertility”, “fertility”, “assisted reproductive technology”, “in vitro fertilization”, “intracytoplasmic sperm injection”, “embryo transfer”, “pregnancy”, “live birth”, “oocyte” and “fertilization”. There were no geographical restrictions.

Eligibility Criteria

Original comparative studies were eligible if they contained an endometriosis group of women of reproductive age who had been diagnosed with clinically, surgically, ultrasonographically or histologically diagnosed endometriosis and a comparator group of women without endometriosis. Eligible outcomes were live birth, cumulative live birth, clinical pregnancy, cumulative clinical pregnancy, pregnancy loss, oocyte yield, mature or metaphase-II oocytes and fertilized or two-pronuclear oocytes.

Randomized trials or prospective or retrospective comparative cohort studies were

taken into account. Reviews, meta-analyses, editorials, conference abstracts with inadequate data, case reports, animal studies and non-comparative studies were not included. Only studies that included only adenomyosis were included. Biomarkers, surgical interventions or stimulation protocols were not included in the primary endometriosis-versus-control meta-analyses, but were included in the within-endometriosis comparisons for qualitative review.

Study Selection and Parent-Study Identification

Records were deduplicated before title and abstract screening. Full text was assessed for potentially eligible articles, according to the prespecified criteria. Reports of one parent study were linked if they were multiple publications from the same population. The 2024 and 2025 Alson reports were not entered as separate samples in the same model, but were considered as a single parent cohort, and the 2024 report was used as a baseline to compare with the 2025 report.

21 independent parent studies (21 eligible reports) were retained. There were four parent studies published from 2022 to 2026. Variations in the number of studies contributing to each pooled analysis were due to differences in outcomes, comparators, reporting format and denominator units between studies.

Data Extraction

Information from the study characteristics and outcome data was transferred to a standardized format. Data collected consisted of author, year of publication, study design, setting, diagnostic method, endometriosis phenotype and severity, comparator, sample size, ART protocol, outcome definition, denominator, and follow-up period. Event and total counts were obtained for dichotomous outcomes, and means and standard deviations were obtained for continuous outcomes.

Percentages with invalid integer denominators, conditional outcomes with unconvertible summary statistics, and medians with unconvertible summary statistics were not included in the corresponding conventional meta-analyses. Survival estimates that could not

be converted to ordinary proportions were not entered into the corresponding conventional meta-analyses. Estimates adjusted for separately. If more than one clinically appropriate comparison was reported in a study, only one of these comparisons was used in a particular model to prevent double counting.

Outcomes

Main outcomes were live birth per treatment attempt or embryo transfer, and cumulative live birth per woman. Secondary outcomes were clinical pregnancy, cumulative clinical pregnancy, pregnancy loss, number of retrieved oocytes, number of mature or metaphase-II oocytes, and number of fertilized or two-pronuclear oocytes.

The denominator was used to divide outcomes. The distinction between live birth per woman or initiated cycle and live birth per embryo transfer and cumulative live birth was made. Pregnancy-based denominators were used to analyze pregnancy loss. ART outcomes were not included in the analysis of natural-fertility outcomes.

Statistical Analysis

The risk ratios (RR) with 95% confidence intervals (CI) were computed for dichotomous outcomes. Continuous outcomes reported in similar units were reported as mean differences (MDs) with 95% CIs. Restricted maximum likelihood estimation of between-study variance was used to fit random-effects models. Pooled confidence intervals were adjusted for Hartung-Knapp. A continuity correction of 0.5 was used for comparisons that had zero-event cells.

The Cochran Q test, I^2 statistic, and between-study variance (τ^2) were used to assess statistical heterogeneity. Prediction intervals were computed when applicable to provide information about the distribution of effects in a similar future study. A two-sided p-value of < 0.05 was considered to be statistically significant.

Subgroup analyses were performed for exploratory purposes by outcome denominator. Studies with repeated-cycle observations and outcome measures that were proxies for imperfect measures were not included in the sensitivity analyses. Cumulative live birth was assessed by leave-one-out analysis to assess the influence of individual studies. Formal funnel-plot asymmetry testing was not performed as there were not enough independent studies in the pooled analyses to provide adequate power and may be misleading.

Risk of bias and certainty of evidence

We used the ROBINS-I framework [35] to assess risk of bias in non-randomized studies and an appropriate trial-specific tool for randomized studies. Judgments of risk of bias and certainty of evidence did not affect the reported statistical calculations. They are required to complete their final study-level assessments before manuscript submission.

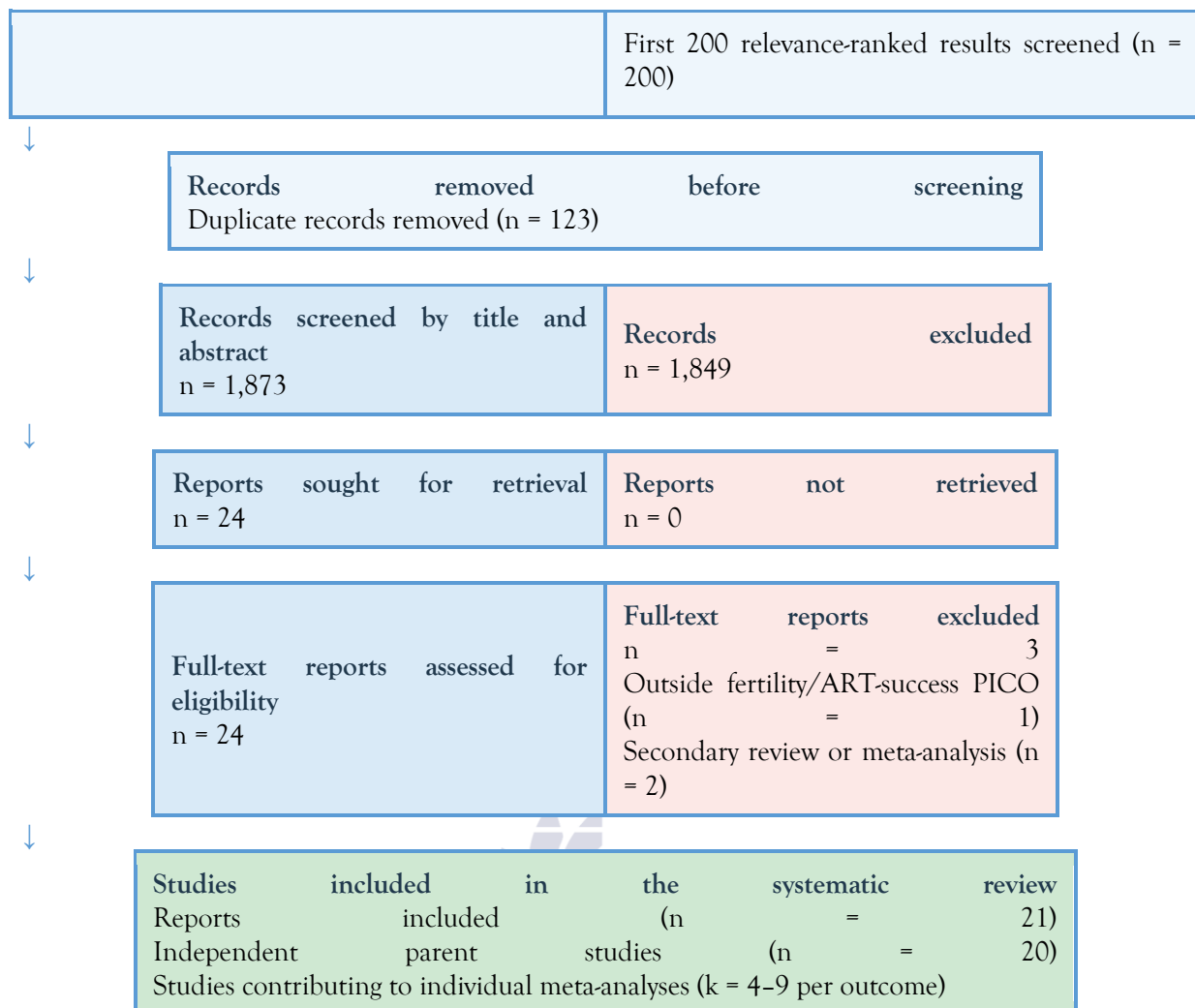
Results

Study Selection

A complete-text corpus consisted of 24 reports. Three reports were excluded after full-text assessment: one original cohort assessed adverse pregnancy outcomes after conception and was not within the fertility/ART success PICO, and two reports were secondary reviews. Twenty-one reports were retained, which were eligible reports from 20 independent parent studies. The 2024 and 2025 Alson publications were from a common cohort of parents and were considered one parent study. The 14 parent studies published between 2022 and 2026 accounted for 70.0% of the total number of parent studies. Database-level identification, deduplication, and title/abstract screening counts were not saved and were not reconstructed.

Figure 1. PRISMA 2020-style flow diagram for the auditable full-text corpus.

Records identified from databases and registers		Records identified through other methods	
PubMed/MEDLINE	(n = 724)	Google Scholar: approximately 15,500 results displayed	
Cochrane CENTRAL	(n = 1,072)		
Total database records (n = 1,796)			



Note. PubMed/MEDLINE and Cochrane CENTRAL searches yielded 1,796 records. Google Scholar displayed approximately 15,500 results; the first 200 relevance-ranked results were screened. The title/abstract exclusion count (n = 1,849) was arithmetically reconciled as records screened minus reports sought. Searches were executed on 4 September 2026 with a publication-coverage cutoff of 29 August 2026. The Alson 2024 and 2025 reports were treated as one overlapping parent study.

Statistical-analysis note

For dichotomous outcomes, risk ratios (RRs) were calculated and for continuous count outcomes, mean differences (MDs) were calculated. Random-effects models were estimated using restricted maximum likelihood (REML) and Hartung-Knapp confidence intervals. The tables with no cells were given a continuity correction of 0.5. Whenever possible, outcomes were broken out by clinical definition and denominator. A single matching contrast was selected for each independent parent study and included in a model. Negative MDs and RRs <1 are worse in the endometriosis group.

Study inclusion for quantitative synthesis

Twenty independent parent studies were included in the systematic review, with 21 eligible reports (due to an overlapping cohort in the Alson 2024 and 2025 reports). Seven of the parents were published (70.0%) from 2022 to 2026. The number of studies included in individual meta-analyses varied from four to nine studies due to differences in outcome definitions, reporting formats, comparators and denominator units. Percentages without exact numbers of events, outcomes with un-resolved conditional denominators, medians without means and SDs, and comparisons of within-

endometriosis treatments were not included in the main etiologic models.

Summary of pooled results

Table 1. Summary of random-effects meta-analyses.

Outcome	k	Measure	Pooled effect	95% CI	P	I ²	τ^2	95% prediction interval
Live birth per treatment attempt or transfer	5	Risk ratio	0.86	0.68 to 1.08	0.136	57.7%	0.018	0.52 to 1.41
Cumulative live birth per woman	5	Risk ratio	0.84	0.73 to 0.95	0.019	0.0%	0.000	0.72 to 0.97
Clinical pregnancy	9	Risk ratio	0.91	0.81 to 1.03	0.121	42.7%	0.006	0.73 to 1.14
Cumulative clinical pregnancy per woman	4	Risk ratio	0.81	0.72 to 0.91	0.011	0.0%	0.001	0.66 to 0.99
Pregnancy loss per pregnancy	4	Risk ratio	0.96	0.47 to 1.94	0.861	75.9%	0.129	0.16 to 5.87
Oocytes retrieved	9	Mean difference	-1.61	-2.44 to -0.78	0.002	77.7%	0.808	-3.90 to 0.68
MII oocytes	8	Mean difference	-0.92	-1.88 to -0.04	0.058	81.5%	0.991	-3.55 to 1.71
2PN or fertilized oocytes	6	Mean difference	-0.28	-0.60 to 0.05	0.082	0.0%	0.000	-0.63 to 0.08

Live-birth outcomes

Five studies contributed to the analysis of live birth per treatment attempt or embryo transfer. The association with endometriosis was not statistically significant with a lower point estimate (RR 0.86, 95% CI 0.68–1.08; $p=0.136$). Heterogeneity was moderate ($I^2=57.7\%$, $\tau^2=0.018$; Q-test $p=0.051$), and the 95% prediction interval crossed the null (0.52–1.41). The cumulative live birth per woman was reported in five independent studies. The cumulative live-birth probability was significantly reduced in women with endometriosis (RR 0.84, 95% CI 0.73–0.95; $p=0.019$). Statistical heterogeneity was not detected ($I^2=0.0\%$, $\tau^2=0.000$; Q-test $p=0.595$). The prediction interval was still within the range of less than 1 (0.72–0.97).

Clinical-pregnancy outcomes

Clinical-pregnancy data were provided by nine studies. The pooled RR was 0.91 (95% CI 0.81–1.03; $p=0.121$), showing no statistically conclusive difference. Heterogeneity was moderate ($I^2=42.7\%$, $\tau^2=0.006$; Q-test $p=0.083$). Four studies reported cumulative clinical pregnancy/woman. The cumulative clinical-pregnancy probability (CP) was significantly lower in women with endometriosis (RR 0.81, 95% CI 0.72–0.91; $p=0.011$) and there was no important observed heterogeneity ($I^2=0.0\%$, $\tau^2=0.001$).

Pregnancy loss

Pregnancy loss data was available from four studies based on pregnancy denominators. There was no statistically significant difference between the pooled estimate (RR 0.96, 95% CI 0.47–1.94; $p=0.861$). Heterogeneity was substantial ($I^2=75.9\%$, $\tau^2=0.129$; Q-test $p=0.006$), and the prediction interval was very wide (0.16–5.87). The result should be interpreted with caution as positive pregnancy and clinical pregnancy and fresh-transfer pregnancy denominators were included in the definition.

Oocytes and fertilization Outcomes

Nine studies reported mean and SD for the number of oocytes. Women with endometriosis yielded significantly fewer oocytes (MD -1.61,

95% CI -2.44 to -0.78; $p=0.002$). There was considerable heterogeneity ($I^2=77.7\%$, $\tau^2=0.808$) and the prediction interval spanned no difference (-3.90 to 0.68), suggesting that the size and perhaps direction of the difference could differ in a new context.

In eight studies, the number of mature/MII oocytes was found to be lower in the endometriosis group, with the confidence interval just crossing the zero line (MD -0.92, 95% CI -1.88 to 0.04; $p=0.058$). Heterogeneity was high ($I^2=81.5\%$, $\tau^2=0.991$).

Fertilized/2PN oocyte data were provided by six studies. The pooled difference was not statistically conclusive (MD -0.28, 95% CI -0.60 to 0.05; $p=0.082$), with no observed statistical heterogeneity ($I^2=0.0\%$, $\tau^2=0.000$).

Denominator subgroup analyses

Table 2. Exploratory subgroup analyses according to outcome denominator.

Subgroup	K	RR	95% CI	P	I^2
Live birth – embryo-transfer denominator	3	0.86	0.50–1.50	0.368	75.3%
Live birth – initiated cycle or participant denominator	2	0.82	0.69–0.98	0.028	0.0%
Clinical pregnancy – embryo-transfer denominator	4	0.91	0.72–1.16	0.310	50.7%
Clinical pregnancy – initiated cycle, cycle, or participant denominator	5	0.91	0.70–1.18	0.357	47.6%

These subgroup results were exploratory. The live-birth initiated-cycle/participant subgroup contained only two studies; its apparently significant estimate should not be treated as definitive. Neither clinical-pregnancy denominator subgroup showed a statistically conclusive association.

Sensitivity analyses

Excluding Radzinsky 2019, which included repeated cycles within women, did not materially change the oocyte-yield result (MD -1.57, 95% CI -2.52 to -0.61; $I^2=79.7\%$).

Excluding the Zimmermann embryo-count proxy from the fertilized/2PN analysis produced a similar non-significant estimate (MD -0.39, 95% CI -0.81 to 0.03; $I^2=0.0\%$).

Table 3. Leave-one-out sensitivity analysis for cumulative live birth.

Omitted study	RR	95% CI	I ²
Bourdon 2018	0.84	0.71–0.98	0.0%
Deng 2022	0.82	0.70–0.96	0.0%
Zimmermann 2023	0.83	0.71–0.98	0.0%
Alson 2024	0.85	0.72–1.01	0.0%
Lu 2025	0.85	0.69–1.03	0.0%

The direction of the cumulative live-birth association was stable in all leave-one-out analyses. Statistical significance was attenuated when Alson 2024 or Lu 2025 was omitted, reflecting reduced precision rather than a reversal of direction.

Publication-bias assessment

No formal funnel-plot asymmetry testing was done as none of the meta-analyses contained at least 10 independent studies. Such tests would have low power and could be misleading, as there are only four to nine studies per outcome.

Overall Interpretation

The quantitative data suggest endometriosis is most consistently linked to decreased cumulative reproductive success and decreased oocyte yield. No statistically significant differences were observed for single-attempt live birth or clinical pregnancy, but there were significant differences for cumulative live birth and cumulative clinical pregnancy. This trend indicates that fewer oocytes or embryos available during a treatment cycle are associated with lower cumulative success, even if the success of each transfer is relatively maintained. Evidence of pregnancy loss was inconclusive and very heterogeneous.

Forest plots

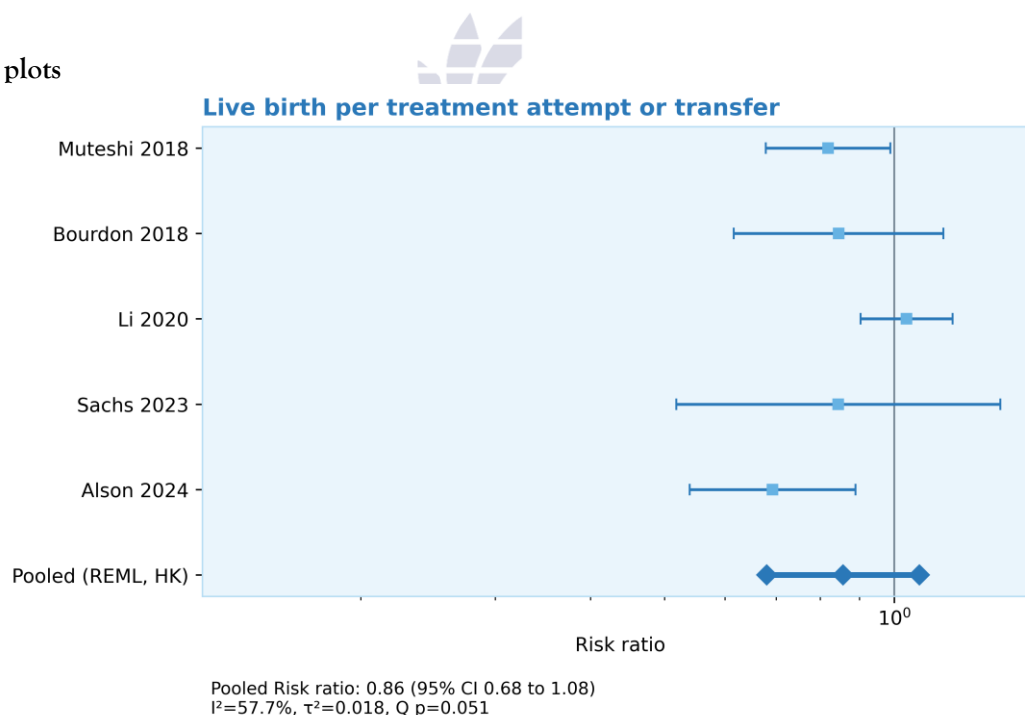


Figure 2. Live birth per treatment attempt or transfer

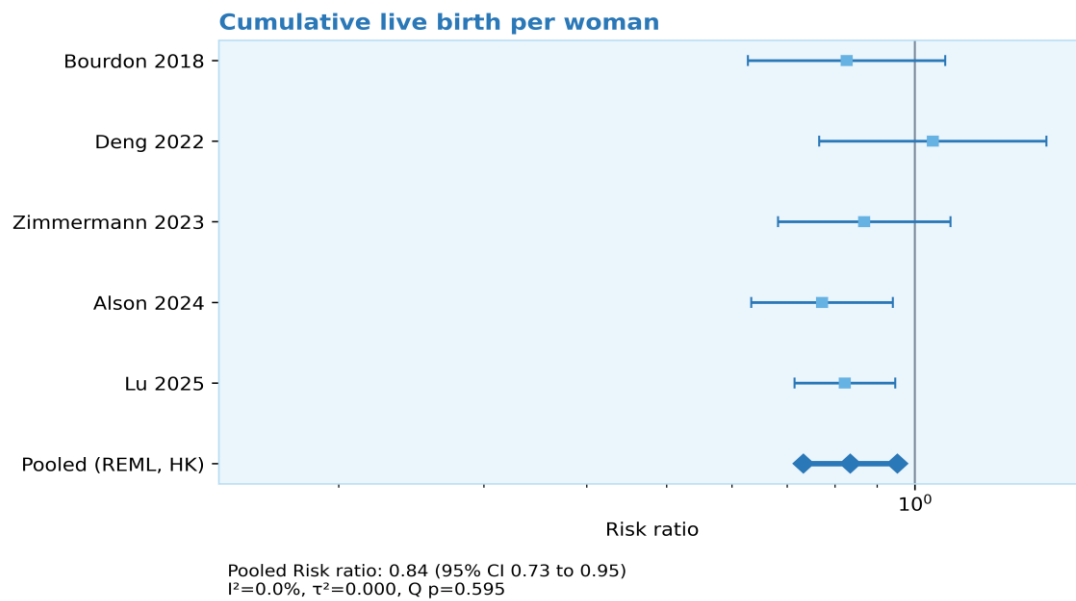


Figure 3. Cumulative live birth per woman.

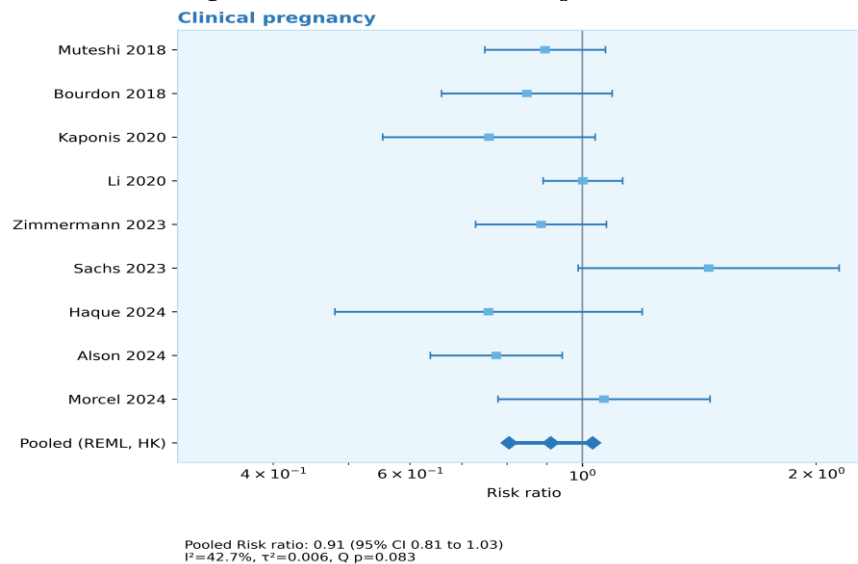


Figure 4. Clinical pregnancy

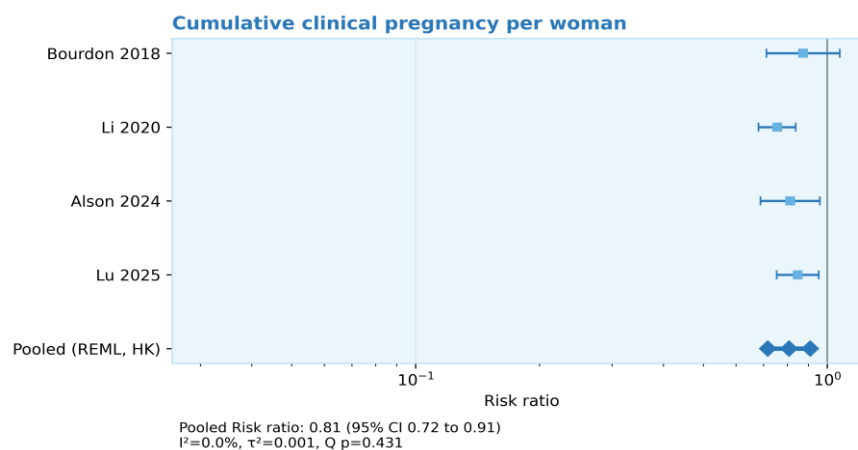


Figure 5. Cumulative clinical pregnancy per woman

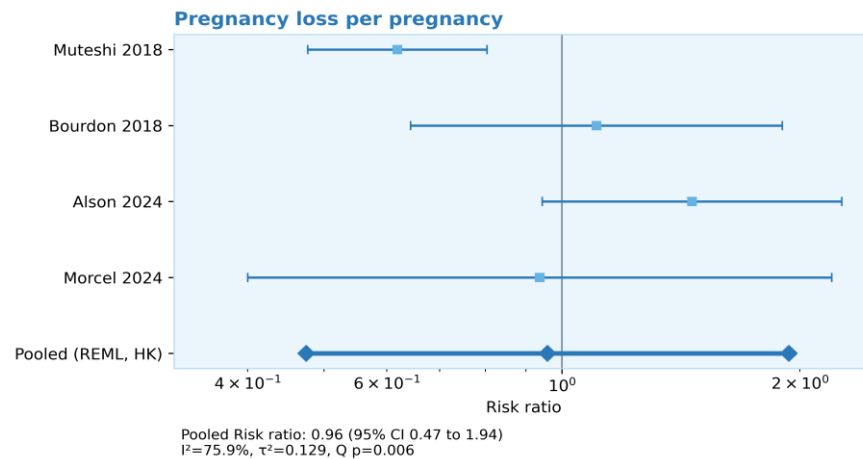


Figure 6. Pregnancy loss per pregnancy

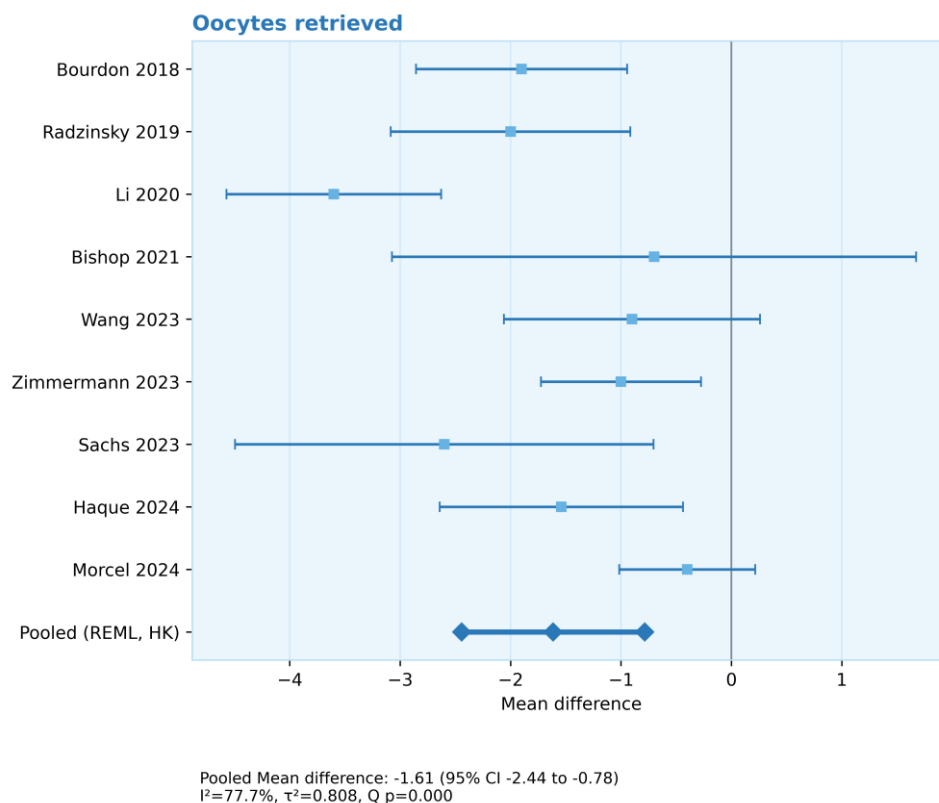


Figure 7. Number of oocytes retrieved

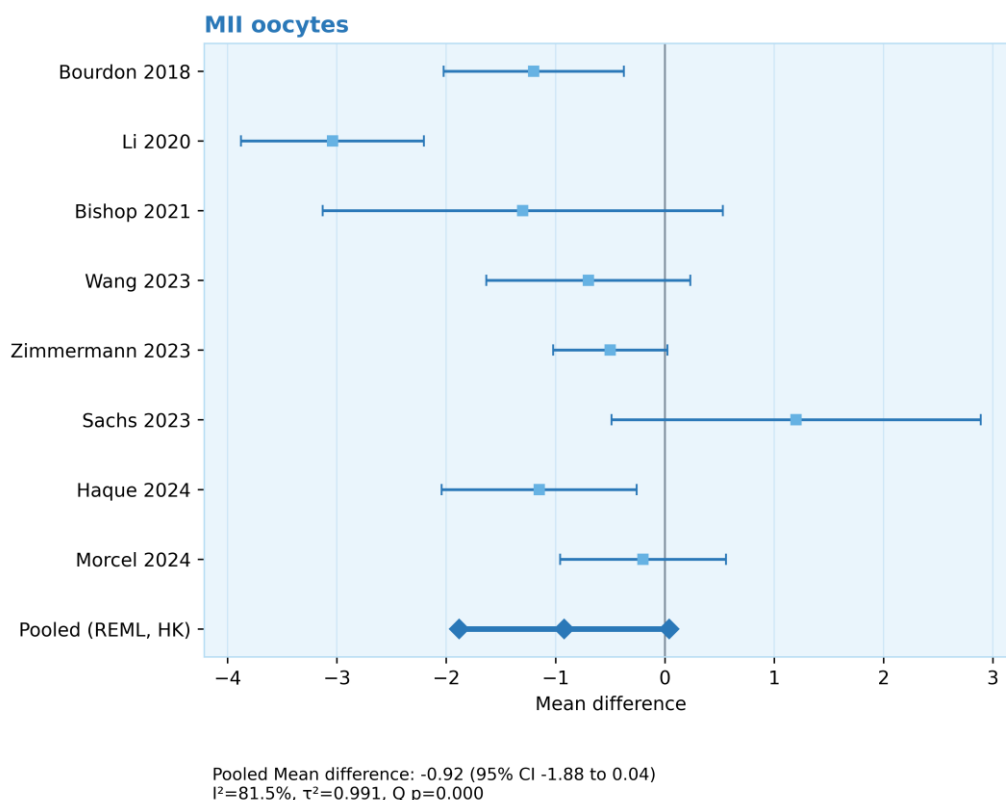


Figure 8. Number of mature/MI oocytes.

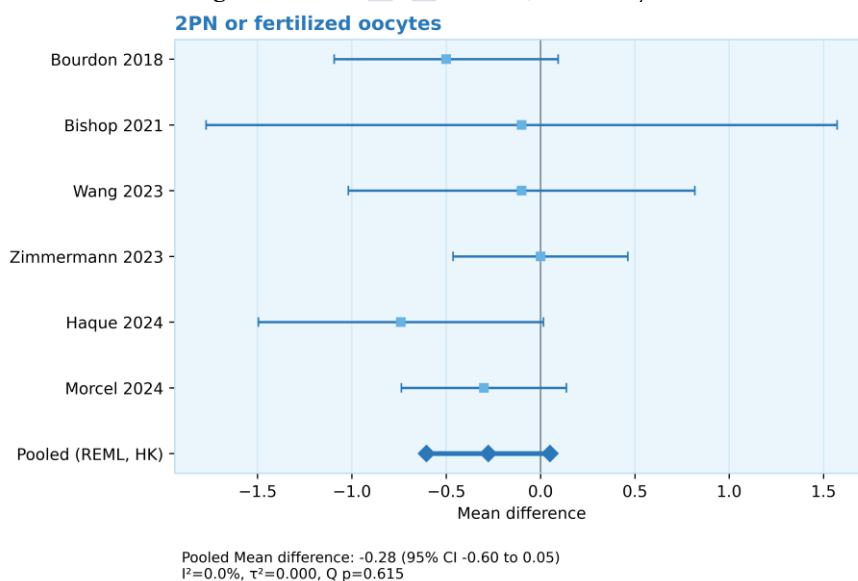


Figure 9. Number of fertilized/2PN oocytes

Discussion

Principal Findings

The results of this systematic review and meta-analysis suggest that endometriosis has a significant impact on overall reproductive success, but not necessarily on the success of each embryo transfer. The probabilities of cumulative live-birth and cumulative clinical-pregnancy were significantly lower in women

with endometriosis. Live birth and clinical pregnancy rates per treatment attempt or embryo transfer were numerically decreased but not statistically significant. This is clinically relevant as cumulative outcomes take into account the total reproductive potential of an ovarian stimulation cycle (fresh and subsequent frozen embryo transfers) while transfer-based outcomes only consider embryos that have been

transferred. The observed pattern is in line with recent cohort studies showing decreased cumulative reproductive success in women with endometriosis, but the magnitude of the association has been inconsistent across studies, depending on disease phenotype, diagnostic method, age, comparator population and denominator of analysis [1,2,13,25,27,31,39].

The number of oocytes retrieved was about 1.6 fewer in the presence of endometriosis. The number of mature oocytes was also reduced, but the confidence interval was quite wide and contained no difference, and the numbers of fertilized or two-pronuclear oocytes were not significantly decreased. The results indicate that the main laboratory effect is not on the level of the competence of fertilization of mature oocytes, but on the level of ovarian response and availability of oocytes. In women with ovarian endometriomas, ovarian endometriosis and ovarian diminished ovarian reserve, similar reductions in the number of oocytes have been reported [13,18,23,25]. However, the prediction interval for oocyte yield is broad and the heterogeneity is large, suggesting that this effect is not consistent in clinical situations.

The decreased ovarian response may be due to several biological mechanisms. Chronic inflammation, oxidative stress, disruption of steroid signaling, fibrosis and disruption of the ovarian microenvironment are all associated with endometriotic lesions. These processes could affect follicular recruitment, the function of granulosa cells, mitochondrial activity and oocyte maturation [7,11,15,16]. Ovarian endometriomas can also lead to mechanical distortion, local tissue damage and loss of functional ovarian cortex, and previous cystectomy can also deplete the follicular pool [8,18,22]. Endometriosis is also now known to be a heterogeneous systemic disease and not just a localized pelvic condition, which could account for the wide variation in reproductive outcomes between superficial, ovarian and deep infiltrating phenotypes [36,40].

The lack of a statistically significant difference in the number of fertilized oocytes does not imply that the competence of the oocytes or embryos is not completely affected. Some individual studies have described stage-dependent variations in the number of mature oocytes, embryo

development, quality of the cleavage stage and fertilization rate [14,19,20]. But the laboratory results are highly dependent on maternal age, stimulation protocol, ovarian reserve, fertilization method, embryo-culture methods and unit of analysis. Percentages per oocyte cannot be added directly to the mean numbers per woman or treatment cycle. This methodological variability is likely to have also led to some differences in individual reports and the overall results [12,16,22].

The relatively good results seen following embryo transfer may suggest that there is not a consistent reduction in endometrial receptivity after the availability of a transferable embryo. There have been few or no reports of a decrease in live birth rate due to endometriosis alone in studies using frozen transfer of euploid blastocysts and/or oocyte-donation cycles [6,29]. Results of embryo morphokinetic and receptivity studies are not as consistent, with some reporting changes in embryo development or embryo implantation, and others reporting similar transfer results [10,12,19]. The present results therefore do support a model in which the availability of oocytes or embryos is reduced, resulting in a decrease in cumulative success, but the implantation potential of selected embryos may be relatively maintained.

There was no significant association between pregnancy loss and endometriosis, although this was not precise and was very heterogeneous. The studies that contributed to this analysis had varying starting denominators, such as positive pregnancy tests, clinical pregnancies and pregnancies after fresh transfer. In certain cohorts, there have been reports of higher miscarriage rates following selected populations, such as unbiopsied frozen blastocyst transfer, while others have not observed any significant difference [33,38]. However, the large confidence intervals and prediction intervals in this analysis do not allow for a definite statement about pregnancy loss.

Comparison with Existing Evidence

Previous meta-analyses tended to show a lower rate of fertilization, implantation, clinical-pregnancy or live-birth rates in women with endometriosis, especially in advanced endometriosis, but with conflicting results

depending on the studies included and the methods used [4]. Other more recent reviews have also indicated that ovarian endometriosis affects the number of oocytes retrieved and matured, but may not affect the embryo competence or pregnancy outcome after embryo transfer [24,26]. The present analysis builds upon this evidence by stratifying cumulative outcomes from outcomes reported per cycle or transfer, and keeping compatible definitions of the denominator within each pooled model.

The difference between cumulative and transfer specific outcomes might help to explain some of the conflicting results found in the literature. A single transfer study may only include women who have embryos that are appropriate for transfer and exclude women with cancelled cycles, failed fertilization or no embryo(s) available for transfer. This list can be misleading in terms of the total reproductive burden of endometriosis. Cumulative live birth takes into account more of the treatment pathway and may therefore give a more patient-centered estimate of the probability of a live birth from an initiated treatment course [1,2,31]. The reduced cumulative outcomes in this analysis are also consistent with reports of poor ovarian response or fewer embryos retrieved, but good pregnancy rates per transfer [17,28,32].

Clinical heterogeneity due to disease severity and disease phenotype still exist. The relationship between moderate to severe and minimal to mild endometriosis with ovarian response and cumulative success is inconsistent, with poorer ovarian response and lower cumulative success rates seen with moderate to severe disease [14,21,25,27,39]. Women with endometriomas or deep disease may be excluded from ultrasound-defined cohorts and symptomatic or advanced disease may be overrepresented in surgically confirmed cohorts. The differences in the diagnostic pathways also impact on the classification of cases and generalisability of study findings.

The impact of surgery prior to assisted reproduction is also complicated. Surgery can help alleviate pain, restore the anatomy or provide access to the follicles, but cystectomy can cause a loss of healthy ovarian tissue and a decrease in ovarian reserve. There is no consistent evidence that routine surgery prior to

IVF has a beneficial effect on live-birth rates [3,9]. Previous ovarian surgery was often linked to poor ovarian response in the cohorts included, but it is possible that this is due to disease severity [8,18]. Current evidence and clinical guidance therefore support the individual approach to treatment based on symptoms, age, ovarian reserve, lesion characteristics, previous surgery and reproductive priorities over routine surgery for all endometriomas prior to IVF [5,34].

Clinical Implications

The results should be presented in a neutral way. Many women with endometriosis become pregnant and live birth with ART and it does not imply that ART is not going to be successful. However, patients should be told that they might not have as many oocytes to harvest and might have a slightly lower chance of success over a series of treatments. The counselling based on pregnancy per embryo transfer may give an incomplete estimate as it does not take into consideration the number of embryos available for transfer or the number of frozen embryos available for subsequent transfer, or cycle cancellation.

The following factors should be taken into account when planning the treatment of the patient in the clinic: age, ovarian reserve, disease phenotype, previous ovarian surgery, bilateral ovarian involvement and the number of usable embryos. Women with low ovarian reserve or women who have had more than one endometrioma may need to be referred to reproductive specialists earlier and have a discussion with them about fertility preservation. But the evidence is not strong enough to justify denying ART because of endometriosis, automatically choosing a particular stimulation protocol or routinely performing ovarian surgery prior to ART. Individualization of protocol is recommended since the evidence that extended gonadotropin-releasing hormone suppression or specific stimulation protocol is beneficial for live birth is still not clear [5,21,34].

It is also important to note that there is a difference between natural fertility and ART outcomes. The findings from the nationwide register indicate that there may be a negative association between surgically confirmed

endometriosis and first birth rate and overall fertility throughout the reproductive life course [37]. ART can overcome some anatomical and fertilization barriers, but cannot overcome the diminished ovarian reserve or limited number of oocytes. Therefore, cumulative ART success should be considered in the context of the reproductive history of each patient, not as a result of a single treatment cycle.

Strengths and Limitations

One of the key features of this review was the ability to split clinically distinct outcomes and denominator units. The live birth per transfer was not simply added to cumulative live birth per woman and pregnancy loss was analysed with pregnancy denominators. To minimize the possibility of double counting of overlapping samples, only one compatible contrast was included in a given model from each independent parent study. Robustness and clinical variability of the findings were explored using random-effects models, heterogeneity estimates, prediction intervals, and denominator-based subgroup analyses and leave-one-out sensitivity analyses. The selection and reporting of studies were done following the PRISMA 2020 guidelines [30].

There are a number of constraints to be taken into account. The majority of the studies that contributed were observational, and thus were susceptible to selection bias, residual confounding and differences in treatment indication. Not all of the following factors were controlled: age, ovarian reserve, and disease severity, duration of infertility, previous surgery, adenomyosis and male factor infertility. Diagnostic criteria were based on surgery, histology or ultrasound or clinical records; and control groups comprised women with tubal, male-factor, unexplained or other causes of infertility. These differences restrict the ability to make causal inferences.

There was also some variation in the reporting of outcomes. Some studies reported results per woman, per initiated cycle, per oocyte retrieval, per embryo transfer, or per pregnancy, and some studies reported results per woman, per initiated cycle, per oocyte retrieval, per embryo transfer, or per pregnancy, but did not account for within-woman correlation. There were several

potentially relevant results that could not be pooled as percentages, medians, or adjusted estimates or incompletely defined denominators were available. These restrictions led to a decrease in the number of studies that were included in each synthesis and to some heterogeneity.

There was significant between-study heterogeneity for the pregnancy-loss and the oocyte outcomes, and the prediction intervals for each of these outcomes were wide, ranging from clinically important effects to no difference. Funnel-plot asymmetry tests were not performed because there were no outcomes with at least 10 independent studies. Selective reporting and small study effects can therefore not be ruled out. The observational evidence should be interpreted with the use of an appropriate risk of bias assessment (e.g., ROBINS-I) and certainty ratings should consider inconsistency, imprecision and residual confounding [35].

The second is that the evidence base is continually changing. Large cohorts and laboratory studies recently published may yield more accurate estimates, but may also involve overlapping clinical populations or cycle-level observations [20,31]. The reports must be therefore tied at the parent-study level, as was done for the overlapping Alson publications [1,2]. Otherwise, the cumulative results may be over-represented statistically.

Implications for Future Research

Standardization of definitions of live birth, cumulative live birth, clinical pregnancy, miscarriage, implantation and cycle cancellation should be used in future studies. Ideally, outcomes should be reported per woman and per ovarian-stimulation cycle, and fresh and frozen transfers should be reported to the cycle they were initiated from. To allow for inclusion in future meta-analyses, the number of events, denominators, means and standard deviations should be provided.

Future multicenter studies should include stratification of superficial, ovarian and deep infiltrating endometriosis and include documentation of disease stage, laterality, endometrioma size, adenomyosis, ovarian reserve, previous surgery and infertility

diagnosis. Repeated cycles in women should be taken into account in analyses and major prognostic factors should be adjusted. Comparisons with euploid embryo transfer and donor oocytes and fertility preservation may help to differentiate the effects of ovarian response, embryo competence and endometrial receptivity.

Patient-centered cumulative outcomes should also be a focus of research, rather than focusing primarily on pregnancy per transfer. When comparing direct comparisons of surgery, expectant management and immediate ART, live birth, time to pregnancy, ovarian reserve, treatment burden, complications, and cost-effectiveness should be included. Mechanistic studies of follicular inflammation and oocyte competence are useful, but should be related to clinically relevant reproductive outcomes and not be viewed as stand-alone.

Conclusion

Lower cumulative live-birth and clinical-pregnancy probabilities were found to be associated with endometriosis, as well as fewer retrieved oocytes. However, live birth and clinical pregnancy per individual treatment attempt/embryo transfer did not significantly decrease, and no significant differences were observed for mature oocytes, fertilized oocytes, or pregnancy loss. The results indicate that endometriosis may harm the number of reproductive opportunities created during ART, and may have a less uniform impact on the success of a chosen embryo transfer. The clinical and methodological diversity should be taken into account and interpreted with caution. Counselling and treatment should, therefore, be tailored to the individual, based on age, ovarian reserve, disease phenotype, previous surgery and reproductive priorities, and future studies should employ woman-level cumulative outcomes.

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