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Reproductive, obstetric, and perinatal outcomes of women with adenomyosis and endometriosis: a systematic review and meta-analysis

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BACKGROUND: The reproductive impact of adenomyosis and endometriosis is widely researched but the extent of these impacts remains elusive. It has been demonstrated that endometriosis, in particular, is known to result in subfertility but endometriosis and adenomyosis are increasingly linked to late pregnancy complications such as those caused by placental insufficiency. At the molecular level, the presence of ectopic endometrium perturbs the endometrial hormonal, cellular, and immunological milieu, negatively influencing decidualization, placentation, and developmental programming of the embryo. It is unclear if and how such early aberrant reproductive development relates to pregnancy outcomes in endometriosis and adenomyosis.

OBJECTIVE AND RATIONALE: The aims of this systematic review and meta-analysis were to (i) investigate the association of adenomyosis and endometriosis with fertility, obstetric, and neonatal outcomes of women through both assisted reproduction and natural conception and (ii) determine whether endometriosis disease subtypes have specific impacts on different stages of the reproductive process.

SEARCH METHODS: A systematic literature review of NHS evidence electronic databases and the Cochrane database identified all comparative and observational studies between 1980 and December 2018 in any language on adenomyosis and endometriosis with fertility, obstetric, and neonatal outcomes (23 search terms used). A total of 104 papers were selected for data extraction and meta-analysis, with use of Downs and Black standardized checklist to evaluate quality and bias.

OUTCOMES: We found that endometriosis consistently leads to reduced oocyte yield and a reduced fertilization rate (FR), in line with current evidence. Milder forms of endometriosis were most likely to affect the fertilization (FR OR 0.77, CI 0.63–0.93) and earlier implantation processes (implantation rate OR 0.76, CI 0.62–0.93). The more severe disease by American Society for Reproductive Medicine staging (ASRM III and IV) influenced all stages of reproduction. Ovarian endometriosis negatively affects the oocyte yield (MD −1.22, CI −1.96, −0.49) and number of mature oocytes (MD −2.24, CI −3.4, −1.09). We found an increased risk of miscarriage in both adenomyosis and endometriosis (OR 3.40, CI 1.41–8.65 and OR 1.30, CI 1.25–1.35, respectively), and endometriosis can be associated with a range of obstetric and fetal complications including preterm delivery (OR 1.38, CI 1.01–1.89), caesarean section delivery (OR 1.98 CI 1.64–2.38), and neonatal unit admission following delivery (OR 1.29, CI 1.07–1.55).

WIDER IMPLICATIONS: Adenomyosis and the subtypes of endometriosis may have specific complication profiles though further evidence is needed to be able to draw conclusions. Several known pregnancy complications are likely to be associated with these conditions. The complications are possibly caused by dysfunctional uterine changes leading to implantation and placentation issues and therefore could potentially have far-reaching consequences as suggested by Barker's hypothesis. Our findings would suggest that women with these conditions should ideally receive pre-natal counselling and should be considered higher risk in pregnancy and at delivery, until evidence to the contrary is available. In order to expand our knowledge of these conditions and better advise on future management of these patients in reproductive and maternal medicine, a more unified approach to studying fertility and reproductive outcomes with longer term follow-up of the offspring and attention to the subtype of disease is necessary.

Key words: adenomyosis / endometriosis / fertility / obstetric outcome / perinatal outcome / neonatal outcome / healthy baby rate / pregnancy complications / Barker's hypothesis / developmental origins of health and disease

Introduction

Endometriosis and adenomyosis are characterized by the presence of endometrial stroma and glands outside the uterine cavity and within the myometrium, respectively. It affects up to 10% of reproductive age women and is present in 30–50% of women with infertility. The presence of such ectopic endometrial glands and stroma is associated with inflammation (Burney and Giudice, 2012), fibrosis, and aberrant angiogenesis.

Evidence is now emerging pertaining to the detrimental reproductive impact of endometriosis and adenomyosis in both natural as well as assisted conception. The negative impact on fertility is in part anatomical, where fibrosis and adhesion formation interfere with oocyte pick up and transportation, but there is also evidence of aberrant uterine contractility at the endometrium–myometrium interface interfering with favourable implantation. Deranged inflammatory processes occur within the peritoneal, uterine, and endometrial environment (Gupta *et al*., 2008). Pathological processes involving inflammation, immune modulation, oxidative stress, extracellular matrix remodelling, aberrant angiogenesis, and genetic and epigenetic changes have been implicated in altered oocyte development, uterine receptivity, implantation, successful maintenance of pregnancy, and birth (Gupta *et al*., 2008; Kokcu, 2013; Vigano *et al*., 2015).

Evidence suggests that the suboptimal intrauterine environment created by an imbalance between embryotrophic and embryo toxic factors, in the context of a uterine and peritoneal inflammatory condition, influences embryo programming and alters fetal development and the growth trajectory after birth (Robertson *et al*., 2018). Mechanistically, such an influence may be via embryo bio-sensing interacting with the secretome of the reproductive tract (Cheong *et al*., 2013; Ng *et al*., 2018), coupled with uterine selectivity for implantation (Macklon and Brosens, 2014). Despite the biological plausibility and *in vitro* experimental evidence of endometriosis and adenomyosis on the early gamete, embryo, and fetal development, the overt clinical impact of the disease severity and subtypes on processes of folliculogenesis, oocyte quality, fertilization, implantation, and embryo quality are still controversial.

The potential impact on post-implantation stages of reproduction is also less understood. The association between endometriosis and adenomyosis and negative obstetric outcomes is, however, beginning to emerge (Maggiore *et al*., 2016; Maggiore *et al*., 2017, Lalani *et al*., 2018) but longer follow-up studies for obstetric and neonatal outcomes have not often been undertaken in the current literature; therefore, the true longitudinal impact of the diseases on late pregnancy and health of the offspring remains unclear. With growing interest in the developmental origin of health and disease theory, and knowledge that aberrant decidualization and placentation within a disturbed uterine environment can be linked not only to problems relating to placental insufficiency but also to childhood and adult diseases, the condition of endometriosis and adenomyosis in this context has not yet been explored. Studies looking at the influence of the aforementioned conditions on reproduction are often polarized, with either an obstetric or gynaecology focus, which does not provide a comprehensive overview of the entire reproductive process. There is also less attention to whether different subtypes of the disease have specific influence on different stages of the reproductive cycle thereby limiting our understanding of the effect profiles of disease subtypes. Given the prevalence and associative morbidity of adenomyosis and endometriosis, it is prudent that the reproductive impact is better understood.

The aims of this systematic review and meta-analysis are to (i) investigate the association of adenomyosis and endometriosis with reproductive, obstetric, and neonatal outcomes of women through both ART and natural conception and (ii) determine whether endometriosis disease subtypes have specific impacts on different stages of the reproductive course.

Methods

Search strategy

A systematic search of all published and unpublished studies from January 1980 to December 2018 with no language restriction was performed following Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines. The systematic review and meta-analysis were registered on PROSPERO (registration ID CRD42017083567).

Electronic searches

NHS evidence healthcare databases AMED, EMBASE, HMIC, BNI, Medline, CINAHL, and Health Business Elite as well the Cochrane electronic database were searched by two independent reviewers (J.H. & M.S.) using the keywords adenomyosis, endometriosis, endometrioma, deep infiltrating endometriosis (DIE), stage I, stage II, stage III, stage IV, and mild, moderate, and severe together with 23 search terms (Supplementary Table SI: Search terms) covering fertility, obstetric, and neonatal outcomes.

Other resources

Systematic reviews, meta-analyses, and literature reviews found in the search were hand-searched and cross-referenced by the reviewers for relevant articles.

Types of studies

We included cohort, case–control, and observational studies with an appropriate control group. No randomized control trials were returned by our search as expected. Systematic reviews and meta-analyses are included for qualitative and quantitative data where appropriate. We translated non-English papers and also included relevant case studies and material such as abstracts for conferences or other personal communication.

Types of participants

We included studies that examined the reproductive outcomes of women with adenomyosis or endometriosis who (NC) or through IVF with or without ICSCI (IVF/ICSI). Population studies, where the mode of conception cannot be differentiated to be exclusively NC as they were likely to include a subgroup of women undergoing ART, were analysed separately (NC/ART).

Adenomyosis studies were included if the diagnosis of adenomyosis was made by imaging modalities or by ICD 10 coded medical records (N80.0 endometriosis of the uterus). Studies on endometriosis and its subtypes were included if the diagnosis was made by visualization of lesions at laparoscopy/laparotomy, histology,

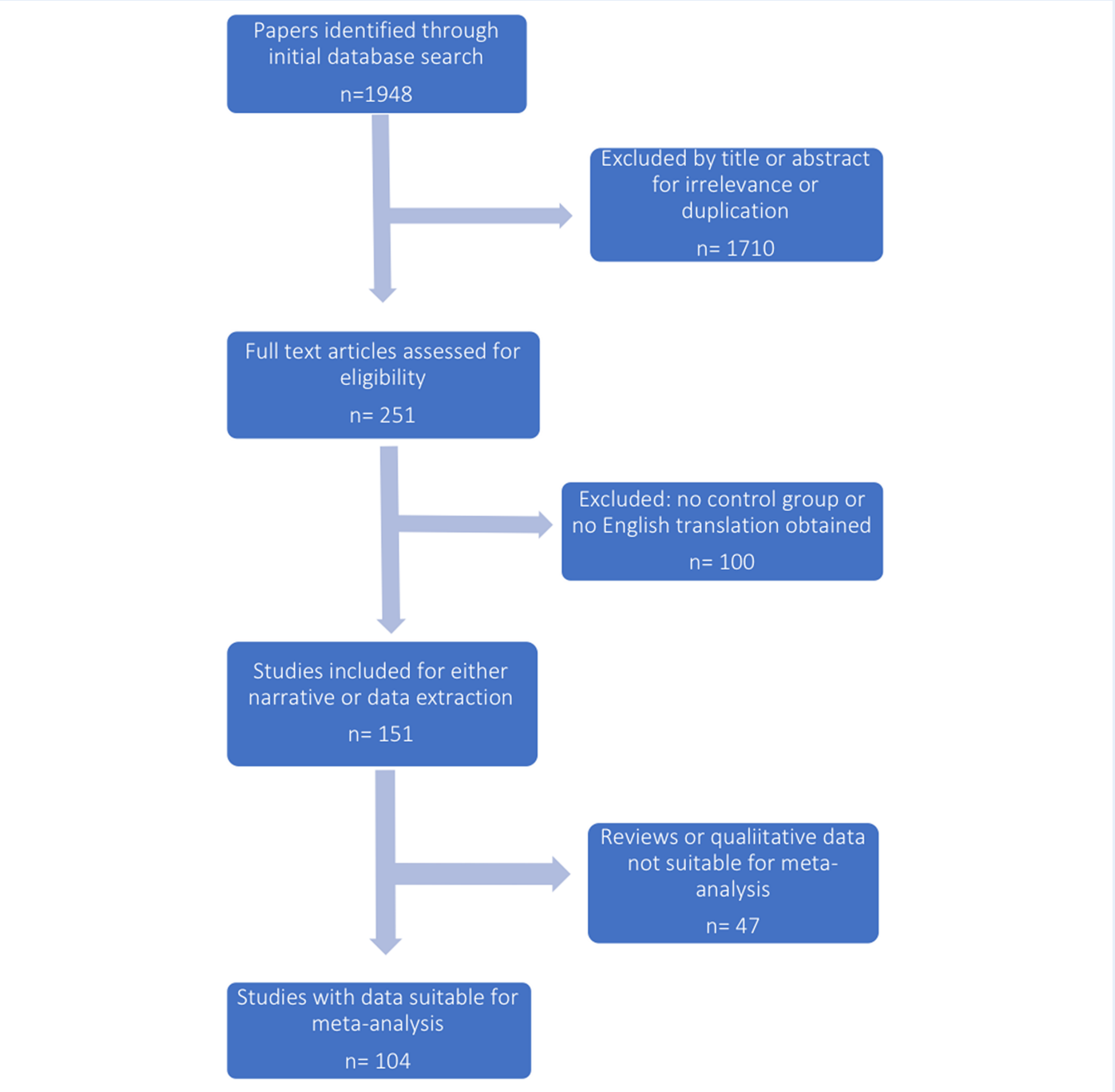

Figure 1 PRISMA flow chart of selection process.

imaging modalities where endometrioma was diagnosed, or ICD 10 coded medical records. Studies involving donor or recipient oocyte treatments, or women with known poor ovarian response, were excluded.

The control group consisted of women with a negative laparoscopy or no known adenomyotic or endometriotic disease including those with tubal infertility, male factor infertility, unexplained infertility, or mixed aetiology infertility.

Types of outcome measures

The primary outcome was the healthy baby rate, defined as a live singleton birth, at term, of appropriate birthweight for the gestational period. It was anticipated that a healthy baby rate would be calculated from data presented in studies. The secondary outcomes were the main pregnancy outcomes of live birth rate (LBR), clinical pregnancy rate (CPR; defined as a viable intrauterine pregnancy on ultrasound scan (USS)), and miscarriage rate (MR; spontaneous pregnancy loss before 24 weeks gestation). Other fertility, pregnancy, and delivery complications were grouped as follows.

Late pregnancy complications were pre-eclampsia (PET), pregnancy-induced hypertension (PIH), antepartum haemorrhage (APH; any bleeding per vagina after 24 weeks pregnancy), placenta praevia (PP), placental abruption (PA), small for gestational age fetus (SGA; defined as birthweight <10th centile for gestational age), preterm

delivery (PTD; delivery >24 weeks and <37 weeks gestation), lower segment caesarean section (LSCS) delivery, gestational diabetes (GDM), intrauterine death (IUD) and post-partum haemorrhage (PPH; excessive bleeding following delivery).

Neonatal complications were as follows: admission to the neonatal unit for any reason (NNU; admission between birth and 28 days old) and neonatal death (NND; death between birth and 28 days old).

Outcomes pertaining to parameters of IVF/ICSI treatment were as follows: oocyte yield (number of oocytes retrieved per cycle), number of mature oocytes per cycle (meiosis II oocytes suitable for fertilization), fertilization rate (FR; total number of fertilized oocytes), implantation rate (IR; number of clinical pregnancies per embryo transferred), and cycle cancellation rate (CR).

Selection of studies

Following an initial screen of titles and abstracts retrieved by the search, the full text of all potentially eligible studies were retrieved. The full texts were examined for eligibility, and articles satisfying the aforementioned inclusion criteria were selected. The results of this search are presented (Fig. 1).

Data extraction

Data were extracted by a reviewer (J.H.) using a pre-defined criteria and a second reviewer (M.S.) independently performed data extraction on a sample of included studies (those published between October 2000 and October 2010). A comparison was made between the data extracted by the first and second reviewer, and no discrepancies were found. If any discrepancies had been found the opinion of a third reviewer (Y.C.) would have been sought, and data extraction from all studies would have been performed by the second reviewer. Reviewers were selected based on their expertise in the subspecialty of endometriosis, reproductive medicine, and methodology in performing meta-analyses. Data extraction included study characteristics and outcome data (Supplementary Table SII).

Comparative analysis

We examined our outcomes (primary, secondary, and those pertaining to pregnancy and neonatal complications and IVF/ICSI parameters) according to mode of conception (NC, IVF/ICSI, and NC/ART) compared to controls by the following disease subgroups: Adenomyosis, endometriosis overall (subtype/severity unspecified), treated endometriosis (surgical and/or medical treatment), untreated endometriosis and subtypes of endometriosis (ASRM stages I and II endometriosis, ASRM stages III and IV endometriosis, endometrioma, and DIE).

Data analysis

All included studies are presented in Table I. Meta-analysis was performed using Review Manager version 5.3, and PRISMA guidance was followed where possible. Statistical data were drawn from the original papers or calculated by the reviewer J.H. when suitable raw data were presented.

Data were analysed by outcome in different modes of conception for each disease subgroup. Dichotomous data and continuous data were analysed using Mantel–Hansel odds ratio or the mean difference and the CIs between groups, respectively. Publication bias was tested with funnel plot analysis. Sensitivity analyses were performed first by combining any mode of conception subgroup data, or by adding data from excluded papers, or by removing outlying data. Sensitivity analysis results are shown in Supplementary Table SIII.

Assessment of heterogeneity

Included studies were scrutinized for clinical and methodological similarity and suitability of data for clinically meaningful meta-analysis. Statistical heterogeneity among included studies was measured by I2 with an accepted limit of <50%. I2 scores below this indicated that data could be analysed by a fixed effects model whereas scores ≥50% were analysed by a random effects model assuming that the effects being analysed in the different studies were not identical but followed similar distributions.

Assessment of study quality

Reviewer J.H. assessed the methodological quality of the studies using a modified Downs and Black standardized checklist for the quality of the individual studies, which rates 27 items across the domains of study quality, external validity, study bias, and confounding and selection bias. Items pertaining to power, blinding, randomizing, and intervention adverse events were removed from the checklist as they were not relevant to the included studies and when data were combined in a meta-analysis (Supplementary Table SII).

Results

Description of studies and participants

The systematic search retrieved 1948 articles; 251 studies were potentially eligible, and their full texts were reviewed (Fig. 1). Of these 104 studies met our inclusion criteria and 100 presented data suitable for inclusion in a meta-analysis (Table I). The remaining four studies were included for qualitative data.

Eleven papers compared fertility and obstetric outcomes in women with adenomyosis, diagnosed by USS or MRI features, to a control group (Table I: studies labelled AD for subgroup). One paper used uterine enlargement without distinct masses (Chiang *et al.*, 1999) rather than the full spectrum of USS diagnostic features. Five of the studies involved patients who also had endometriosis in the case and control groups (Costello *et al.*, 2011; Youm *et al.*, 2011; Salim *et al.*, 2012; Thalluri and Tremellen, 2012; Yan *et al.*, 2014). The 11 papers addressing adenomyosis were grouped as follows: IVF/ICSI ($n = 7$), NC/ART ($n = 4$), and NC ($n = 0$). All papers had data that could be used in a meta-analysis.

We included 63 papers where either the subtype or severity of endometriosis was unspecified or where data were presented for endometriosis as one cohort rather than by subtype or severity (Table I: studies labelled EN). Of these papers, 15 were NC/ART studies, 2 were NC studies, and 46 were IVF/ICSI studies.

There were 18 papers that analysed treated endometriosis patients specifically (Table I: studies labelled TxEN); one paper met the inclusion criteria but did not present outcome data in a format that could be used in our meta-analysis (Wyns and Donnez, 2003). The papers included in our meta-analysis were grouped as follows: IVF/ICSI ($n = 14$), NC/ART ($n = 4$), and NC ($n = 0$). Only one paper examined the effects of untreated endometriosis compared to controls (Geber *et al.*, 1995).

Table I **All included studies.**

IVF/ICSI conception studies							
Author & year	**Country**	**Study**	**Study group**	**Control group**	**Mode of conception**	**Outcomes**	**Subgroup of analysis**
Al-Azemi *et al.* (2000)	UK	Single centre prospective case–control	Surgically proven ovarian endometriosis and had ≥3 cycles of ICSI, *N* = 40	Laparoscopically proven tubal infertility and had ≥3 cycles of ICSI, *N* = 80	ICSI	↑CR ↓oocytes ↑dose HMG ↔cumulative pregnancy and live birth rate	OMA
Al-Fadhli *et al.* (2006)	Canada	Single centre matched case–control	Primary/secondary infertility due to endometriosis mixed stages treated at laparoscopy, *N* = 87	Age matched control primary/secondary infertility; tubal (*n* = 22); male (*n* = 28); PCOS (*n* = 5); unexplained (*n* = 32), *N* = 87	IVF	↓FR ↑dose of FSH ↔oocytes ↔MII oocytes ↔CPR ↔IR ↔duration of stimulation	EN, TxEN
AlKudmani *et al.* (2018)	Canada	Single centre case control	Infertility and surgically treated endometriosis, *N* = 216	Infertility with no endometriosis at laparoscopy, *N* = 209	IVF/ICSI	↓oocytes ↓CPR ↔duration of stimulation ↔dose FSH ↔MII oocytes ↔FR ↔IR	TxEN
Arici *et al.* (1996)	USA	Single centre case–control	Infertility secondary to endometriosis diagnosed and staged at laparoscopy, *N* = 35 (89 cycles)	Tubal factor infertility diagnosed at laparoscopy, *N* = 70 (147 cycles); Unexplained infertility with normal laparoscopy, *N* = 15 (48 cycles)	IVF	↓oocytes ↓FR ↓IR ↓CPR ↓LBR ↓no. of embryos transferred ↔MR ↔oocyte quality ↔embryo quality	EN, I and II, III and IV
Ashrafi *et al.* (2014)	Iran	Single centre prospective cohort	Infertility and untreated endometriomas <3 cm on USS, *N* = 47	Mild male factor infertility, *N* = 57	IVF/ICSI	↓oocytes ↓MII oocytes ↑FR ↑no. of embryos transferred ↔follicles ↔ IR ↔CPR ↔good quality embryos ↔CR	OMA
Benaglia *et al.* (2013)	Italy	Multicentre age matched case–control	First cycle of IVF/ICSI with endometriomas on USS, *N* = 39	First cycle of IVF/ICSI normal USS no history of endometriosis, *N* = 78	IVF/ICSI	↓oocytes ↓follicles ↓MII oocytes ↔CR ↔CPR ↔LBR ↔IR ↔no. of embryos transferred ↔high grade embryos ↔Dose FSH	OMA
Benaglia *et al.* (2012)	Italy	Multicentre cohort	Singleton IVF/ICSI pregnancy with endometriomas on USS, *N* = 78	Singleton IVF/ICSI pregnancy with normal USS, *N* = 156	IVF/ICSI	↓Oocytes ↑Dose FSH ↔no. of embryos transferred ↔LBR ↔MR ↔PTD ↔SGA ↔LSCS	OMA
Benaglia *et al.* (2015)	Italy	Single centre cohort	Infertility with untreated endometriomas on USS, *N* = 46; Infertility with surgically treated endometriomas, *N* = 55; Infertility with recurrent endometriomas on USS (previous surgical treatment), *N* = 23	Infertility with no endometriomas on USS and no history of endometriomas, *N* = 42	IVF	↓Follicles ↔duration of stimulation ↔dose FSH ↔CR	EN, OMA

Continued

Table I *Continued*

IVF/ICSI conception studies							
Author & year	**Country**	**Study**	**Study group**	**Control group**	**Mode of conception**	**Outcomes**	**Subgroup of analysis**
Benaglia *et al.* (2016)	Italy	Multicentre matched case–control	Singleton IVF/ICSI pregnancy with history of surgery for endometriosis or endometrioma on USS, $N = 239$	Singleton IVF/ICSI pregnancy, no history/symptoms of endometriosis and normal USS, $N = 239$	IVF/ICSI	↓Oocytes ↑PP ↔dose FSH ↔no. of embryos transferred ↔no. of blastocysts ↔LBR ↔MR ↔SGA ↔PTD ↔LGA ↔PIH ↔PET ↔NNU admission ↔PA ↔LSCS ↔IUD ↔GDM ↔PPROM	EN
Bergendal *et al.* (1998)	Sweden	Single centre retrospective matched case–control	Infertility secondary to endometriosis diagnosed at laparoscopy, $N = 48$ (65 cycles)	Tubal factor infertility matched to endometriosis patients by oocyte retrieval +/− 1 week, $N = 98$ (98 cycles)	IVF	↓FR ↓cleaved oocytes ↔oocytes ↔dose FSH ↔duration of stimulation ↔embryo score at transfer ↔follicles > 10 mm ↔IR ↔CPR ↔MR	EN, TxEN
Bongioanni *et al.* (2011)	Italy	Multicentre case–control	Endometrioma diagnosed on USS untreated (+/− male factor) $N = 142$; Endometrioma with laparoscopic cystectomy (+/− male factor) $N = 112$	Tubal infertility (+/− male factor) diagnosed at laparoscopy, $N = 174$	IVF/ICSI	↓oocytes (untreated)↑dose FSH(untreated) ↑CR(treated &untreated) ↔FR ↔IR ↔CPR ↔LBR ↔MII oocytes ↔no. of embryos transferred	OMA
Borges *et al.* (2015)	Brazil	Single centre cohort	Infertility with stages III and IV endometriosis, $N = 431$	Mixed aetiology infertility no known endometriosis, $N = 2510$	ICSI	↓follicles ↓oocytes ↓IR ↑dose FSH ↓no. of embryos transferred ↓high quality embryos ↔FR ↔CPR ↔CR ↔MR ↔MII oocytes ↔blastocysts	EN, III and IV
Brosens *et al.* (2007)	Belgium	Multicentre case–control	IVF pregnancy in endometriosis-related infertility diagnosed at laparoscopy, $N = 245$	IVF pregnancy with male factor infertility, $N = 274$	IVF	↓PET	EN
Bukulmez *et al.* (2001)	Turkey	Single centre case–control	Male factor infertility and endometriosis stages I and II at laparoscopy, $N = 25$ (49 cycles); Male factor infertility and stages III and IV endometriosis at laparoscopy or endometrioma on USS, $N = 19$ (29 cycles)	Male factor infertility with negative laparoscopy, $N = 588$ (895 cycles)	ICSI	↔oocytes ↔dose of GnRH ↔MII oocytes ↔FR ↔IR ↔no. of embryos transferred ↔CPR	EN, I and II, III and IV

Continued

Table I *Continued*

IVF/ICSI conception studies							
Author & year	**Country**	**Study**	**Study group**	**Control group**	**Mode of conception**	**Outcomes**	**Subgroup of analysis**
Canis *et al.* (2001)	?	Single centre cohort	Endometrioma with laparoscopic cystectomy, *N* = 39; Endometriosis but no endometrioma treated laparoscopically, *N* = 128	Tubal infertility, *N* = 59	IVF	↔oocytes ↔no. of embryos ↔CPR	TxEN
Chang *et al.* (1997)	Taiwan	Single centre cohort	Stages I and II endometriosis at laparoscopy, *N* = 60; Stages III and IV endometriosis at laparoscopy, *N* = 48	Infertility of mixed aetiology—no endometriosis at laparoscopy, *N* = 156	GIFT (COH data used)	↓oocytes ↓follicles ↓no. of embryos frozen ↔dose of FSH ↔FR	III and IV
Chiang *et al.* (1999)	Taiwan	Single centre age matched case–control	Infertility with adenomyosis uterine enlargement with no distinct masses on USS, *N* = 19	Infertility (cause not specified) with normal USS, *N* = 144	IVF	↑MR ↔oocytes ↔dose of FSH ↔follicles ↔FR ↔LBR ↔no. of embryos transferred ↔CPR	AD
Coccia *et al.* (2011)	Italy	Single centre cohort	Stages I and II endometriosis at surgery, *N* = 54 (55 cycles); Stages III and IV endometriosis at surgery, *N* = 94 (109 cycles)	Tubal infertility, *N* = 72 (80 cycles)	IVF	↓oocytes ↓follicles ↓CPR ↓no. of embryos ↓no. of embryos transferred ↑dose FSH/hMG ↔CR ↔FR ↔IR ↔duration of stimulation	EN, TxEN
Coelho Neto *et al.* (2015)	Brazil	Single centre cohort	Main study group: pregnancy achieved via IVF cycle, *N* = 184; Subgroup: women with endometriomas, *N* = 39	No pregnancy achieved with IVF cycle, *N* = 333; Subgroup: women without endometrioma, *N* = 478	IVF/ICSI	Age and no. of oocytes were independent predictors of pregnancy ↔oocytes ↔CPR ↔no. of embryos	EN
Coelho Neto *et al.* (2016)	Brazil	Single centre cohort	Infertility undergoing first cycle IVF with endometriosis diagnosed on USS +/− confirmed at laparoscopy, *N* = 241	Infertility undergoing first cycle IVF with no endometriosis on USS +/− negative laparoscopy, *N* = 546	IVF/ICSI	↓oocytes ↑CR ↔CPR ↔LBR	OMA
Costello *et al.* (2011)	Australia	Single centre cohort	Infertility of any cause other than ovarian failure and adenomyosis on USS, *N* = 37	Infertility of any cause other than ovarian failure and no adenomyosis on USS, *N* = 164	IVF/ICSI	↔dose FSH ↔oocytes ↔CR ↔FR ↔no. of embryos transferred ↔CPR ↔LBR ↔IR ↔MR	AD
Dong *et al.* (2013)	China	Single centre cohort	Infertility due to stages I and II endometriosis, *N* = 152; Infertility due to stages III and IV endometriosis, *N* = 279	Tubal infertility diagnosed at laparoscopy, *N* = 596	IVF/ICSI	↓oocytes ↓no. of embryos ↓ FR ↑dose FSH ↓IR ↓high grade embryo rate ↔CPR ↔LBR ↔MR ↔ectopic ↔CR	EN, TxEN

Continued

Table I *Continued*

IVF/ICSI conception studies							
Author & year	**Country**	**Study**	**Study group**	**Control group**	**Mode of conception**	**Outcomes**	**Subgroup of analysis**
Falconer *et al.* (2009)	Sweden	Single centre cohort	Infertility due to stages I and II endometriosis (+/−male factor) diagnosed at surgery, *N* = 34	Tubal factor infertility (+/−male factor) diagnosed at laparoscopy, *N* = 38	IVF/ICSI	↓FR ↓no. of embryos ↔follicles ↔oocytes ↔dose FSH ↔CR ↔CPR	I and II
Fernando *et al.* (2009)	Australia	Single centre cohort	IVF singleton births with peritoneal endometriosis, *N* = 535; IVF singleton births with endometrioma, *N* = 95	IVF singleton births with mixed aetiology infertility but no history of endometriosis, *N* = 1201; Fertile natural conception singleton births matched by age to study groups, *N* = 1260 & 1140, respectively	IVF/ICSI	Endometrioma group: ↑PTD ↑SGA Endometriosis group: ↔PTD ↔SGA	OMA
Frydman and Belaisch-Allart (1987)	France	Multicentre observational cohort	Infertility due to endometriosis entered in database, *N* = 53	Tubal infertility entered in database, *N* = 933	IVF/ICSI	↓FR ↓embryo transfers ↔no. of embryos transferred ↔CPR	EN, OMA
Frydman and Belaisch-Allart (1987)	France	Multicentre observational cohort	Infertility due to endometriosis entered in database, *N* = 8; Infertility with endometriomas on database, *N* = 26	Tubal infertility entered in database, *N* = 544	IVF/ICSI	↔FR ↔no. of embryos transferred	EN, OMA
Fujii *et al.* (2016)	Japan	Single centre cohort	Singleton IVF delivery with endometriosis diagnosed and staged at laparoscopy, *N* = 92	Singleton IVF delivery with normal USS +/− negative laparoscopy, *N* = 512	IVF/ICSI	↑PTD ↑PP ↔SGA	EN, III and IV
Geber *et al.* (1995)	UK	Single centre age matched case–control	Infertility due to endometriosis diagnosed at laparoscopy, *N* = 140 (182 cycles)	Male factor infertility, *N* = 44 (45 cycles); Unexplained infertility, *N* = 161 (196 cycles); Tubal factor infertility, *N* = 885 (1139 cycles)	IVF/ICSI	↓no. of embryo transfers (endometriosis to tubal group) ↔FR ↔IR ↔CPR ↔MR ↔ectopic	EN
González-Comadran *et al.* (2017)	Spain	Multicentre prospective cohort	Infertility associated with endometriosis in the medical records, *N* = 3583	Tubal, endocrine, or unexplained infertility, *N* = 18833	IVF/ICSI	↓oocytes ↑CR ↔FR ↔CPR ↔MR ↔LBR	EN
González-Foruria *et al.* (2016)	Spain	Single centre cohort	Infertility due to endometriosis, *N* = 101 (326 cycles)	Male factor infertility, *N* = 68 (202 cycles); Tubal factor infertility, *N* = 44 (125 cycles); Unexplained infertility, *N* = 81 (243 cycles); Mixed aetiology, *N* = 26 (51 cycles)	IVF	↔oocytes ↔CR ↔MII oocytes ↔FR ↔no.of embryos ↔CPR ↔MR	EN

Continued

Table I *Continued*

IVF/ICSI conception studies							
Author & year	**Country**	**Study**	**Study group**	**Control group**	**Mode of conception**	**Outcomes**	**Subgroup of analysis**
Guler *et al.* (2017)	Turkey	Cohort	Peritoneal endometriosis treated laparoscopically, *N* = 48 (91 cycles); Endometrioma treated laparoscopically, *N* = 25 (57 cycles); Endometrioma untreated, *N* = 53 (65 cycles)	Tubal infertility diagnosed laparoscopically, *N* = 24 (44 cycles)	ICSI	↓oocytes ↓MII oocytes ↓dominant follicles ↓FR ↓CR ↓CPR ↔LBR ↔dose FSH	OMA
Healy *et al.* (2010)	Australia	Multicentre cohort	IVF/ICSI singleton delivery, *N* = 6730; Subgroup analysis IVF/ICSI with (*N* = 1265) or without history of endometriosis (*N* = 5465)	General population NC/ART singleton delivery, *N* = 24 619; General population non ART singleton delivery, *N* = 2167	IVF/ICSI	PP, APH, PPH	EN
Hickman (2002)	USA	Single centre cohort	Infertility due to endometriosis diagnosed at laparoscopy, *N* = 27 (31 cycles); Stages I and II, *N* = 18 (20 cycles); Stages III and IV, *N* = 9 (11 cycles)	Tubal factor infertility diagnosed at laparoscopy, *N* = 104 (118 cycles)	IVF	↔oocytes ↔FR ↔IR ↔CPR ↔LBR ↔MR	EN, I and II, III and IV
Hull *et al.* (1998)	UK	Cohort	Infertility due to stages I and II endometriosis diagnosed at laparoscopy, *N* = 194 (219 cycles)	Unexplained infertility negative laparoscopy, *N* = 327 (343 cycles); Tubal factor infertility without hydrosalpinx, *N* = 509 (680 cycles)	IVF	↓oocytes ↓FR ↓no. of embryos and no.of embryos transferred ↔IR ↔CPR	EN, I and II
Jacques *et al.* (2016)	France	Single centre age matched case–control	IVF/ICSI pregnancies >22/40 associated with endometriosis diagnosed at laparoscopy, *N* = 113; Subgroups: stages I and II endometriosis, *N* = 59; Stages III and IV endometriosis, *N* = 52	IVF/ICSI pregnancies >22/40 associated with male factor infertility diagnosed at laparoscopy, *N* = 113	IVF/ICSI	↑First trimester bleeding ↑PTD ↑threatened PTD ↑PET ↓birthweight ↑LSCS ↑NNU admission ↔PROM ↔IUGR ↔GDM ↔OC ↔PP ↔PPH	EN, I and II, III and IV
Kim *et al.* (2011)	Korea	Single centre cohort	Stages III and IV endometriosis related infertility, *N* = 20 (20 cycles)	Tubal factor infertility, *N* = 20 (20 cycles)	IVF	↓IR ↔oocytes ↔MII oocytes ↔no. of embryos transferred ↔CPR ↔LBR ↔MR ↔duration of stimulation ↔dose FSH ↔no. of high grade embryos	III and IV

Continued

Table I *Continued*

IVF/ICSI conception studies							
Author & year	**Country**	**Study**	**Study group**	**Control group**	**Mode of conception**	**Outcomes**	**Subgroup of analysis**
Kiran *et al.* (2012)	Turkey	Single centre cohort	Endometrioma on USS at IVF cycle, *N* = 29	Unexplained infertility with no endometrioma on USS at IVF cycle, *N* = 51	IVF	↔oocytes ↔MII oocytes	OMA
Kuivasaari *et al.* (2005)	Finland	Single centre prospective observational	Stages I and II endometriosis related infertility diagnosed and treated at laparoscopy, *N* = 31 (58 cycles); Stages III and IV endometriosis related infertility diagnosed and treated at laparoscopy, *N* = 67 (150 cycles)	Tubal factor infertility diagnosed surgically or HSG, *N* = 87 (184 cycles)	IVF/ICSI	↓IR ↓LBR ↓ectopic ↔oocytes ↔FR ↔MR ↔no. of high grade embryos ↔no. of embryos transferred	EN, I and II, III and IV
Kuivasaari-Pirinen *et al.* (2012)	Finland	Single centre cohort	Endometriosis related infertility, *N* = 49	Tubal factor infertility, *N* = 38; Male factor infertility, *N* = 43; Anovulation infertility, *N* = 68; Unexplained infertility, *N* = 30	IVF/ICSI	↑PTD ↓SGA ↓birthweight ↑PP ↑NNU admission ↔IUGR ↔GDM ↔PET ↔PA	EN
Kuroda *et al.* (2009)	Japan	Single centre case–control	Endometrioma on USS or MRI at time of cycle, *N* = 18 (31 cycles); Endometrioma treated laparoscopically, *N* = 36 (51 cycles); Endometriosis without endometrioma treated laparoscopically, *N* = 7 (15 cycles)	Tubal infertility, *N* = 21 (27 cycles)	IVF/ICSI	↓no. of embryos transferred ↓follicles ↔oocytes ↔FR ↔IR ↔CPR ↔LBR ↔MR ↔high grade embryo rate	EN, TxEN, OMA
Leonardi *et al.* (2016)	Italy	Multicentre matched case–control	Singleton pregnancy with history of endometriosis diagnosed at surgery or endometrioma on USS, *N* = 313	Singleton pregnancy with no endometriosis at laparoscopy, *N* = 313	IVF/ICSI	↓oocytes ↑dose FSH ↔duration of stimulation ↔no. of embryos transferred ↔MR ↔day of embryo transfer	EN, TxEN
Lin *et al.* (2012)	China	Single centre cohort	Infertility with endometriosis diagnosed surgically; Stages I and II, *N* = 64; Stages III and IV, *N* = 113	Mixed aetiology infertility, *N* = 4267	IVF/ICSI	↔FR ↔IR ↔CPR ↔cleavage rate ↔high quality embryo rate	EN, I and II, III and IV
Matalliotakis *et al.* (2011)	USA	Single centre cohort	Infertility due to endometriosis diagnosed at laparoscopy; Stages I and II, *N* = 75 (144 cycles); Stages III and IV, *N* = 55 (114 cycles)	Tubal infertility diagnosed at laparoscopy, *N* = 104 (206 cycles); Male factor infertility negative laparoscopy, *N* = 59 (133 cycles)	IVF/ICSI	↓oocyte ↔CR ↔FR ↔IR ↔CPR ↔LBR ↔MR ↔ectopic ↔no. of embryos transferred per cycle ↔no. of embryos	EN, I and II, III and IV

Continued

Table I *Continued*

IVF/ICSI conception studies							
Author & year	**Country**	**Study**	**Study group**	**Control group**	**Mode of conception**	**Outcomes**	**Subgroup of analysis**
Matson and Yovich (1986)	Australia	Cohort	Endometriosis diagnosed at surgery; Stages I and II, *N* = 40 (61 cycles); Stages III and IV, *N* = 56 (93 cycles)	Tubal infertility, *N* = 28 (40 cycles)	IVF	↓CPR ↔oocytes ↔follicles ↔FR ↔no. of embryos transferred	EN, TxEN
Meden-Vrtovec *et al.* (2000)	Slovenia	Cohort	Infertility with stages I and II endometriosis diagnosed at laparoscopy, *N* = 7339 cycles	Tubal infertility, *N* = 612 cycles	IVF	↓no. of embryos ↑CPR ↑LBR ↑MR ↑dose hMG ↔oocytes ↔FR ↔ectopic	I and II
Mekaru *et al.* (2013)	Japan	Single centre case–control	Infertility with stages I and II endometriosis diagnosed at laparoscopy, *N* = 18 (39 cycles)	Unexplained infertility with negative laparoscopy, *N* = 17 (41 cycles)	IVF	↓grade 1 embryos ↑dose hMG ↔oocytes ↔no. of embryos transferred ↔FR ↔IR ↔CPR ↔LBR ↔OHSS	EN, TxEN
Mohamed *et al.* (2011)	UK	Single centre cohort	Infertility with endometriosis diagnosed at laparoscopy, *N* = 415 cycles	Mixed aetiology infertility, *N* = 6871 cycles	IVF	↔CPR ↔LBR ↔MR	EN
Motte *et al.* (2016)	France	Single centre matched case–control	Infertility with endometriosis treated laparoscopically, *N* = 37 (63 cycles)	Mixed aetiology infertility, *N* = 74 (177 cycles)	IVF/ICSI	↓oocytes ↓CPR ↓LBR ↔CR ↔FR ↔IR ↔MR ↔ectopic ↔dose FSH ↔follicles ↔MII oocytes ↔cleavage rate ↔no. of embryos transferred ↔ embryo quality by grade	EN, TxEN
Murta *et al.* (2018)	Brazil	Multicentre cohort	Endometriosis diagnosed at laparoscopy, *N* = 1749	Tubal factor and unexplained infertility, *N* = 5747	IVF/ICSI	↓oocytes ↓MII oocytes ↓FR ↓no. of embryos transferred ↑CPR ↑LBR ↓MR ↔ectopic	EN
Muteshi *et al.* (2018)	UK	Single centre cohort	Endometriosis diagnosed at laparoscopy, *N* = 531	Unexplained infertility with negative laparoscopy, *N* = 737	IVF	↓oocytes ↓MII oocytes ↓FR ↓blastocyst rate ↓IR ↓LBR ↓biochemical pregnancy rate ↓MR ↔CPR ↔PTD ↔duration of stimulation ↑dose FSH	EN
Nakagawa *et al.* (2016)	Japan	Single centre prospective cohort	Endometrioma on USS & MRI +/−male factor, *N* = 26	Male factor or unexplained infertility normal USS +/− negative laparoscopy, *N* = 29	IVF/ICSI	↔dose FSH ↔oocytes ↔FR ↔MR ↔CPR	OMA
Nejad *et al.* (2009)	Iran	Single centre cohort	Infertility due to endometriosis diagnosed at laparoscopy, Stages I and II, *N* = 32; Stages III and IV, *N* = 48	Tubal infertility diagnosed at laparoscopy, *N* = 57	IVF/ICSI	↔oocyes ↔IR ↔CPR ↔MR ↔dose FSH ↔duration of stimulation ↔OHSS ↔no. of embryos transferred	EN, I and II, III and IV

Continued

Table I *Continued*

IVF/ICSI conception studies							
Author & year	**Country**	**Study**	**Study group**	**Control group**	**Mode of conception**	**Outcomes**	**Subgroup of analysis**
Oehninger *et al.* (1988)	USA	Single centre cohort	Mixed aetiology infertility with stages I and II endometriosis diagnosed at laparoscopy, $N = 91$ (191 cycles); Mixed aetiology infertility with stages III and IV endometriosis diagnosed at laparoscopy, $N = 22$ (35 cycles)	Tubal infertility, $N = 447$ (917 cycles)	IVF	Outcomes: Oocytes, immature oocytes, FR, no. of embryos transferred, CPR, MR but no significances given	EN, TxEN, I and II, III and IV
Olivennes *et al.* (1995)	USA	Single centre cohort	Infertility due to endometriosis diagnosed at laparoscopy, $N = 147$ (236 cycles); Stages I and II, $N = 81$ (196 cycles); Stages III and IV, $N = 9$ (29 cycles); Endometrioma, $N = 57$ (11 cycles)	Tubal infertility, $N = 111$ (160 cycles)	IVF	Outcomes: Oocytes, CR, FR, CPR, LBR, MR, no. of embryos transferred, dose FSH, significances not given	EN, I and II, III and IV, OMA
Omland *et al.* (2006)	Norway	Single centre cohort	Undergoing ICSI for failed IVF cycle with infertility due to stage I endometriosis diagnosed at laparoscopy, $N = 43$	Male factor, $N = 91$; Unexplained infertility with negative laparoscopy and >1 failed IVF cycle, $N = 48$	ICSI	↓FR ↔oocytes ↔dose FSH ↔IR ↔CPR ↔MR ↔no.of embryos transferred ↔duration of stimulation ↔MII oocytes ↔molar pregnancy	I and II
Opøien *et al.* (2012)	Norway	Single centre cohort	Infertility due to endometriosis diagnosed at laparoscopy; Stages I and II, $N = 724$; Stages III and IV $N = 350$	Tubal infertility diagnosed at laparoscopy/laparotomy, $N = 1171$	IVF/ICSI	↓oocytes ↓FR ↑dose FSH ↔CR ↔IR ↔CPR ↔MR ↔MII oocytes	EN, I and II, III and IV
Ozgur *et al.* (2018)	Turkey	Single centre matched case–control	Infertility and untreated endometrioma >10 mm on USS, $N = 30$	Infertility with no normal USS and no history of endometriosis, $N = 60$	IVF/FET	↑duration of stimulation ↔oocytes ↔MII oocyes ↔FR ↔blastocysts grade ↔IR ↔biochemical pregnancy rate ↔ongoing pregnancy $>14/40$	OMA

Continued

Table I *Continued*

IVF/ICSI conception studies							
Author & year	**Country**	**Study**	**Study group**	**Control group**	**Mode of conception**	**Outcomes**	**Subgroup of analysis**
Pabuccu *et al.* (2004)	Turkey	Single centre prospective case control	Endometrioma drained transvaginally at the beginning of cycle, *N* = 41; Endometrioma untreated at the beginning of cycle, *N* = 40; Previous surgery for endometrioma none seen on USS at cycle, *N* = 44	Tubal infertility but no hydrosalpinx, no endometriosis at laparoscopy, *N* = 46	ICSI	↓follicles ↓MII oocytes↑duration of stimulation dose ↔FSH ↔FR ↔IR ↔CPR ↔MR	OMA
Pellicer *et al.* (1998)	Spain	Single centre case–control	Infertility due to endometriosis diagnosed at laparoscopy, *N* = 17; Stages I and II, *N* = 5; Stages III and IV, *N* = 12	Tubal infertility diagnosed at laparoscopy, *N* = 19	IVF	↔oocytes ↔duration of stimulation ↔no. of fertilized oocytes ↔no. of embryos transferred ↔IR ↔follicle volume	EN, I and II, III and IV
Polat *et al.* (2014)	Turkey	Single centre case–control	Infertility due to endometriosis stages I and II diagnosed at laparoscopy, *N* = 72; Stages III and IV diagnosed at laparoscopy or USS with endometrioma >3 cm, *N* = 413	Tubal infertility diagnosed at laparoscopy, *N* = 131	IVF	↓oocytes, no. of embryos transferred & ↑dose FSH (stages III and IV only) ↓MII oocytes ↑CR ↔FR ↔IR ↔CPR ↔LBR ↔MR ↔duration of stimulation ↔no. good quality embryos	EN, I and II, III and IV
Pop-Trajkovic *et al.* (2014)	Serbia	Multicentre cohort	Infertility with stages I and II endometriosis treated laparoscopically, *N* = 40; Infertility with stages III and IV endometriosis treated laparoscopically, *N* = 38	Tubal infertility diagnosed at laparoscopy, *N* = 157	IVF	↓Oocytes ↓follicles ↓FR ↓IR ↓cumulative pregnancy rate ↓LBR ↓no. of embryos ↑dose of FSH ↑CR ↑duration of stimulation ↔MR	EN, TxEN
Salim *et al.* (2012)	UK	Single centre prospective observational	Infertility of any cause other than ovarian failure and adenomyosis on USS, *N* = 19	Infertility of any cause other than ovarian failure and no adenomyosis on USS, *N* = 256	IVF/ICSI	↓IR ↓CPR ↑MR ↔dose GnRH ↔oocytes ↔no. of embryos transferred ↔MII oocytes	AD
Saucedo-de-la-Llata *et al.* (2004)	Mexico	Single centre cohort	Infertility due to endometriosis; Stages I and II, *N* = 111; Stages III and IV, *N* = 132	Tubal infertility, *N* = 268; Male factor, *N* = 261	IVF/ICSI	↓MII oocytes (stages I and II only) ↓FR ↔oocytes ↔CPR ↔follicles	I and II, III and IV
Scarselli *et al.* (2011)	Italy	Single centre cohort	Infertility due to endometriosis diagnosed surgically or endometriosis at IVF cycle, *N* = 144	Tubal infertility, *N* = 70	IVF	↓follicles ↓no. of embryos ↓no. of embryos transferred ↑CPR ↑dose FSH ↔FR ↔CR ↔oocytes	EN, I and II, OMA

Continued

Table I *Continued*

IVF/ICSI conception studies							
Author & year	**Country**	**Study**	**Study group**	**Control group**	**Mode of conception**	**Outcomes**	**Subgroup of analysis**
Senapati *et al.* (2016)	USA	Multicentre population-based cohort	Infertility due to endometriosis, *N* = 12 335	Tubal infertility, *N* = 22 778; Unexplained infertility, *N* = 38 713	IVF/ICSI	↓oocyte ↓IR ↓blastocyst transfer ↓LBR ↔CR ↔FR ↔MR ↔ectopic	EN
Sharma *et al.* (2018)	India	Single centre cohort	Endometriosis stages III and IV diagnosed at laparoscopy, *N* = 355; Adenomyosis diagnosed on USS and no endometriosis at laparoscopy, *N* = 64	Tubal infertility diagnosed on HSG or laparoscopy, *N* = 466	IVF/ICSI	Endometriosis: dose GnRH ↔MII oocytes ↔FR ↔no. grade 1/2 embryos ↔CPR ↔LBR ↔MR ↔PET ↔PPH ↔IUD ↔IUGR Adenomyosis: dose GnRH ↔MII oocytes ↔FR ↔no. grade 1/2 embryos ↓CPR ↓LBR ↑MR	III and IV, AD
Shebl *et al.* (2017)	Austria	Single centre matched case–control	Infertility with endometriosis diagnosed at laparoscopy +/− male factor or PCO, *N* = 114 (129 cycles)	Mixed aetiology infertility with a negative laparoscopy, *N* = 119 (129 cycles)	IVF/ICSI	↓FR ↓MII oocytes ↔IR ↔biochemical pregnancy rate ↔LBR ↔MR ↔gestation at delivery ↔birthweight ↔malformations ↔dose FSH ↔grade I&2 embryos	EN, I and II, III and IV
Simón *et al.* (1994)	Spain	Single centre case control	Infertility secondary to endometriosis diagnosed at laparoscopy or by endometrioma on USS; Stages I and II, *N* = 9 (14 cycles); Stages III and IV, *N* = 50 (82 cycles)	Tubal infertility, *N* = 78 (96 cycles)	IVF	↓CPR ↓IR ↓no. of grade I embryos transferred ↔oocytes ↔FR	EN, I and II, III and IV
Suzuki *et al.* (2005)	Japan	Single centre cohort	Infertility due to endometriosis diagnosed at laparoscopy, *N* = 248 cycles; Infertility and endometrioma aspiration at IVF cycle, *N* = 80 cycles	Tubal infertility diagnosed at laparoscopy, *N* = 283 cycles	IVF	↓oocytes ↓no. of embryos transferred ↔FR ↔IR ↔biochemical pregnancy ↔LBR ↔grade 1&2 embryos	OMA
Takemura *et al.* (2013)	Japan	Single centre cohort	Placenta praevia in pregnancy and endometriosis diagnosed at laparoscopy or on imaging, *N* = 53	Placenta praevia in pregnancy and no history of endometriosis, *N* = 265	IVF/ICSI	↑PP	EN

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Table I *Continued*

IVF/ICSI conception studies							
Author & year	**Country**	**Study**	**Study group**	**Control group**	**Mode of conception**	**Outcomes**	**Subgroup of analysis**
Tanbo *et al.* (1995)	Norway	Single centre cohort	Infertility due to endometriosis stage I diagnosed at laparoscopy, *N* = 143 (285 cycles)	Tubal infertility diagnosed at laparoscopy, *N* = 180 (353 cycles); Unexplained infertility negative laparoscopy, *N* = 215 (385 cycles)	IVF/ICSI	↓cleavage rate ↔oocytes ↔no. of embryos transferred ↔CPR	I and II
Thalluri and Tremellen (2012)	Australia	Single centre cohort	Mixed aetiology infertility with adenomyosis on USS, *N* = 38	Mixed aetiology infertility with no adenomyosis on USS, *N* = 175	IVF	↓biochemical pregnancy ↓CPR ↔oocytes ↔FR ↔miscarriage & ectopic ↔embryo grade	AD
Queiroz Vaz *et al.* (2017)	Brazil	Single centre cohort	Deep infiltrating endometriosis diagnosed at laparoscopy or on MRI, *N* = 27	Tubal infertility, *N* = 51; Male factor infertility, *N* = 65; PCOS, *N* = 20; Unexplained infertility, *N* = 18	FET	↔pregnancy rate ↔MR	DIE
Wardle *et al.* (1985)	UK	Single centre cohort	Infertility with stages I and II endometriosis at laparoscopy, *N* = 17	Tubal infertility, no endometriosis at laparoscopy, *N* = 47; Unexplained infertility, negative laparoscopy, *N* = 21	IVF	↓FR ↓no. of embryo transfer procedures ↔Oocytes ↔CPR	I and II
Wyns and Donnez (2003)	Belgium	Single centre case control	Infertility due to endometriosis treated surgically; Peritoneal endometriosis, *N* = 42 (71 cycles); Endometrioma, *N* = 85 (187 cycles)	Tubal infertility, *N* = 193 (422 cycles); Unexplained infertility, *N* = 135 (275 cycles)	IVF	↔dose hCG ↔follicles ↔MII oocytes ↔no. of embryos transferred ↔FR ↔IR ↔CPR	TxEN
Yamamoto *et al.* (2017)	USA	Single centre cohort	Undergoing first cycle IVF with diagnosis of endometriosis on USS or laparoscopically, *N* = 68	Undergoing first cycle IVF with no diagnosis of endometriosis, *N* = 649	IVF	↔oocytes ↔FR ↔CPR ↔CR	EN

Continued

Table I *Continued*

IVF/ICSI conception studies							
Author & year	**Country**	**Study**	**Study group**	**Control group**	**Mode of conception**	**Outcomes**	**Subgroup of analysis**
Yan *et al.* (2014)	China	Single centre cohort	Infertility with adenomyosis diagnosed on USS, *N* = 77	Infertility with normal pelvic USS, *N* = 77	IVF/ICSI	↓LBR ↔MR ↔CPR	AD
Youm *et al.* (2011)	Korea	Single centre case–control	Mixed aetiology infertility myometrial thickness 2–2.49 cm on USS, *N* = 63 (81 cycles); Myometrial thickness > 2 .5cm, *N* = 48 (73 cycles); No other uterine abnormalities	Mixed aetiology infertility myometrial thickness < 2 cm on USS no other uterine abnormalities, *N* = 302 (397 cycles)	IVF	↓IR ↓CPR ↑MR ↓LBR ↔oocytes ↔no. of embryos transferred ↔FR ↔ectopic ↔no. of embryos transferred	AD
Yovich and Matson (1990)	Australia	Single centre cohort	Subgroup analysis: infertility with endometriosis at laparoscopy; Stages I and II, *N* = 40 (61 cycles); Stages III and IV, *N* = 56 (93 cycles)	Subgroup analysis: mixed aetiology infertility, no endometriosis at laparoscopy, *N* = 35 (49 cycles)	IVF	↓CPR ↔oocyte per follicle rate ↔FR	I and II, III and IV
Natural Conception and ART Population Studies							
Author & year	**Country**	**Study**	**Study group**	**Control group**	**Mode of conception**	**Outcomes**	**Subgroup of analysis**
Aris (2014)	Canada	Multicentre population-based cohort	Delivery with diagnosis of endometriosis by ICD10 in medical records, *N* = 784	Delivery with no diagnosis of endometriosis by ICD10 in medical records, *N* = 30 284	NC/ART	↑MR ↑IUD ↔PTD ↔PIH ↔GDM ↔PET ↔IUGR	EN
Berlac *et al.* (2017)	Denmark	Multicentre population-based cohort	Endometriosis in medical records, *N* = 11 739 (19 331 births); Endometriosis treated surgically in medical records, *N* = 4465 (3926 births)	No diagnosis of endometriosis on medical records, *N* = 615 533 (1 071 920 births)	NC/ART	↑PET ↑abruption ↑PP ↑APH ↓PPH ↑LSCS ↑SGA ↑Apgar<7 at 5 min ↑NND ↑IUD ↑PTD (<34/40), ↔PIH other complications in labour	EN, TxEN
Chen *et al.* (2018)	China	Multicentre population-based cohort	Singleton delivery with surgically diagnosed endometriosis by ICD 10 code in medical records, *N* = 469	Singleton delivery with no history of endometriosis in medical records, *N* = 51 733	NC/ART	↑MR ↑PP ↑LSCS ↔PIH/PET ↔PA ↔PROM ↔PPH ↔PTD ↔SGA ↔NNU	EN

Continued

Table I *Continued*

Natural Conception and ART Population Studies							
Author & year	**Country**	**Study**	**Study group**	**Control group**	**Mode of conception**	**Outcomes**	**Subgroup of analysis**
Conti *et al.* (2015)	Italy	Multicentre cohort	Singleton delivery with history of laparoscopically treated endometriosis, *N* = 316	Singleton delivery, no history of endometriosis, *N* = 1923	NC/ART	↑PTD ↑SGA ↑PPROM ↑GDM ↑NNU admission ↔PIH ↔PET ↔PPH ↔mode of delivery ↔ PROM ↔duration of NNU admission	EN, TxEN
Glavind *et al.* (2017)	Denmark	Multicentre population-based cohort	Singleton delivery with endometriosis by ICD 10 code in medical records, *N* = 1719 deliveries (1213 patients)	Singleton delivery no endometriosis by ICD 10 code in medical records, *N* = 81 074 deliveries (54 616 patients)	NC/ART	↑LSCS ↑PTD ↑PET ↔PPH ↔SGA ↔IUD	EN
Hadfield *et al.* (2009)	Australia	Population based longitudinal	First singleton delivery ICD10 coded endometriosis on medical records, *N* = 3239; Subgroup ovarian endometriosis, *N* = 846	First singleton delivery no ICD10 coded endometriosis on medical records, *N* = 205 640; Subgroup no endometriosis IVF pregnancy, *N* = 841	NC/ART	↔PIH ↔PET	EN
Harada *et al.* (2016)	Japan	Multicentre prospective cohort	Singleton pregnancy with history of endometriosis, *N* = 330	Singleton pregnancy with no history of endometriosis, *N* = 8856	NC/ART	↑PTD ↑LSCS ↑PP ↑PA ↑threatened PTD ↔PET ↔GDM ↔IUGR ↔PROM ↔birthweight	EN
Hashimoto *et al.* (2018)	Japan	Multicentre cohort	Singleton pregnancy with adenomyosis diagnosed on USS or MRI, *N* = 49	Singleton pregnancies with normal pelvic USS, *N* = 245	NC/ART	↑Second trimester miscarriage ↑PET ↑PIH ↑PP ↑PTD ↑GDM ↑LSCS ↑SGA ↔malpresentation ↔PPH ↔Apgar <7 at 5 min	AD
Hjordt Hansen *et al.* (2014)	Denmark	Multicentre matched case–control	Endometriosis on medical records, *N* = 39 555 pregnancies (24 667 patients)	No endometriosis on medical records, *N* = 161 083 pregnancies (98 668 patients)	NC/ART	↓LBR ↑MR ↑ectopic ↑molar pregnancy ↔termination of pregnancy	EN
Juang *et al.* (2007)	Taiwan	Single centre nested case–control	Preterm delivery with pre-pregnancy USS/MRI, *N* = 104	Term delivery with pre-pregnancy USS/MRI, *N* = 208	NC/ART	Adenomyosis associated with risk ↑PTD ↑PPROM	AD
Kohl Schwartz *et al.* (2017)	Switzerland	Multicentre observational cohort	Multiparous women with history of surgically treated endometriosis, *N* = 143 (240 pregnancies)	Multiparous women with no history of endometriosis at annual gynaecology check-up, *N* = 143 (268 pregnancies)	NC/ART	↑MR	TxEN

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Table I *Continued*

Natural Conception and ART Population Studies							
Author & year	**Country**	**Study**	**Study group**	**Control group**	**Mode of conception**	**Outcomes**	**Subgroup of analysis**
Kortelahti *et al.* (2003)	Finland	Single centre matched case–control	Endometriosis diagnosed at laparoscopy and histology, *N* = 137	Laparoscopic tubal sterilization or infertility of mixed aetiology. No history of endometriosis, *N* = 137	NC/ART	↔PTD ↔SGA ↔NNU ↔PET ↔PP ↔PA ↔LSCS ↔IUD ↔pH <7.15 at delivery ↔Apgar <7 at 1 min ↔Apgar <7 at 5 min ↔mean gestational age ↔Rh immunization ↔abnormal CTG in labour ↔meconium ↔placental weight	EN
Li *et al.* (2017)	China	Single centre cohort	Pregnancy with history of surgically diagnosed endometriosis; Stages I and II *N* = 45; Stages III and IV, *N* = 30	Pregnancy with no history of gynaecological diseases, *N* = 300	NC/ART	↑PPH ↔GDM ↔PA ↔PIH/PET ↔PP ↔LSCS ↔Apgar score < 7 at 5 min ↔birthweight	EN
Mannini *et al.* (2017)	Italy	Single centre cohort	Pregnancy with history of surgically treated endometriosis, DIE *N* = 40 Non-DIE *N* = 222	Pregnancy with no history or USS signs of endometriosis, *N* = 524	NC/ART	↔LSCS ↔PP ↔IUGR ↔PIH ↔GDM ↔PTD ↔PPH	TxEN
Mardanian *et al.* (2016)	Iran	Single centre cohort	First pregnancy following laparoscopic findings of endometriosis, *N* = 101	First pregnancy following negative laparoscopy, *N* = 101	NC/ART	↔PIH ↔PET	EN
Mochimaru *et al.* (2015)	Japan	Single centre age matched case–control	Adenomyosis on USS or MRI +/− fibroids, *N* = 36	No adenomyosis on USS, *N* = 144	NC/ART	↑PTD ↑SGA ↑PPROM ↑severe PPH ↑LSCS ↔PET ↔extreme prematurity ↔IUD ↔NNU ↔Apgar scores	AD
Santulli *et al.* (2016)	France	Single centre cohort	Laparoscopy/laparotomy for pelvic pain, infertility, or benign pelvic mass and endometriosis diagnosed, *N* = 284	Laparoscopy/laparotomy for pelvic pain, infertility, or benign pelvic mass and no endometriosis found, *N* = 466	NC/ART	↑MR	I and II, III and IV, DIE
Saraswat *et al.* (2017)	UK	Multicentre population-based cohort	First singleton delivery following surgical diagnosis of endometriosis, *N* = 8280	Singleton delivery no history or symptoms of endometriosis, *N* = 5375	NC/ART	↑MR ↑ectopic ↑PTD ↑hypertensive disorders ↑APH ↑PP ↑PPH ↑LSCS ↑instrumental delivery ↔IUGR ↔IUD ↔PA ↔NND	EN

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Table I *Continued*

Natural Conception and ART Population Studies							
Author & year	**Country**	**Study**	**Study group**	**Control group**	**Mode of conception**	**Outcomes**	**Subgroup of analysis**
Shin *et al.* (2018)	Korea	Single centre case control	Singleton delivery >20/40 with adenomyosis diagnosed on USS at 7/40, *N* = 72	Singleton delivery >20/40 with no adenomyosis on USS at 7/40, *N* = 8244	NC/ART	↑PTD ↓birthweight ↔LSCS NC subgroup analysis: ↔PTD ↓birthweight	AD
Shmueli *et al.* (2017)	Israel	Single centre cohort	Singleton delivery with history of endometriosis, *N* = 135	Singleton delivery with no history of endometriosis, *N* = 61 400	NC/ART	↑LSCS ↑PP ↑PPH ↑NNU ↑neonatal comorbidities analysed eg sepsis, HIE etc. ↓birthweight ↔PIH ↔PET ↔GDM ↔Apgar <7 at 5mins	EN
Stephansson *et al.* (2009)	Sweden	Multicentre population-based cohort	Singleton delivery history of endometriosis by ICD 10 code in medical records, *N* = 13 090 deliveries	Singleton delivery no history of endometriosis by ICD 10 code in medical records, *N* = 1 429 585 deliveries	NC/ART	↑PTD ↑PET ↑APH ↑LSCS ↔SGA ↔IUD	EN
Tzur *et al.* (2018)	Israel	Single centre population based cohort	Singleton delivery with surgically diagnosed endometriosis, *N* = 35	Singleton delivery with no history of endometriosis, *N* = 467	NC/ART	↑PTD ↑LSCS ↔PPH ↔PA ↔Apgar <7 at 5 min ↔hypertensive disorders ↔IUGR ↔birthweight	EN, I and II, III and IV
Natural Conception Studies							
Author & year	**Country**	**Study**	**Study group**	**Control group**	**Mode of conception**	**Outcomes**	**Subgroup of analysis**
Exacoustos *et al.* (2016)	Italy	Multicentre observational cohort	Pregnancy with incomplete surgical treatment for DIE with remaining posterior DIE nodule, *N* = 200	Pregnancy with no history of endometriosis or adenomyosis, *N* = 300	NC	↑PTD ↑PP ↑PA ↑LSCS ↓NVD ↑PIH ↔GDM ↔SGA ↔instrumental delivery	DIE
Lin *et al.* (2015)	China	Single centre cohort	Singleton first pregnancy with history of endometriosis diagnosed at laparoscopy, *N* = 249	Singleton first pregnancy with normal USS and no clinical or surgical history of endometriosis, *N* = 249	NC	↑PTD ↑PP ↑LSCS ↔SGA ↔IUGR ↔PIH ↔PA	EN
Stern *et al.* (2015)	USA	Multicentre population-based cohort	Live birth with diagnosis of endometriosis by ICD10 code in medical records, *N* = 590	Live birth with no diagnosis of endometriosis by ICD10 code in medical records, *N* = 297 987	NC (NC/ART data had no control)	↑primary LSCS ↑PTD ↓birthweight ↔SGA ↔PIH ↔GDM	EN

There were 26 papers that examined stages I and II endometriosis separately from other forms of endometriosis (Table I: studies labelled I and II). All papers in this part of the analysis reported endometriosis staging by ASRM at laparoscopy or laparotomy but did not comment on whether the endometriosis was treated. Two studies examined women who conceived naturally or with ART (NC/ART), and all other studies were carried out in the IVF/ICSI treatment setting.

There were 24 papers that analysed fertility and reproductive outcome for ASRM stages III and IV endometriosis included in the review (Table I: studies labelled III and IV). Two papers were NC/ART studies; all other studies were in the IVF/ICSI setting, and there were no NC studies.

There were 18 studies that addressed endometrioma alone (Table I: studies labelled OMA). In six studies, the diagnosis of endometrioma and peritoneal endometriosis was made at laparoscopy/laparotomy. The mode of conception in all studies was IVF/ICSI. Thirteen studies diagnosed endometrioma either on cyst aspiration or on USS and had no peritoneal and DIE based on ultrasound findings.

Three studies examined the effects of DIE (Table I: studies labelled DIE) and did not present data suitable for meta-analysis. The findings of these studies have been reviewed.

There were 23 meta-analyses and systematic reviews returned in our literature search, which were analysed for their data and included studies (Barnhart *et al.*, 2002; Carvalho *et al.*, 2012; Falconer, 2012; Maheshwari *et al.*, 2012; Harb *et al.*, 2013; Asif *et al.*, 2014; Barbosa *et al.*, 2014; Vercellini *et al.*, 2014b,b; Hamdan *et al.*, 2015a,b; Somigliana *et al.*, 2015; Yang *et al.*, 2015; Rossi and Prefumo, 2016; Dueholm, 2017; Minebois *et al.*, 2017; Younes and Tulandi, 2017; Zullo *et al.*, 2017; Bruun *et al.*, 2018; Gasparri *et al.*, 2018; Jeon *et al.*, 2018; Lalani *et al.*, 2018; Pérez-López *et al.*, 2018). Twelve literature and systematic reviews analysing uncommon adverse maternal outcomes were included for qualitative analysis (Maheshwari *et al.*, 2012; Masouridou *et al.*, 2012; Vigano *et al.*, 2015; Maggiore *et al.*, 2016; Daraï *et al.*, 2017; Lier *et al.*, 2017a,b; Maggiore *et al.*, 2017; Vlahos *et al.*, 2017; Glavind *et al.*, 2018; Koninckx *et al.*, 2018; Soave *et al.*, 2018).

Primary outcome

No studies reported the healthy baby rate or presented data allowing a healthy baby rate to be determined.

Study design and setting

Studies examined the reproductive outcomes of spontaneously conceived pregnancies alone (NC; $n = 3$) or as a result of IVF/ICSI using their own gametes ($n = 79$). The population-based studies examined reproductive outcomes of all types of conception including those conceived through assisted reproduction (NC/ART; $n = 22$).

In the majority of studies, endometriosis or absence of endometriosis is diagnosed at laparoscopy. Some studies used USSs to guide diagnosis where endometriomas were identified. The control groups were women with tubal infertility ($n = 42$), male factor infertility ($n = 6$), unexplained infertility ($n = 3$), or infertility of mixed aetiology ($n = 28$) where endometriosis was excluded at laparoscopy or was not indicated in clinical history in combination with a normal pelvic USS.

Treatment of endometriosis was surgical (excision/ablation of lesions, adhesiolysis, cystectomy/drainage of endometrioma; $n = 12$), medical (gonadotrophin-releasing hormone analogues, continuous combined contraceptive; $n = 1$), or a surgical and medical treatment (gonadotrophin-releasing hormone analogues, use of continuous combined contraceptive pill or androgens; $n = 5$).

Quality of included studies and risk of bias

Downs and Black scores are shown in Table II.

Adenomyosis

Secondary outcomes were reported in the following study groups for women with adenomyosis compared to controls (Fig. 2).

CPR, LBR, and MR

No NC or NC/ART studies reported CPR, LBR, or MR. In IVF/ICSI studies, CPR was reduced (OR 0.57, CI 0.43–0.76, $P < 0.001$; $n = 7$), LBR was reduced (OR 0.45, CI 0.24–0.86, $P = 0.02$; $n = 5$), and there was an increased risk of miscarriage (OR 3.49, CI 1.41–8.65, $P = 0.007$; $n = 6$).

Late pregnancy and neonatal complications

No NC studies reported late pregnancy or neonatal complications. NC/ART studies found an increased risk of PTD (OR 2.74, CI 1.89–3.97, $P < 0.001$; $n = 5$), SGA (OR 3.90, CI 2.10–7.25, $P < 0.001$; $n = 2$), LSCS (OR 2.62, CI 1.00–6.89, $P = 0.05$; $n = 3$), and PET (OR 7.87, CI 1.26–49.20, $P = 0.03$; $n = 2$). One study found an increased risk of PP and PPH, no increased risk of PIH, and reduced risk of GDM. One study found women with adenomyosis had no increased risk of IUD but did have an increased risk of NNU admissions following delivery.

IVF/ICSI treatment outcomes

IR was reduced (OR 0.56, CI 0.39–0.8, $P = 0.001$; $n = 3$). There was no difference in oocyte yield ($n = 3$) or CR ($n = 2$; Costello *et al.*, 2011; Yan *et al.*, 2014). No other outcomes were reported.

Endometriosis

Secondary outcomes were reported in the following study groups for women with endometriosis (no subtype, severity unspecified) compared to controls (Figs 3–5).

CPR, LBR, and MR

No NC or NC/ART studies reported CPR. One NC/ART study reported reduced LBR and demonstrated that LBR was also affected in the NC subgroup analysis. IVF/ICSI studies demonstrate a reduced CPR (OR 0.85, CI 0.74–0.98, $P = 0.02$; $n = 29$) and no difference in LBR (16) or MR ($n = 17$). NC/ART studies found an increased MR (OR 1.30, CI 1.25–1.35, $P < 0.001$; $n = 3$). One NC/ART study found an increase in MR in the NC subgroup.

Late pregnancy and neonatal complications

A summary of late pregnancy and neonatal complications with endometriosis is reported in Table III.

NC studies found the risks of PIH (OR 1.29, CI 1.01–1.66, $P = 0.04$; $n = 2$), PTD (OR 1.42, CI 1.31–1.53, $P < 0.001$; $n = 3$), and LSCS (OR 1.82, CI 1.56–2.13, $P < 0.001$; $n = 2$) were increased but the risk of SGA was not ($n = 2$). No other late pregnancy outcomes were reported. They did not report neonatal outcomes.

Table II Risk of bias Downs and Black score.

	IVF/ICSI conception studies				
Study	**Study quality & reporting /8**	**External validity /3**	**Study bias /4**	**Confounding & selection bias /3**	**Total score /18**
Al-Azemi *et al.* (2000)	5	2	3	2	12
Al-Fadhli *et al.* (2006)	6	2	3	3	14
AlKudmani *et al.* (2018)	6	2	3	2	13
Arici *et al.* (1996)	5	2	3	2	12
Ashrafi *et al.* (2014)	7	1	4	3	15
Benaglia *et al.* (2013)	7	2	3	3	15
Benaglia *et al.* (2012)	8	2	3	3	16
Benaglia *et al.* (2015)	7	2	3	3	15
Benaglia *et al.* (2016)	7	2	3	2	14
Bergendal *et al.* (1998)	6	2	3	2	13
Bongioanni *et al.* (2011)	6	2	2	1	11
Borges *et al.* (2015)	6	2	3	2	13
Brosens *et al.* (2007)	5	2	3	2	12
Bukulmez *et al.* (2001)	4	2	3	2	11
Canis *et al.* (2001)	4	2	3	2	11
Chang *et al.* (1997)	6	2	3	2	13
Chiang *et al.* (1999)	7	2	3	3	13
Coccia *et al.* (2011)	7	2	3	2	12
Coelho Neto *et al.* (2015)	7	2	3	2	12
Coelho Neto *et al.* (2016)	7	2	3	3	13
Costello *et al.* (2011)	7	3	4	2	16
Dong *et al.* (2013)	6	2	3	3	14
Falconer *et al.* (2009)	5	2	3	2	12
Fernando *et al.* (2009)	5	2	3	2	12
Frydman and Belaisch-Allart (1987)	2	1	2	2	7
Frydman and Belaisch-Allart (1987)	2	1	2	2	7
Fuji *et al.* (2016)	7	2	3	3	15
Geber *et al.* (1995)	3	1	3	2	9
González-Comadran *et al.* (2017)	6	2	4	2	14
González-Foruria *et al.* (2016)	6	2	3	2	13
Guler *et al.* (2017)	5	2	2	1	10
Healy *et al.* (2010)	6	3	3	2	14
Hickman (2002)	5	2	3	2	12
Hull *et al.* (1998)	6	2	3	2	13
Jacques *et al.* (2016)	6	2	3	1	12
Kim (2011)	6	2	3	1	12
Kiran *et al.* (2012)	6	2	2	1	11
Kuivasaari *et al.* (2005)	5	2	3	2	12
Kuivasaari-Pirinen *et al.* (2012)	5	2	3	3	13
Kuroda *et al.* (2009)	6	2	3	2	13
Leonardi *et al.* (2016)	7	2	3	3	15
Lin *et al.* (2012)	5	2	3	2	12
Matalliotakis *et al.* (2011)	6	2	3	2	13
Matson and Yovich (1986)	3	0	2	0	5

Continued

Table II *Continued*

IVF/ICSI conception studies					
Study	**Study quality & reporting /8**	**External validity /3**	**Study bias /4**	**Confounding & selection bias /3**	**Total score /18**
Meden-Vrtovec *et al.* (2000)	5	2	3	3	13
Mekaru *et al.* (2013)	6	1	3	2	12
Mohamed *et al.* (2011)	7	2	3	3	15
Motte *et al.* (2016)	7	3	3	2	15
Murta *et al.* (2018)	6	3	3	2	14
Muteshi *et al.* (2018)	7	2	3	2	14
Nakagawa *et al.* (2016)	5	2	3	2	12
Nejad *et al.* (2009)	6	2	3	2	13
Oehninger *et al.* (1988)	3	1	4	3	11
Olivennes *et al.* (1995)	6	2	3	3	14
Omland *et al.* (2006)	6	2	3	2	13
Opøien *et al.* (2012)	6	2	2	2	12
Ozgur *et al.* (2018)	7	2	4	2	15
Pabuccu *et al.* (2004)	5	2	3	2	12
Pellicer *et al.* (1998)	4	2	3	0	9
Polat *et al.* (2014)	6	2	3	2	13
Pop-Trajkovic *et al.* (2014)	6	2	3	1	12
Salim *et al.* (2012)	5	3	4	2	14
Saucedo-de-la-Llata *et al.* (2004)	6	2	3	2	13
Scarselli *et al.* (2011)	5	2	3	2	12
Senapati *et al.* (2016)	6	3	3	4	16
Sharma *et al.* (2018)	6	3	3	2	14
Shebl *et al.* (2017)	7	2	3	3	15
Simon *et al.* (1994)	5	2	3	2	12
Suzuki *et al.* (2005)	5	2	3	2	12
Takemura *et al.* (2013)	5	2	3	2	12
Tanbo *et al.* (1995)	5	2	3	3	13
Thalluri and Tremellen (2012)	7	2	3	3	15
Queiroz Vaz et al. (2017)	5	2	4	2	13
Wardle *et al.* (1985)	5	2	3	1	11
Wyns and Donnez (2003)	4	2	3	2	11
Yamamoto *et al.* (2017)	6	3	4	3	16
Yan *et al.* (2014)	8	3	3	3	17
Youm *et al.* (2011)	6	2	3	3	14
Yovich and Matson (1990)	2	1	3	1	7
Natural Conception and ART Population Studies					
Study	**Study quality & reporting /8**	**External validity /3**	**Study bias /4**	**Confounding & selection bias /3**	**Total score /18**
Aris (2014)	5	3	3	2	13
Berlac *et al.* (2017)	5	2	3	2	12
Chen *et al.* (2018)	7	3	3	3	16
Conti *et al.* (2015)	6	2	3	2	13
Glavind *et al.* (2017)	8	2	2	3	15

Continued

Table II *Continued*

IVF/ICSI conception studies					
Study	**Study quality & reporting /8**	**External validity /3**	**Study bias /4**	**Confounding & selection bias /3**	**Total score /18**
Hadfield *et al.* (2009)	5	2	3	2	12
Harada *et al.* (2016)	5	3	4	3	15
Hashimoto *et al.* (2018)	7	3	3	3	16
Hjordt Hansen *et al.* (2014)	5	2	3	3	13
Juang *et al.* (2007)	7	2	3	3	15
Kohl Schwartz *et al.* (2017)	8	3	3	3	17
Kortelahti *et al.* (2003)	6	3	3	2	14
Li *et al.* (2017)	7	2	4	3	16
Mannini *et al.* (2017)	7	1	4	3	15
Mardanian *et al.* (2016)	5	2	2	2	11
Mochimaru *et al.* (2015)	7	2	3	2	14
Santulli *et al.* (2016)	7	2	3	4	16
Saraswat *et al.* (2017)	7	3	3	2	15
Shin *et al.* (2018)	8	3	4	3	18
Shmueli *et al.* (2017)	7	2	3	3	15
Stephansson *et al.* (2009)	6	2	3	2	13
Tzur *et al.* (2018)	7	2	3	3	15
Natural Conception Studies					
Study	**Study quality & reporting /8**	**External validity /3**	**Study bias /4**	**Confounding & selection bias /3**	**Total score /18**
Exacoustos *et al.* (2016)	5	2	4	1	12
Lin *et al.* (2015)	7	3	3	2	15
Stern *et al.* (2015)	5	2	3	2	12

NC/ART studies demonstrated an increased risk of PTD (OR 1.38, CI 1.01–1.89, $P = 0.04$; $n = 11$), PP (OR 3.09, CI 2.04–4.68, $P < 0.001$; $n = 9$), LSCS (OR 1.98 CI 1.64–2.38, $P < 0.001$; $n = 10$), PET (OR 1.18, CI 1.03–1.36, $P = 0.02$; $n = 11$), PA (OR 1.87, CI 1.65–2.13, $P < 0.001$; $n = 8$), and IUD (OR 1.25, CI 1.08–1.45, $P = 0.003$; $n = 5$) while the risks of GDM ($n = 6$), PIH ($n = 6$), PPH ($n = 9$), and SGA ($n = 6$) were not increased. An increased risk of NNU admission was demonstrated (OR 1.29, CI 1.07–1.55, $P = 0.007$; $n = 5$). NND was increased in one study.

In IVF/ICSI studies there was increased risk of PTD (OR 1.50, CI 1.10–2.03, $P = 0.009$; $n = 6$), PP (OR 3.31, CI 1.26–8.71, $P = 0.02$; $n = 6$), and LSCS (OR 1.73, CI 1.00–3.00, $P = 0.05$; $n = 3$). There was no difference in risk of SGA ($n = 3$), PPH ($n = 3$), PET ($n = 6$), or PIH ($n = 3$). One study reported no difference in risk of abruption or GDM. Risk of IUD was not reported. There was an increased risk of NNU admissions (OR 1.91, CI 1.12–3.26, $P = 0.02$; $n = 2$) but NND rates were not reported.

IVF/ICSI treatment outcomes

There was a reduced oocyte yield (MD −1.33, CI −1.83, −0.84, $P < 0.001$; $n = 18$), reduced FR per oocyte (OR 0.92, CI 0.86–0.99, $P = 0.03$; $n = 2$), and reduced IR (OR 0.82, CI 0.74–0.92, $P < 0.001$; $n = 12$). We also found an increased CR (OR 1.50, CI 1.22–1.84, $P < 0.001$; $n = 12$). No difference in mature oocyte yield was found ($n = 6$).

Treated endometriosis

Secondary outcomes were reported in the following study groups for women with treated endometriosis compared to controls.

CPR, LBR, and MR

No NC or NC/ART studies reported CPR, LBR, or MR. In IVF/ICSI studies, there was no difference in CPR ($n = 8$), LBR ($n = 4$), or MR ($n = 5$).

Late pregnancy complications

No NC or IVF/ICSI studies reported late pregnancy or neonatal complications. Three NC/ART studies reported late pregnancy complications. There was no increased risk of LSCS ($n = 3$). Individual studies reported other late pregnancy outcomes and found an increased risk of GDM, increased risk of PTD, PP, PPH, PIH, PET, abruption, and SGA

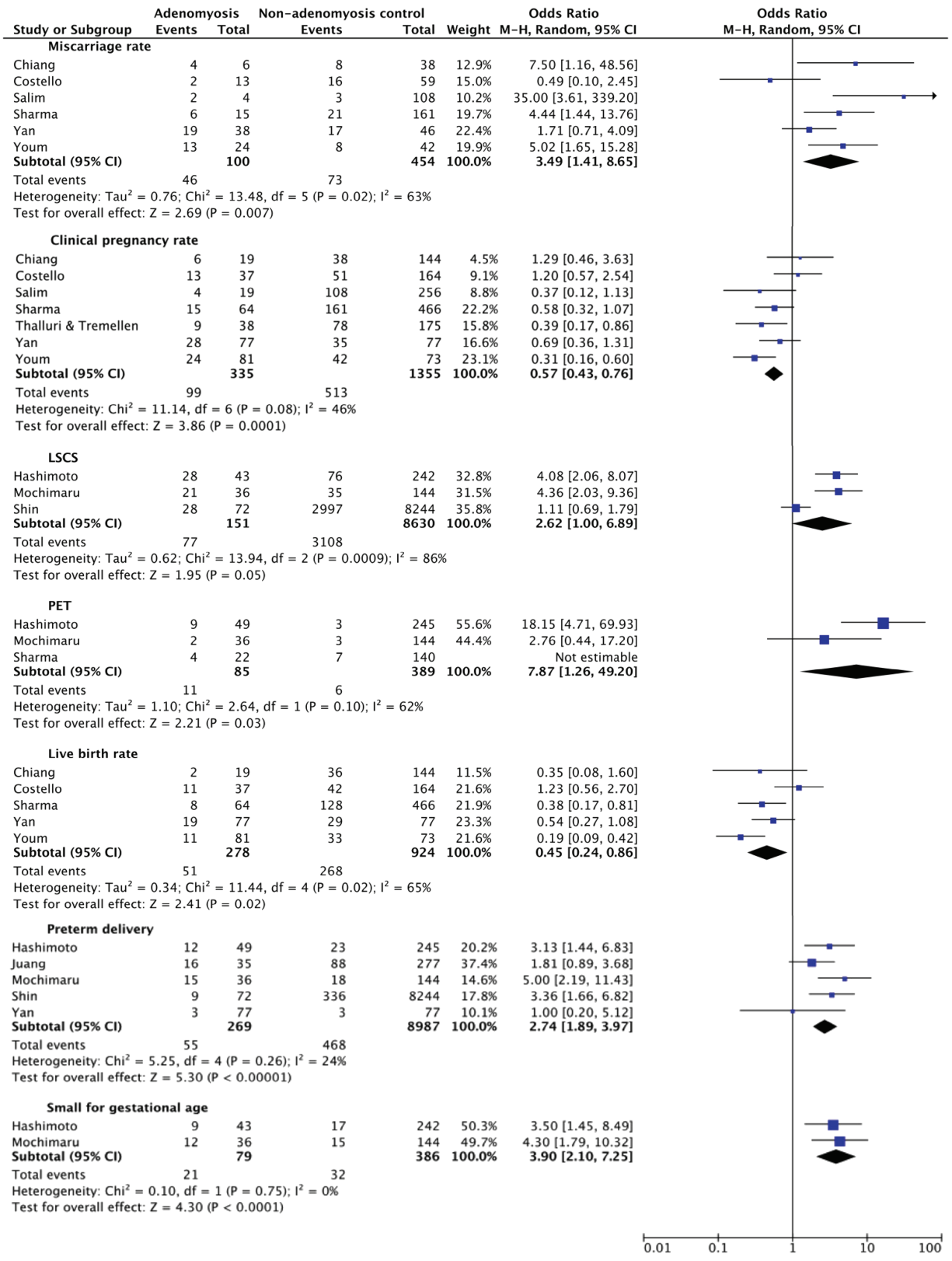

Figure 2 **Clinical pregnancy rate, miscarriage rate, live birth rate, and late pregnancy outcomes for women with adenomyosis compared to non-adenomyosis controls**.

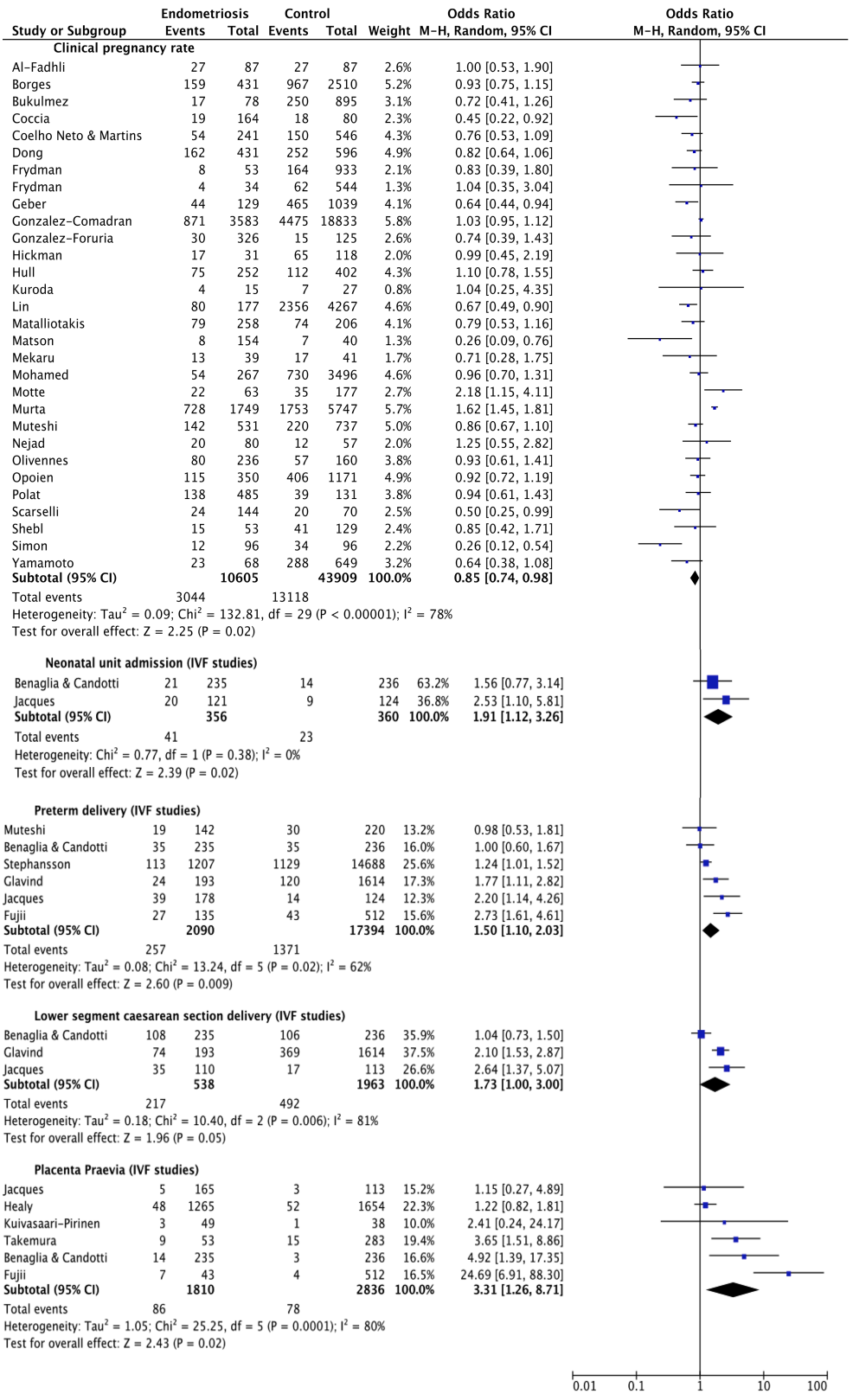

Figure 3 **Outcomes for women conceiving via IVF/ICSI with endometriosis compared to non-endometriosis controls.**

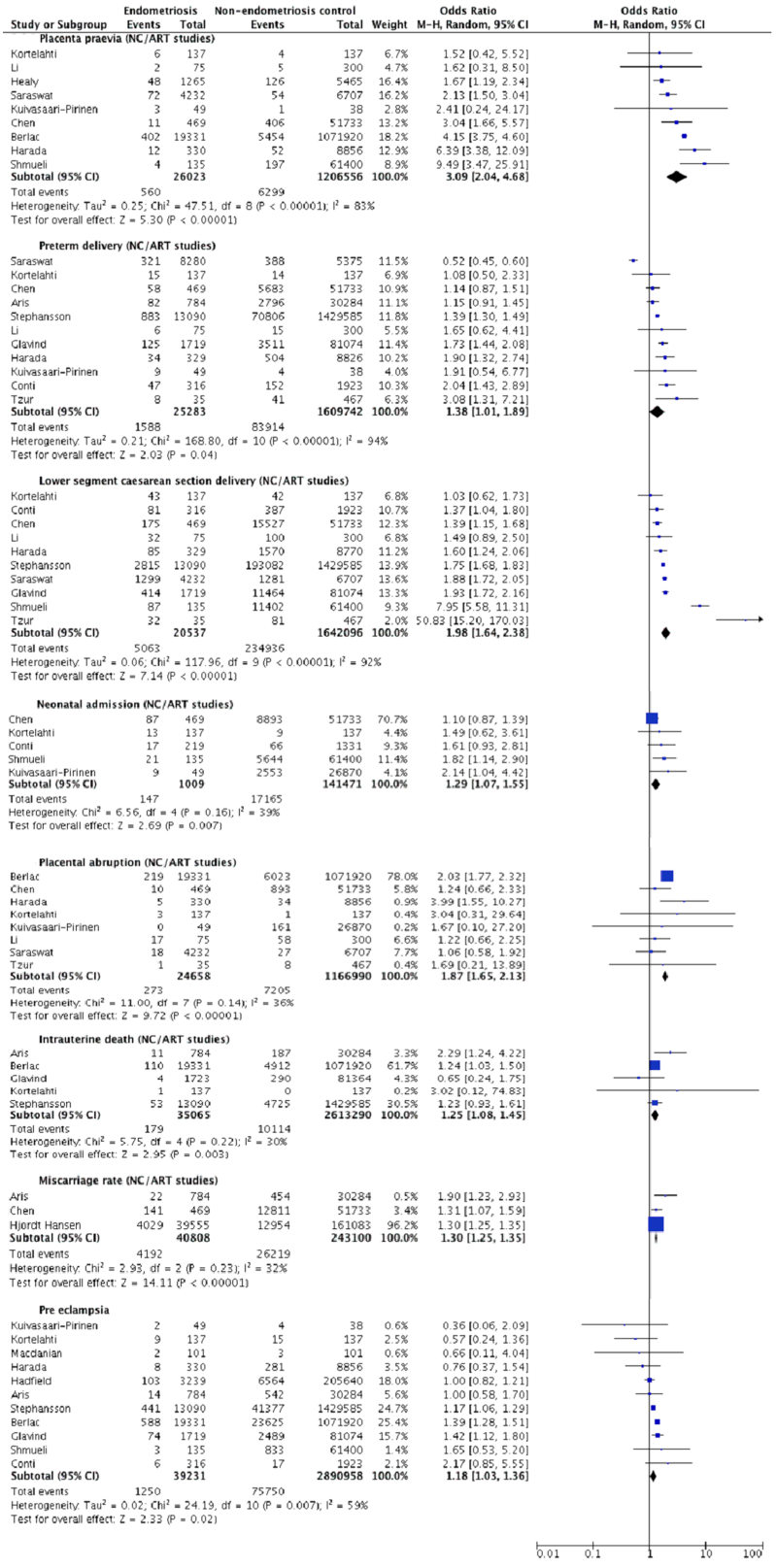

Figure 4 **Outcomes for women conceiving by NC/ART with endometriosis compared to those non-endometriosis controls**.

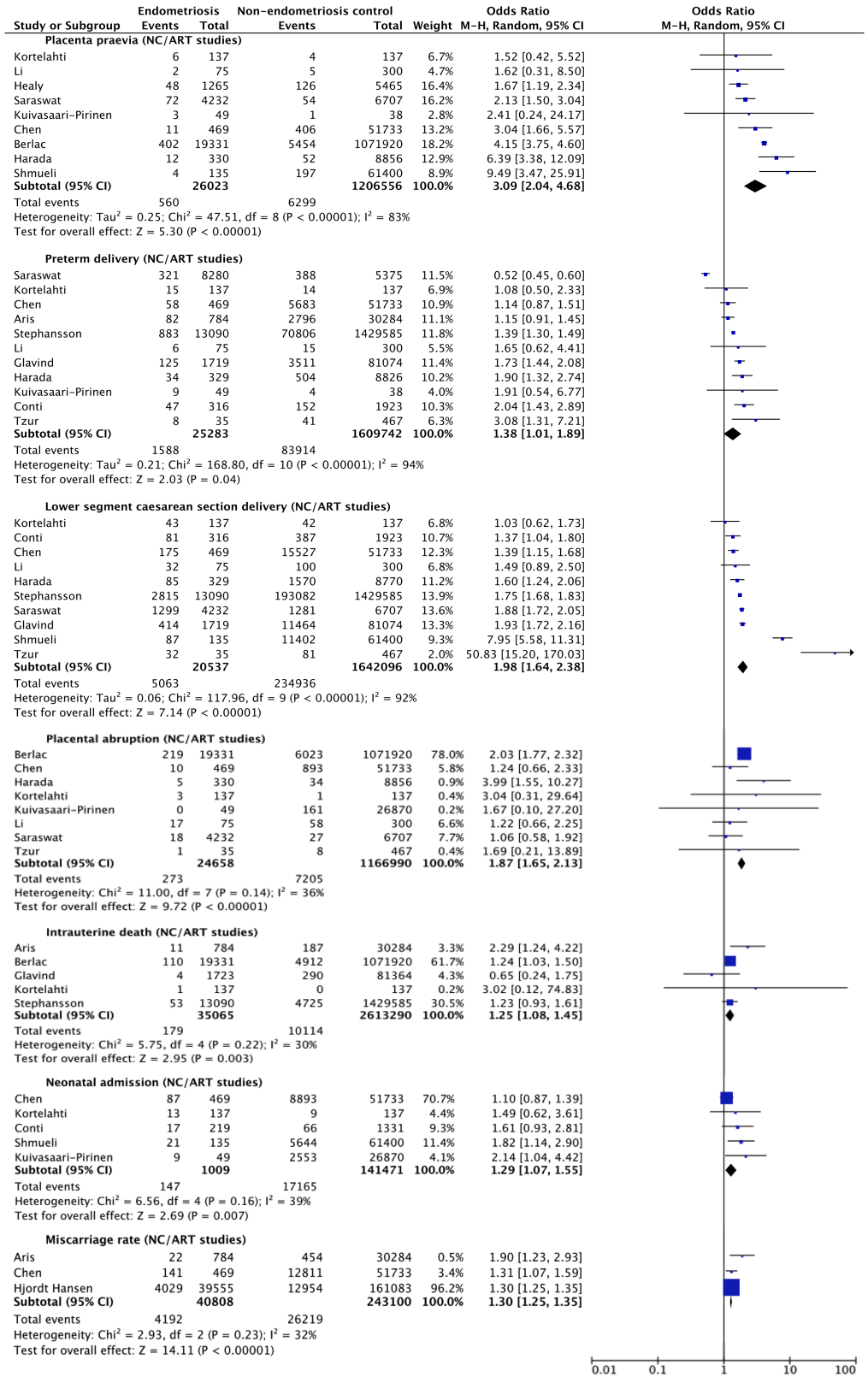

Figure 5 **Outcomes for women conceiving naturally with endometriosis compared to non-endometriosis controls**.

Table III A summary of the risk of late pregnancy and neonatal complications in endometriosis compared to controls according to the mode of conception.

Endometriosis	NC	NC/ART	IVF/ICSI
Preterm delivery	↑	↑	↑
Small for gestational age	↔	↔	↔
Lower segment caesarean section rate	↑	↑	↑
Placenta praevia		↑	↑
Placental abruption		↑	
Gestational diabetes		↔	
Post-partum haemorrhage		↔	↔
Pregnancy induced hypertension	↑	↔	↔
Pre-eclampsia		↑	↔
Intrauterine death		↑	
Neonatal admission		↑	↑
Neonatal death			

↑, risk significantly increased in endometriosis; ↔, no difference in risk; blank, no data for meta-analysis.

and no difference in risk of IUD. One study reported an increased risk of NND.

IVF/ICSI treatment outcomes

Oocyte yield (MD −1.21, CI −1.40, −1.02, $P < 0.001$; $n = 6$), mature oocyte yield (MD −1.27, CI −1.45, −1.08, $P < 0.001$; $n = 3$), and FR were reduced (OR 0.92, CI 0.86–0.99, $P = 0.03$; $n = 2$). There was no difference in IR ($n = 3$) or CR ($n = 3$).

Untreated endometriosis

One study examined the effect of untreated endometriosis on fertility and reproductive outcomes and found no difference in CPR, MR, oocyte yield, FR, or IR.

Endometriosis subtypes analysis

Stages I and II endometriosis

Secondary outcomes were reported in the following study groups for women with stages I and II endometriosis compared to controls.

CPR, LBR, and MR. No NC studies reported any of our secondary, late pregnancy, or neonatal outcomes. One NC/ART study reported an increased MR, and no other secondary, late pregnancy, or neonatal outcomes were reported. IVF/ICSI studies showed no difference in CPR ($n = 14$) or LBR ($n = 8$) but demonstrated an increased MR (OR 1.39, CI 1.05–1.85, $P = 0.02$; $n = 10$).

Late pregnancy and neonatal complications. One IVF/ICSI study found no increased risk of LSCS, PPH, GDM, PET, PP, PTD, or NNU admission. No other studies examined late pregnancy complications.

IVF/ICSI treatment outcomes. There was a reduced FR (OR 0.77, CI 0.63–0.93, $P = 0.007$; $n = 8$) and IR (OR 0.76, CI 0.62–0.93, $P = 0.008$; $n = 8$) and an increased CR (OR 1.74, CI 1.13–2.67, $P = 0.01$; $n = 4$). There was no difference in oocyte yield ($n = 11$) or number of mature oocytes ($n = 3$).

Stages III and IV endometriosis

Secondary outcomes were reported in the following study groups for women with stages III and IV endometriosis compared to controls.

CPR, LBR, and MR. No NC studies reported any of our secondary, late pregnancy, or neonatal outcomes. One NC/ART study reported an increased MR, and no other secondary, late pregnancy, or neonatal outcomes were reported. In IVF/ICSI studies, there was no difference in CPR ($n = 14$) but there was a reduced LBR (OR 0.78, CI 0.65–0.95, $P = 0.01$; $n = 10$) and an increased MR (OR 1.31, CI 1.03–1.67, $P = 0.03$; $n = 10$).

Late pregnancy and neonatal complications. IVF/ICSI studies found no difference in risk of PET ($n = 2$) or PPH ($n = 2$). One IVF/ICSI study reported an increased risk of LSCS, PTD, and risk of NNU admission but no difference in risk of PP or GDM, and another found no increased risk of IUD.

IVF/ICSI treatment outcomes. There was a significant reduction in oocyte yield (MD −1.69, CI −2.45, −0.92, $P < 0.001$; $n = 11$), mature oocyte yield (MD −0.76, CI −1.48, −0.05, $P = 0.04$; $n = 4$), and IR (OR 0.80, CI 0.70–0.92, $P = 0.001$; $n = 11$). There was no difference in FR ($n = 7$) or CR ($n = 4$).

Endometrioma

Secondary outcomes were reported in the following study groups for women with endometrioma compared to controls.

CPR, LBR, and MR. There were no NC or NC/ART studies eligible for inclusion. Studies in IVF/ICSI conceived pregnancies found no difference in CPR ($n = 9$), LBR ($n = 5$), or MR ($n = 4$).

Late pregnancy and neonatal complications. There was no difference in risk of PTD or SGA ($n = 2$) in IVF/ICSI studies. One study demonstrated no increased risk of LSCS. No other late pregnancy or neonatal complications were reported.

IVF/ICSI treatment outcomes. There was lower oocyte yield (MD −1.22, CI −1.96, −0.49 $P = 0.001$; $n = 12$) and lower mature oocyte

Table IV Summary of findings.

	Adenomyosis			Endometriosis Overall			Treated Endometriosis			Stage I-II Endometriosis			Stage III-IV Endometriosis			Endometrioma			DIE		
	NC	NC/ART	IVF/ICSI	NC	NC/ART	IVF/ICSI	NC	NC/ART	IVF/ICSI	NC	NC/ART	IVF/ICSI	NC	NC/ART	IVF/ICSI	NC	NC/ART	IVF/ICSI	NC	NC/ART	IVF/ICSI
Primary Outcome																					
HBR																					
Secondary Outcomes																					
CPR			⇓ n=7			⇓ n=29			↔ n=8			↔ n=14			↔ n=14			↔ n=9			↔ n=1
LBR			⇓ n=5	↓ n=1	↓ n=1	↔ n=16			↔ n=4			↔ n=8			⇓ n=10			↔ n=5			
Early Pregnancy Complications																					
Miscarriage			⇑ n=6	↑ n=1	⇑ n=3	↔ n=17			↔ n=5		↑ n=1	⇑ n=10		↑ n=1	⇑ n=10	↑ n=1		↔ n=4		↑ n=1	↔ n=1
Late Pregnancy Complications																					
PIH		↔ n= 1		⇑ n=2	↔ n=6	↔ n=3		↑ n=1												↔ n=1		
PET		⇑ n= 2			⇑ n=11	↔ n=6		↑ n=1				↔ n=1			↔ n=2						
GDM		↓ n=1			↔ n=6	↔ n=1		↑ n=1				↔ n=1			↔ n=1					↔ n=1	
PTD		⇑ n=5		⇑ n=3	⇑ n=11	⇑ n=6		↑ n=1				↔ n=1			↑ n=1			↔ n=2		↑ n=1	
SGA		⇑ n=2		↔ n=2	↔ n=6	↔ n=3		↑ n=1										↔ n=2		↔ n=1	
PP		↑ n=1			⇑ n=9	⇑ n=6		↑ n=1				↔ n=1			↔ n=1					↑ n=1	
PA					⇑ n=8	↔ n=1		↑ n=1												↑ n=1	
PPH		↑ n=1			↔ n=9	↔ n=3		↑ n=1				↔ n=1			↔ n=2						

Continued

Table IV *Continued*

	Adenomyosis			Endometriosis Overall			Treated Endometriosis			Stage I-II Endometriosis			Stage III-IV Endometriosis			Endometrioma			DIE		
	NC	NC/ART	IVF/ICSI	NC	NC/ART	IVF/ICSI	NC	NC/ART	IVF/ICSI	NC	NC/ART	IVF/ICSI	NC	NC/ART	IVF/ICSI	NC	NC/ART	IVF/ICSI	NC	NC/ART	IVF/ICSI
LSCS		↑ n= 3		↑ n=2	↑ n=10	↑ n=3		↔ n=3				↔ n=1			↑ n=1			↔ n=1	↑ n=1		
IUD		↔ n=1			↑ n=5			↔ n=1							↔ n=1						
Neonatal Complications																					
NNU		↑ n=1			↑ n=5	↑ n=2						↔ n=1			↑ n=1						
NND					↑ n=1			↑ n=1													
Fertility Outcomes																					
OR			↔ n=3			↓ n=18			↓ n=6			↔ n=11			↓ n=11			↓ n=12			
MII			↔ n=1			↔ n=6			↓ n=3			↔ n=3			↓ n=4			↓ n=4			
CR			↔ n=2			↑ n=12			↔ n=3			↑ n=4			↔ n=4			↔ n=5			
FR			↔ n=1			↓ n=2			↓ n=2			↓ n=8			↔ n=7			↑ n=1 ↔ n=1			
IR			↓ n=3			↓ n=12			↔ n=3			↓ n=8			↓ n=11			↔ n=3			

Key: HBR, healthy baby rate; PTD, preterm delivery; PPH, post-partum haemorrhage; CPR, clinical pregnancy rate; SGA, small for gestational age; LSCS, lower segment caesarean section; LBR, live birth rate; PP, placenta praevia; IUD, intrauterine death; MR, miscarriage rate; PA, placental abruption; NNU, neonatal admission; PIH, pregnancy-induced hypertension; NND, Neonatal death; OR, ovarian response (oocyte yield); PET, pre-eclampsia; M2, mature (MII) oocytes; FR, fertilization rate; GDM, gestational diabetes; CR, cycle cancellation rate; IR, implantation rate; = significantly increased in meta-analysis; ↓, result decreased but insufficient data for meta-analysis; = significantly decreased in meta-analysis; ↑, result increased but insufficient data for meta-analysis; ↔, result equivocal; Blank, no data.

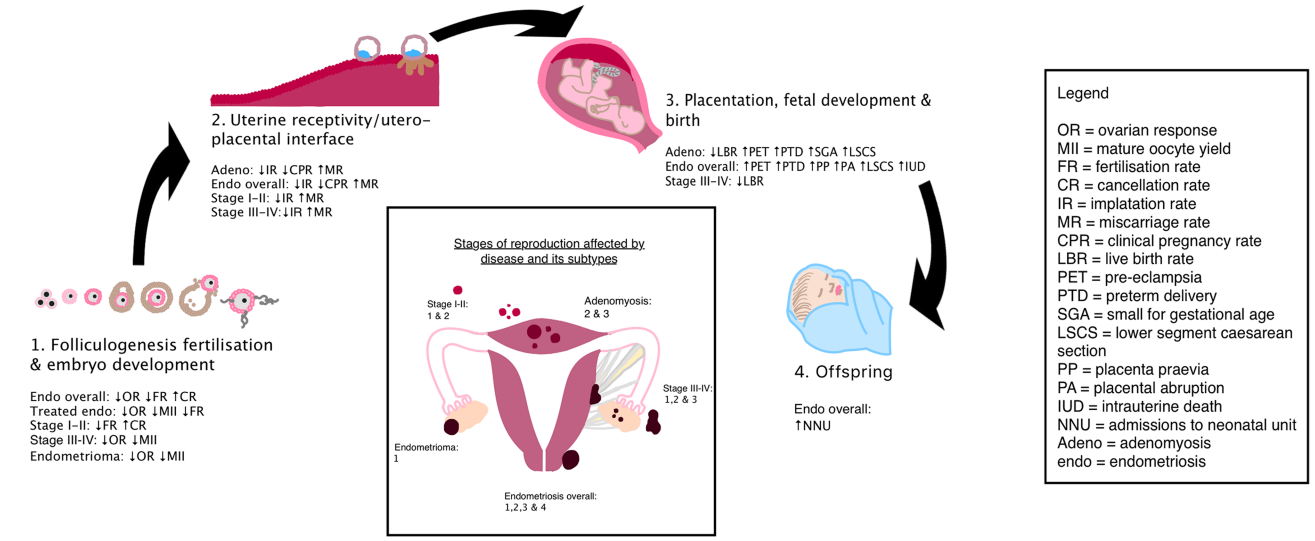

Figure 6 Summary of findings: impact of adenomyosis and endometriosis on fertility, obstetric, and neonatal outcomes.

yield (MD −2.24, CI −3.40, −1.09, $P < 0.001$; $n = 4$). There was no difference in IR ($n = 3$) or CR ($n = 5$). Two studies reported FR, but data could not be combined. One study found an increased FR, and the other found no difference in FR.

DIE

Only three studies met the inclusion criteria for the presence of DIE. One study was an IVF/ICSI study (Queiroz Vaz *et al.*, 2017), one was NC/ART (Santulli *et al.*, 2016), and the other was NC (Exacoustos *et al.*, 2016), and therefore no data could be combined in meta-analysis. Santulli *et al.* (2016) reported that MR was higher in patients with DIE. Queiroz Vaz *et al.* (2017) found no difference in CPR or MR. Exacoustos *et al.* (2016) reported an increased risk of PTD, PP, PA, and LSCS in women with DIE but no difference in risk of PIH, GDM, and SGA.

Qualitative analysis

Uncommon obstetric complications in women with endometriosis

Haemoperitoneum in pregnancy. The overall prevalence of spontaneous haemoperitonium in pregnancy (SHiP) is believed to be 0.4% (Vigano *et al.*, 2015). The retrospective review by Katorza *et al.* (2007) to identify any late pregnancy complications of 800 women with known endometriosis found that three cases of intra-abdominal bleeding occurred in the third trimester from endometriotic lesions and thin-walled varicosities.

Our systematic literature search resulted in five individual case reports (Roche *et al.*, 2008; Reif *et al.*, 2011; Williamson *et al.*, 2011; Cozzolino *et al.*, 2015; Petresin *et al.*, 2016) and five published systematic reviews investigating this complication. A systematic review by Maggiore *et al.* (2017) found 39 cases of SHiP in women with endometriosis, but a more recent review found out of 75 recorded cases of SHiP, 53 of them were in women suffering with endometriosis (Glavind *et al.*, 2018). In a large review by Lier *et al.* (2017b) identifying 59 cases of endometriosis-related SHiP, 56 of the cases were managed surgically, at which time, in 51 out of 56 cases, the cause of bleeding was directly linked to endometriosis. This is higher than a finding in an earlier review (Brosens *et al.*, 2012) where >50% of cases of SHiP were found to be caused by endometriosis.

SHiP may be due to adhesions put under tension as the gravid uterus enlarges, chronic inflammation causing tissues affected by endometriosis to be more friable, invasion of endometriotic lesions into blood vessel walls, or from pre-existing endometriotic lesions undergoing decidualization secondary to the progesterone levels of pregnancy (Maggiore *et al.*, 2016). SHiP carries a high risk of maternal morbidity and is associated with 31% mortality of the fetus (Brosens *et al.*, 2012).

Adnexal masses. Adnexal masses are found in 0.5–1.2% of pregnancies (Maggiore *et al.*, 2016). Ovarian endometriomas are the most common adnexal mass diagnosed in pregnancy (1:200; Brosens *et al.*, 2012). The cyst can increase in size in 5–20% of cases (Vigano *et al.*, 2015), and a rapidly enlarging endometrioma is associated with a risk of abscess formation and rupture (Brosens *et al.*, 2012). Fourteen cases of endometrioma rupture and three cases of infection were found in a review by Maggiore *et al.* (2016). Endometrioma mimicking malignancy has been noted in pregnancy due to extensive decidualization within the cyst in response to increasing progesterone (Barbieri *et al.*, 2009; Taylor *et al.*, 2015; Maggiore *et al.*, 2016). It should also be noted that an endometrioma at the time of oocyte retrieval in IVF/ICSI treatment carries a higher risk of abscess formation than in women without endometrioma (Somigliana *et al.*, 2015).

Other sites of endometriosis. Decidualization of other sites of endometriosis including the bladder, umbilicus, caesarean section scar, and vulva has also been documented in case reports where the lesions are mistaken for malignancy (Maggiore *et al.*, 2016). Distant site decidualization of endometriosis in pregnancy has also been documented in the form of spontaneous pneumothorax (four cases), pseudoaneurysm of the thoracic aorta at the repair site of surgically

corrected coarctation (one case), and para-aortic lymph nodes (one case; Maggiore et al., 2016).

Bowel perforation. Two case reports were identified in our search; one case demonstrated a woman who suffered an ileal perforation with abscess formation during pregnancy, and caesarean section delivery was performed with severe bladder injury due to pelvic endometriosis. The histological findings from the terminal ileum confirmed endometriosis (Nishikawa et al., 2013). Another reported perforation of the rectosigmoid at 33 weeks gestation in a woman with known rectosigmoid stenosis and four previous operative laparoscopies for stage IV endometriosis (Carneiro et al., 2018). Overall, 17 cases of intestinal perforation in pregnancy secondary to endometriosis have been found in systematic reviews by Maggiore et al. (2017) and Glavind et al. (2018).

Appendicitis. Appendiceal endometriosis is rare, with a prevalence of 2.8% in women with endometriosis. Ten cases of acute appendicitis due to appendiceal endometriosis have been documented in pregnancy (Maggiore et al., 2017).

Ureteral rupture. Ureteral rupture has been documented in two case reports. One consisted of a woman who had stage IV endometriosis and a nodule of endometriosis on the right broad ligament where the nodule was found to have caused rupture of the right uterine artery and rupture of the right ureter at the level of the nodule (Vigano et al., 2015), and the other reported uroperitoneum in a woman who previously had a transurethral bladder nodule resection (Maggiore et al., 2015).

Uterine rupture. A large review by Maggiore et al. (2017) has identified 63 cases of uterine rupture of pregnancy in women with endometriosis (five of which also had adenomyosis). Three cases of uterine rupture in women with history of endometriosis surgery have been documented in a review (Vigano et al., 2015). One case has documented rupture due to endometriosis at the level of a uterine scar 6 weeks post-caesarean section delivery (Maggiore et al., 2016).

Uncommon obstetric complications in women with adenomyosis

Abscess formation. Our systematic review has identified one case report of a rapidly increasing adenomyosis resulting in preterm labour and post-partum abscess formation within the myometrium. It is theorized that decidualization and haemorrhage occurred in the adenomyotic foci during the pregnancy and following delivery an ischaemic state occurred giving rise to abscess formation (Kim et al., 2016).

Degeneration. A Japanese case report documented the diagnostic difficulty of distinguishing degeneration of adenomyomas (eventually diagnosed post-natally with CT and MRI) from chorioamnionitis or adenomyosis abscess formation (Hirashima et al., 2018).

Uterine rupture. In a review by Soave et al. (2018), a study was identified that investigated the risk of uterine rupture in a prospective study of 23 women having open abdominal treatment of adenomyosis. Eight women suffered a miscarriage, just over half of the women went on to have a delivery, and 8.7% suffered a uterine rupture.

It has also been proposed that there is an increased risk of severe PPH in women with adenomyosis, supported by a prevalence of 17.2% found histologically in women who have needed a caesarean hysterectomy (Vlahos et al., 2017).

A systematic review by Maheshwari et al., 2012 also found case reports of adenomyosis or adenomyosis surgery resulting in uterine perforation and rupture in pregnancy and ectopic pregnancies within areas of adenomyosis.

Discussion

In this systematic review and meta-analysis, we investigated the reproductive, obstetric, and neonatal outcomes of women with endometriosis and adenomyosis. The data on the impact of the disease on gametes and fertilization were derived from studies with a population of women undergoing IVF/ICSI treatment, where data pertaining to fertilization and embryo development can be obtained from routinely recorded laboratory observations; while the outcomes on early and late pregnancy complications were obtained from the collation of data from a combination of epidemiological data as well as case–control studies.

Main findings

The main findings are reported in Table IV and summarized in Fig. 6.

This analysis found that no studies reported a healthy baby rate, and none presented data whereby a healthy baby rate could be calculated by the reviewers. While CPR and LBR are important outcomes of interest, a healthy baby rate may be more meaningful to women with endometriosis or adenomyosis in light of the growing evidence of obstetric and neonatal complications associated with the diseases.

IVF/ICSI treatment outcomes

All comparative analyses of endometriosis in IVF/ICSI studies of this meta-analysis demonstrate a negative impact of the disease on various IVF parameters, in agreement with current evidence, and give us insight into the effect on early gamete and embryo development. We found endometriosis consistently leads to reduced oocyte yield and a reduction in mature oocytes in the more severe subtype and those affected by endometrioma. This is indicative of altered folliculogenesis and oocyte development; the cause of which may be due to altered steroidogenesis and raised inflammatory markers in the follicular environment. Dysfunctional steroidogenesis in endometriosis patients results in oestrogen levels that are increased in the peritoneal fluid but decreased in the follicular fluid (Gupta et al., 2008; Xu et al., 2015). Elevated interleukins seen in endometriosis patients can cause cell cycle abnormalities such as those preventing p27 breakdown leading to G0 arrest (Gupta et al., 2008), and follicles with higher levels of interleukins are more likely to contain an immature oocyte (Sanchez et al., 2017). We found a reduced FR implicating poorer oocyte quality in line with findings of reactive oxygen species-induced DNA damage, spindle abnormalities, and reduced membrane integrity in endometriosis, which contribute to oocyte damage, degradation, or apoptosis (Gupta et al., 2008). During the ICSI process, reactive oxygen species can also induce embryonic fragmentation and result in fewer blastocysts (Gupta et al., 2008). Morphological differences in oocytes have also been noted in endometriosis patients including increased cytoplasmic granulation, increased zona pellucida hardening, lower mitochondrial content, and a higher proportion of abnormal mitochondria that may have a negative impact on fertilization (Sanchez

et al., 2017). In all stages of endometriosis, we found reduced IR, demonstrating a potential clinical impact of changes found at the molecular level in endometrial gene expression (Taylor, 1999; Kao et al., 2003; Casals et al., 2012), adhesion molecules (Bridges et al., 1994; Lessey, 2002; Lessey et al., 1994) implantation markers, and local response to progesterone (de Ziegler et al., 2016).

Early pregnancy complications

The IVF/ICSI studies also reveal that an increased risk of miscarriage is associated with adenomyosis and endometriosis of all ASRM stages, further supporting a theory of suboptimal implantation and early development.

We found over 3-fold increased risk of miscarriage in adenomyosis patients with IVF pregnancy, and this miscarriage risk was not commonly reported in NC studies. The risk of miscarriage for women with endometriosis was 30% higher than in controls in pregnancy conceived by any mode of conception.

Late pregnancy and neonatal outcomes

We found that endometriosis can be associated with a range of obstetric and fetal complications in IVF pregnancies compared to non-endometriosis IVF controls, including PTD (50% higher risk than controls), caesarean section delivery (73% higher risk), PP (over 3-fold risk), and NNU admission following delivery (~2-fold increased risk). We found similar complications are associated with endometriosis in pregnancies by any mode of conception (NC/ART) compared to non-endometriosis controls including a 38% increased risk of PTD, 18% higher risk of PET, 87% higher risk of PA, 29% higher risk of NNU admission following delivery, 25% higher risk of IUD, nearly 2-fold increase in caesarean section delivery, and over 3-fold increased risk of PP. Women with endometriosis conceiving naturally were shown to have an increased risk of caesarean section delivery (82% higher risk), PTD (42% higher risk), and PIH (29% increased risk) compared to controls.

These findings suggest possible implantation and placentation abnormalities, but data on individual endometriosis subtypes were lacking to draw conclusions regarding subtype-specific complications. Implantation and early placentation is differentially modulated in the endometrium of women with endometriosis compared to those without, for example in the differential expression of key factors in decidualization and implantation by way of aberrant angiogenesis, immune remodelling, alternations in cell adhesion molecules, matrix remodelling, and immune signalling (Lessey, 2002; May et al., 2011; de Ziegler et al., 2016) and the overexpression of vascular endothelial growth factor, angiopoietins, and their receptor. Several changes found in endometriosis could be implicated in the association with placental insufficiency disorders. The thickness of the junctional zone (JZ) has been shown to be increased (Kunz et al., 2000), endometrial blood perfusion is increased (Xavier et al., 2005; de Ziegler et al., 2016), and there may be suppression of HOXA-10 upregulation that regulates endometrium receptivity to implantation (de Ziegler et al., 2016). Suboptimal placentation can also result from defective spiral artery remodelling at the JZ of the myometrium–endometrium interface together with the size of placental bed and distribution of spiral artery transformation within the placental bed favouring the centre to the periphery (Brosens et al., 2011; de Ziegler et al., 2016), although this has not been investigated specifically in endometriosis or adenomyosis. These known pathological processes could give rise to increased risk of miscarriage, PET, PIH, preterm labour, IUD, PA, and PP. The higher risk of LSCS delivery was found in IVF/ICSI and NC/ART studies but was not found in women conceiving naturally. This outcome is possibly a consequence of the aforementioned obstetric complications or may be influenced by conceiving through ART, either through additional physiological differences in these pregnancies or through a lower threshold to deliver by caesarean in women who have struggled with infertility. Whether the presence of these abnormalities in women with endometriosis and adenomyosis is responsible for the increased risk of early miscarriages and/or later obstetrics complications will need to be borne out of future longitudinal large cohort studies.

Disease subtype-specific outcomes

Disease and subtype-specific outcomes are also observed in our meta-analysis and systematic review although sensitivity analysis for these subgroups revealed that a number of findings must be viewed with caution due to results being influenced by small numbers of studies in these areas (Supplementary Table SIII). Milder forms of endometriosis are more likely to affect the fertilization and earlier implantation processes and impact on miscarriage risk as depicted in Fig. 6. The more severe diseases (ASRM III and IV) influence all stages of reproduction, from the stages of oocyte and gamete development to early and later pregnancy complications (Fig. 6). Ovarian endometriosis negatively affects the oocyte yield and number of mature oocytes per IVF/ICSI cycle compared to controls. Our group and others have shown that conditions with elevated reactive oxidative species such as endometriosis can detrimentally impact on follicular maturation with resultant meiotic spindle and oocyte DNA damage (Gupta et al., 2008; Hamdan et al., 2016). The evidence that can be collated on DIE is less complete due to the lack of studies with suitable control groups, and many studies did not differentiate DIE from ASRM stages III and IV disease. It is, however, observed that DIE is associated with an increased miscarriage risk, and a reduced cumulative pregnancy rate (Ballester et al., 2012), with associated complications antenatally such as those late pregnancy outcomes of our analysis (Table IV). There is also a growing number of case reports highlighting uncommon antenatal complications that pose significant morbidity and mortality risks to both the mother and fetus. In our systematic literature search we identified 12 case reports (Katorza et al., 2007; Roche et al., 2008; Barbieri et al., 2009; Reif et al., 2011; Williamson et al., 2011; Nishikawa et al., 2013; Cozzolino et al., 2015; Taylor et al., 2015; Kim et al., 2016; Petresin et al., 2016; Carneiro et al., 2018; Hirashima et al., 2018) and 12 literature and systematic reviews analysing uncommon adverse maternal outcomes (Maheshwari et al., 2012; Masouridou et al., 2012; Vigano et al., 2015; Maggiore et al., 2016; Daraï et al., 2017; Lier et al., 2017a,b; Maggiore et al., 2017; Vlahos et al., 2017; Glavind et al., 2018; Koninckx et al., 2018; Soave et al., 2018). The reports included uterine rupture, ovarian cyst accidents requiring surgery in pregnancy, spontaneous haemoperitoneum, and spontaneous bowel perforation. Furthermore, DIE and severe endometriosis are associated with third- and fourth-degree tears due to rectovaginal endometriotic lesions (Thomin et al., 2018) and increased surgical complications at caesarean section delivery including bladder injury,

bowel injury, and peripartum hysterectomy. Increased risk of perineal injury may be due to the infiltrating disease causing tissues to be more friable.

Implications for clinical practise

Although collation of all data into a thorough and conclusive meta-analysis to fully explore the impact of endometriosis and adenomyosis on obstetric and fetal complications is hindered by heterogeneity of current studies, evidence of the disease–outcome link is broad. Therefore, we feel the evidence is such that a paradigm shift is required towards an increased awareness of the impact of the disease on preimplantation embryo programming, the obstetric impact on the mother, and the longer-term impact on the health of the children born. While super-specialization is increasingly polarizing obstetrics and gynaecology, the care of women with adenomyosis and endometriosis undoubtedly warrants a more joined-up approach in gynaecological, preconception, and antenatal management. These women, particularly those with more severe stages of disease or following extensive abdominal surgery, should be counselled regarding the risks beyond difficulty trying to conceive. They should be informed of the increased risks of early and late pregnancy complications and the potential morbidity involved, especially in the sphere of ART where the risks may be higher and women are medically assisted to achieve higher-risk pregnancies. The shift in perception of risk with these women should also precipitate into their antenatal and peripartum management where risk-modifying steps may be taken, for example increased antenatal blood pressure monitoring or consideration of aspirin for associated risk of PIH and PET or planned delivery in hospital due to associated risk of LSCS deliveries and neonatal admission. Careful counselling may be indicated for women with severe endometriosis and deeply infiltrating disease, particularly those who have had extensive surgery owing to the associated risks of SHiP, surgical complications at caesarean section, and complications at vaginal delivery. As well as pre-conception advice, particular caution may be warranted in the sphere of ART where clinicians may be taking some responsibility in facilitating a higher risk pregnancy. Clinicians in reproductive medicine should communicate these risks to their obstetric colleagues in early pregnancy.

Explanation of findings

There is no doubt that the reproductive impact of the aforementioned disorders starts at the early stages of gamete and embryo development and that the impact is throughout the life course of reproduction. The Barker's hypothesis, where adverse events during the peri-implantation period may program development and influence disease later in life (Barker, 1990), is extensively studied in relation to overt overnutrition and undernutrition in animal models and human studies. The concept of Barker's hypothesis in the context of endometriosis has only been explored pertaining to the aetiology and how *in-utero* exposure to environmental factors may influence the development of endometriosis in the offspring (Wei *et al*., 2016). However, the abnormally placed endometrial glands and stroma in adenomyosis and endometriosis create a suboptimal developmental environment for the conceptus within the reproductive tract (Robertson *et al*., 2015; Salamonsen *et al*., 2016) and hence has implications that warrant exploration in the context of developmental programming, where aberrant decidualization and placentation within the perturbed uterine environment can be linked not only to problems relating to placental insufficiency but also childhood and adult diseases. Many obstetric complications such as abnormal placentation, PET, preterm birth, and preterm rupture of membranes have complex aetiology, and studies thus far have primarily focussed on the stages of later pregnancy and birth at which point the disease has already been established. Arguably, the fate of the pregnancy may have been determined much earlier on, although how the related aberrant uterine environment perturbs the progression of fertilization, implantation and later pregnancy progression, and birth outcomes in terms of a take-home healthy baby warrants further investigation. No papers currently report on the 'healthy baby rate', defined as a live singleton birth at term of appropriate birthweight for gestation, or the health of the offspring in the context of endometriosis, and this review highlights the need for future studies to consider these key reproductive outcomes and the health of the offspring.

Strengths and weaknesses of the study

This is an extensive review and has attempted to examine all published work on the reproductive impacts of endometriosis and adenomyosis to emphasize the need for a holistic rather than a polarized view of the conditions. The papers included demonstrate low publication bias by funnel plot analysis (Supplementary Table SIII). However, a minimal level of bias may exist towards studies published in English; while five studies were successfully translated for inclusion, this was not possible in two other studies. Owing to the nature of systematic reviews, this meta-analysis is confounded by heterogeneity of the clinical studies included although strict criteria were applied to minimize this. Due to the size of this meta-analysis, literature search and data extraction were performed independently by a second reviewer for studies between the years 2000 and 2010. While no discrepancies were highlighted, a complete second reviewer search and extraction would have reduced the risk of study selection bias. The gold standard for diagnosis of endometriosis and its subtypes is laparoscopy; where studies use database medical records or imaging, it is possible that false positive and false negative error is occurring, and this reduces the reliability of observed results. Control cohorts in IVF/ICSI studies vary widely between mixed aetiology infertility, male factor, tubal factor, or unexplained infertility. These causes of infertility may also influence the fertility and reproductive outcomes of interest and may not represent a consistent control in this analysis. Individual protocols for ovarian stimulation and other factors in the ART treatment between units and countries and across the time period included in our meta-analysis introduce heterogeneity.

Implications for future research

The heterogeneity of studies is difficult to overcome in a review of 104 papers but this meta-analysis highlights that a more unified approach to studying fertility and reproductive outcomes in these patients is essential in improving knowledge in this area and making a real impact on managing subfertility, the antenatal and intra-partum course. It would be of importance to investigate whether through surgical treatment there is the potential to modify health risks highlighted in this review for both women affected by endometriosis and their offspring. Thorough investigation of the risk to women with endometriosis or adenomyosis undertaking oocyte donation IVF is also warranted to extrapolate the risks associated with these pregnancies, where the oocyte and

early embryo development is unaffected by the disease but may be influenced following implantation.

Conclusion

From the current literature, we conclude that adenomyosis and endometriosis have a negative impact on parameters pertaining to the whole reproductive course, from oocyte number and quality to neonatal outcomes. Compared to women without endometriosis, pregnancy outcomes in IVF, ART pregnancies, and spontaneously conceived pregnancies are negatively affected with emerging evidence of an increased risk of PTD, PET, PP, caesarean section delivery, and need for neonatal admission. These complications could be caused by dysfunctional uterine changes impairing the decidualization and placentation process, and therefore these conditions could potentially have far-reaching consequences as suggested by Barker's hypothesis. Studies in this area lack longer term follow-up into the neonatal period and beyond to verify this theory. There is insufficient data on the effect of adenomyosis in IVF parameters, and IUD and NND were under-reported in the available literature.

Subtypes of endometriosis and the disease adenomyosis have specific impacts on different fertility and reproductive outcomes but these are subtle, and the outcome profiles of each subtype are not fully revealed due to the quality and heterogeneity of the studies available.

A more unified and consistent approach to studying fertility and reproductive outcomes in the area of endometriosis and adenomyosis with longer term follow-up of the offspring and attention to the subtype of disease is necessary to explore a possible link with developmental programming and the complication profiles of disease subtypes. In order for clinical data to be useful in future research, a consensus on the diagnosis and grading of adenomyosis and accurate recording of disease subtype in endometriosis is required.

Supplementary data

Supplementary data are available at *Human Reproduction Update*.

Authors' roles

Y.C. conceived and designed the study and reviewed the data analysis and drafts of the manuscript. J.H. contributed to the study design, developed and conducted the literature search, screened the eligible studies and articles, extracted and analysed the data, and wrote the manuscript. M.S. was the second reviewer for screening eligible studies and articles, data extraction, and quality assessment of studies and reviewed drafts of the manuscript. S.L. contributed to study design and reviewed drafts of the manuscript. A.M. contributed to study design and reviewed drafts of the manuscript. T.C.L. contributed substantially to the concept of the study and reviewed drafts of the manuscript. All authors reviewed and approved the final version of the manuscript.

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Conflict of interest

None to declare.

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