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human reproduction **ORIGINAL ARTICLE *Gynaecology***

Pregnancy outcomes in women with endometriosis and/or ART use: a population-based cohort study

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STUDY QUESTION: What is the association between endometriosis and adverse pregnancy outcomes with ART use and non-use?

SUMMARY ANSWER: Endometriosis and ART use are both associated with increased risk of preterm birth, antepartum haemorrhage, placenta praevia and planned birth (caesarean delivery or induction of labour).

WHAT IS KNOWN ALREADY: There are contradictory findings on the association between endometriosis and adverse pregnancy outcomes, and many large studies have not considered the effect of ART use.

STUDY DESIGN, SIZE, DURATION: Population-based cohort study of 578 221 eligible pregnancies during 2006–2015, comparing pregnancy outcomes across four groups (No endo/no ART, No endo/ART, Endo/no ART and Endo/ART).

PARTICIPANTS/MATERIALS, SETTING, METHODS: All female residents of New South Wales, Australia aged 15–45 years and their index singleton pregnancy of at least 20 weeks gestation or 400 g birthweight. Linked hospital, pregnancy/birth and mortality data were used. Modified Poisson regression with robust error variances was used to estimate adjusted risk ratios (aRRs) and 99% CIs, adjusting for sociodemographic and pregnancy factors.

MAIN RESULTS AND THE ROLE OF CHANCE: Compared to women without endometriosis who had pregnancies without ART use, there was increased risk of preterm birth (<37 weeks) in all groups [No endo/ART (aRR 1.85, 99% CI 1.46–2.34), Endo/no ART (aRR 1.24, 99% CI 1.06–1.44), Endo/ART (aRR 1.93, 99% CI 1.11–3.35)] and antepartum haemorrhage [No endo/ART (aRR 1.99, 99% CI 1.39–2.85), Endo/no ART (aRR 1.31, 99% CI 1.03–1.67), Endo/ART (aRR 2.69, 99% CI 1.30–5.56)] among pregnancies affected by endometriosis or ART use, separately and together. There was increased risk of placenta praevia [No endo/ART (aRR 2.26, 99% CI 1.42–3.60), Endo/no ART (aRR 1.66, 99% CI 1.18–2.33)] and planned birth [No endo/ART (aRR 1.08, 99% CI 1.03–1.14), Endo/no ART (aRR 1.11, 99% CI 1.07–1.14)] among pregnancies with endometriosis or ART use, separately. There was increased risk of placental abruption [No endo/ART (aRR 2.36, 99% CI 1.12–4.98)], maternal morbidity [No endo/ART (aRR 1.67, 99% CI 1.07–2.62)] and low birthweight (<2500 g) [No endo/ART (aRR 1.45, 99% CI 1.09–1.93)] among pregnancies with ART use without endometriosis. There was decreased risk of having a large-for-gestational age infant [Endo/no ART (aRR 0.83, 99% CI 0.73–0.94)] among pregnancies with endometriosis without ART use.

LIMITATIONS, REASONS FOR CAUTION: Endometriosis is often under-diagnosed and women with a history of hospital diagnosis of endometriosis may represent those with more symptomatic or severe disease. If the effects of endometriosis on pregnancy are greater for those with more severe disease, our results may over-estimate the effect of endometriosis on adverse pregnancy outcomes at a population level. We were unable to assess the effect of endometriosis stage or typology on the study outcomes.

WIDER IMPLICATIONS OF THE FINDINGS: These results suggest that women with endometriosis including those who used ART to achieve pregnancy are a higher-risk obstetric group requiring appropriate surveillance and management during their pregnancy.

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Key words: endometriosis / pregnancy / assisted reproductive technology / preterm birth / maternal morbidity / antepartum haemorrhage / placenta praevia / caesarean section / induction of labour / low birthweight

Introduction

Endometriosis is a chronic inflammatory disease characterized by the presence of endometrial tissue outside the uterus. Symptoms vary but commonly include chronic pelvic pain and infertility (Giudice and Kao, 2004). The gold standard diagnosis of endometriosis is through surgical assessment and histological confirmation (Greene *et al.*, 2016) and as a result it is often under-diagnosed. Prevalence estimates vary depending on the study population and methodology used. Recent estimates of 1–2% among hospital populations have been reported (Eisenberg *et al.*, 2018; Christ *et al.*, 2021) and an Australian cohort study reported a cumulative prevalence of 6% by 44 years of age for confirmed endometriosis (Rowlands *et al.*, 2021). The aetiology of endometriosis-related infertility is unclear; however, several mechanisms have been proposed including distorted pelvic anatomy, altered peritoneal function, ovulatory abnormalities, impaired implantation and the effects of ovarian endometriosis on gametes and embryos (Giudice and Kao, 2004; Khan, 2020).

There are contradictory findings on the association between endometriosis and several adverse pregnancy outcomes (Harada *et al.*, 2016; Leone Roberti Maggiore *et al.*, 2016), for example, some studies suggest increased risk of preterm birth, pregnancy hypertension and small-for-gestational age among women with endometriosis (Stephansson *et al.*, 2009; Qin *et al.*, 2016). However, many large studies including population-based cohorts have not considered the effect of ART use (Stephansson *et al.*, 2009; Aris, 2014; Saraswat *et al.*, 2017). This is important because women with endometriosis are more likely to have difficulty conceiving and are more likely to undergo treatment with ART (de Ziegler *et al.*, 2010), which has been shown to be associated with adverse pregnancy outcomes (Qin *et al.*, 2016).

The aim of this study is to examine the association between pre-existing endometriosis, with and without the use of ART, on adverse pregnancy outcomes. We hypothesize that ART use rather than endometriosis is associated with increased risk of adverse pregnancy outcomes.

Materials and methods

Study population and data sources

This population-based linked data study included all female residents of New South Wales (NSW), Australia aged 15–45 years and the first singleton pregnancy of at least 20 weeks gestation or 400 g birthweight occurring during the study period 2006–2015, regardless of birth outcome (stillbirth or live birth). Linked hospital, pregnancy/birth and mortality data were utilized. Hospital data were obtained from the NSW Admitted Patient Data collection which includes information on all hospital discharges from public, private and day procedure facilities. Hospital information from medical records were coded using the International Statistical Classification of Diseases and Related Health Problems, Australian modification (ICD10-AM) for diagnoses and the Australian Classification of Health Interventions (ACHI) for procedures. Pregnancy and birth data were obtained from the NSW Perinatal Data Collection, a census capturing demographic, pregnancy and infant information on all live births and stillbirths of ≥20 weeks gestation or ≥400 g birthweight occurring at home and in public and private hospitals. Mortality data were obtained from the NSW Register of Births, Deaths and Marriages which holds vital statistics on all registered deaths in NSW. Probabilistic linkage of individual-level data was conducted by the NSW Centre for Health Record Linkage with false-positive and false-negative rates of <0.5% (Bentley *et al.*, 2012).

Exposure and outcome measures

The study exposures were endometriosis and ART use in the 12 months prior to birth identified using hospital data (ICD10AM and ACHI codes are shown in Supplementary Table SI). Women with a hospital record indicating an initial diagnosis of endometriosis during or after pregnancy were excluded as were women with a diagnosis of adenomyosis (N80.0) without endometriosis of any other site. Endometriosis and ART use have been shown to be accurately and reliably recorded in hospital and pregnancy/birth data with positive predictive values of 97% (Ludvigsson *et al.*, 2011) and 75% (Reigstad *et al.*, 2020), respectively. Linkage of hospital and pregnancy/birth data were used to identify pregnancies with an ART procedure or IVF diagnosis occurring prior to the antenatal period and within 12 months prior to birth. This method of ascertaining ART use has been employed in other population-based studies using these linked data (Baldwin *et al.*, 2018; Morris *et al.*, 2018).

Maternal outcomes were derived from hospital and birth data and included pregnancy hypertension, placenta praevia, placental abruption, antepartum and postpartum haemorrhage, planned birth (induction of labour or caesarean section), maternal morbidity, maternal hospital readmission within 42 days of birth and length of stay in hospital for the birth admission. Maternal morbidity was a validated composite measure derived from hospital and birth data and indicative of severe adverse outcomes, such as cerebrovascular accident, shock, blood transfusion and cardiomyopathy, occurring during the birth admission (Roberts *et al.*, 2008).

Infant outcomes were derived from birth data and included preterm birth (<33 and <37 weeks gestation), low birthweight (<2500 g), small-for-gestational age (birthweight <3rd and <10th population percentile for gestational age and sex) (Dobbins *et al.*, 2012), large-for-gestational age (birthweight >90th population percentile for gestational age and sex) (Dobbins *et al.*, 2012), low Apgar scores at 1 and 5 min, admission to neonatal intensive care unit or special care nursery and perinatal mortality. Preterm birth <37 weeks was further classified as spontaneous or planned. Planned preterm birth was defined as

delivery by induction of labour or caesarean section prior to 37 weeks. Perinatal mortality included stillbirth (foetal death of at least 20 weeks gestation or 400 g birthweight) and neonatal death (death of a live born infant within 28 days of birth).

Covariates

Covariates included maternal age, smoking status, country of birth, socioeconomic status, remoteness, parity, previous caesarean section, pre-existing conditions (hypertension, diabetes, other chronic conditions, number of endometriosis-related hospital admissions), birth facility level, baby's year of birth, baby's sex and antenatal model of care. Socioeconomic status and remoteness were determined using maternal residential postcodes and the Australian Bureau of Statistics Index of Relative Socio-Economic Disadvantage and Accessibility and Remoteness Index of Australia, respectively. Pre-existing conditions were ascertained using hospital data for the 4 years prior to pregnancy. Other chronic conditions included cardiac, renal, thyroid, asthma and chronic obstructive pulmonary disease, psychiatric and autoimmune conditions.

Statistical analysis

The study population was divided into four groups based on combination of exposures (Supplementary Fig. S1). Summary statistics were used to characterize the study population and differences between groups were assessed using Chi-square or Fisher's exact test for categorical variables and Student's T test for normally distributed continuous variables. Modified Poisson regression with robust error variances was used to assess the association between exposure groups and maternal and infant outcomes. Adjusted risk ratios (aRRs) and 99% CIs are presented. Covariates in the multivariate models were selected based on a significant association at alpha <0.05 level in bivariate models. Due to the number of comparisons, statistical significance was set at alpha <0.01 for multivariate models to reduce the likelihood of false-positive results. Subgroup analysis was undertaken with the ART group restricted to IVF procedures to determine any differences in associations by type of ART. Mediation analysis using a counterfactual framework (VanderWeele, 2014) was undertaken as secondary analysis to quantify the potential direct and indirect effects of endometriosis on maternal and infant outcomes with ART use as the mediator. Causal mediation regression models were implemented using the CAUSALMED statement with maternal/pregnancy factors included as confounders. All analyses were performed using SAS 9.4 (SAS Institute, Cary, NC, USA).

Ethics approval

This study was approved by the NSW Population and Health Services Research Ethics Committee (2012/12/430, sub-study 2018/UMB0603; approved 29 June 2018).

Results

During the period 2006–2015, there were 578 221 eligible singleton pregnancies among 578 221 women. Of these women, 6542 (1.1%) had an ART procedure but no endometriosis, 13 406 (2.3%) had a diagnosis of endometriosis but no ART procedure and 1351 (0.27%) had a diagnosis of endometriosis and an ART procedure (Supplementary Fig. S1). The characteristics of the study population are shown in Table I. There were differences between the ART groups (Groups 2 and 4) and the non-ART groups (Groups 1 and 3). Women in the ART groups were more likely to be older, not smoke, more affluent, live in a major city, nulliparous and have their antenatal care provided by a private obstetrician (Table I). Among women with endometriosis, there were similar numbers of endometriosis-related admissions in the 4 years prior to pregnancy [Group 4 (median 2, interquartile range (IQR) 1–2, range 1–15) versus Group 3 (median 1, IQR 1–2, range 1–15)].

The prevalence of adverse maternal outcomes was generally lowest among pregnancies to women who did not have endometriosis or use ART and was highest among those with endometriosis who used ART (Table II). Compared to women without endometriosis who had pregnancies without ART use, there was increased risk of antepartum haemorrhage [No endo/ART (aRR 1.99, 99% CI 1.39–2.85), Endo/no ART (aRR 1.31, 99% CI 1.03–1.67), Endo/ART (aRR 2.69, 99% CI 1.30–5.56)] among women who had pregnancies affected by endometriosis or ART use, separately and together (Table III). There was also increased risk of placenta praevia [No endo/ART (aRR 2.26, 99% CI 1.42–3.60), Endo/no ART (aRR 1.66, 99% CI 1.18–2.33)] and planned birth [No endo/ART (aRR 1.08, 99% CI 1.03–1.14), Endo/no ART (aRR 1.11, 99% CI 1.07–1.14)] among women who had pregnancies affected by endometriosis or ART use, separately. There was increased risk of placental abruption (aRR 2.36, 99% CI 1.12–4.98) and maternal morbidity (aRR 1.67, 99% CI 1.07–2.62) with ART use without endometriosis. While not statistically significant, the results suggest increased risk of placenta praevia [Endo/ART (aRR 2.55, 99% CI 0.90–7.20)] and maternal morbidity [Endo/ART (aRR 1.68, 99% CI 0.60–4.72)] among women with endometriosis who also used ART. Overall, the effect size for adverse outcomes among women with ART use was larger than the effect size among women with endometriosis, although most results did not reach statistical significance. The aRRs for Group 4 (Endo/ART) indicate an additive effect of endometriosis and ART use on maternal outcomes. Similar results were found in subgroup analysis when the ART group was restricted to IVF only (Supplementary Table SII). Mediation analysis showed that the percentage of the endometriosis effect on placenta praevia, antepartum haemorrhage and planned birth that was mediated through ART use was 3.3%, 3.9% and 1.6%, respectively (Supplementary Table SIII).

There was increased risk of preterm birth (<37 weeks) [No endo/ART (aRR 1.85, 99% CI 1.46–2.34), Endo/no ART (aRR 1.24, 99% CI 1.06–1.44), Endo/ART (aRR 1.93, 99% CI 1.11–3.35)] associated with endometriosis and ART use, separately and together (Table IV). The risk of preterm birth associated with ART use (aRR 1.85, 99% CI 1.46–2.34) was higher than the risk of preterm birth associated with endometriosis (aRR 1.24, 99% CI 1.06–1.44). There was increased risk of low birthweight (<2500 g) among pregnancies to women with ART use but no endometriosis (aRR 1.45, 99% CI 1.09–1.93) and decreased risk of having a large-for-gestational baby for women with endometriosis without ART use (aRR 0.83, 99% CI 0.73–0.94) (Table IV). Similar results were found in subgroup analysis when the ART group was restricted to IVF only (Supplementary Table SIV).

Table I Characteristics of the study population by Endometriosis (Endo) and ART use subgroups.

Characteristics	Group 1 No Endo + No ART N = 556 922 n (%)	Group 2 No Endo + ART N = 6542 n (%)	Group 3 Endo + No ART N = 13 406 n (%)	Group 4 Endo + ART N = 1351 n (%)
Maternal age, years: mean (SD)	29.7 (5.7)	35.3 (4.4)	32.0 (5.1)	35.0 (4.2)
Smoking	66 989 (12.0)	126 (1.9)	1085 (8.1)	25 (1.9)
Maternal country of birth				
Australia	355 893 (63.9)	4429 (67.7)	10 267 (76.6)	980 (72.5)
Socioeconomic status	N = 556 753	N = 6536	N = 13 403	N = 1350
1 (most disadvantaged)	69 786 (12.5)	248 (3.8)	1173 (8.8)	66 (4.9)
2	76 475 (13.7)	392 (6.0)	1593 (11.9)	85 (6.3)
3	139 161 (25.0)	951 (14.6)	3446 (25.7)	231 (17.1)
4	128 462 (23.1)	1634 (25.0)	3189 (23.8)	360 (26.7)
5 (least disadvantaged)	142 869 (25.7)	3311 (50.7)	4002 (29.9)	608 (45.0)
Remoteness	N = 556 345	N = 6529	N = 13 385	N = 1348
Major cities	451 614 (81.2)	6058 (92.8)	11 013 (82.3)	1231 (91.3)
Inner regional	81 563 (14.7)	396 (6.1)	1952 (14.6)	102 (7.6)
Outer regional	20 573 (3.7)	67 (1.0)	371 (2.8)	15 (1.1)
Remote and very remote	2595 (0.5)	8 (0.1)	49 (0.4)	–
Parity	N = 555 968	N = 6534	N = 13387	N = 1351
0	357 574 (64.3)	5378 (82.3)	9738 (72.7)	1149 (85.1)
1	113 759 (20.5)	932 (14.3)	2596 (19.4)	174 (12.9)
≥2	84 635 (15.2)	224 (3.4)	1053 (7.9)	28 (2.1)
Previous caesarean delivery*	N = 192 572	N = 1100	N = 3511	N = 195
Yes	49 793 (25.9)	456 (41.5)	1215 (34.6)	74 (38.0)
Pre-existing hypertension**	6718 (1.2)	116 (1.8)	206 (1.5)	17 (1.3)
Pre-existing diabetes**	4572 (0.8)	102 (1.6)	212 (1.6)	18 (1.3)
Chronic conditions**,^	31 915 (5.7)	353 (5.4)	1257 (9.4)	87 (6.4)
Birth facility level				
Non-tertiary, Public	259 923 (46.7)	940 (14.4)	4142 (30.9)	153 (11.3)
Tertiary, Public	170 613 (30.6)	1691 (25.9)	3200 (23.9)	258 (19.1)
Private	126 386 (22.7)	3911 (59.8)	6064 (45.2)	940 (69.6)
Year of birth				
2006–2011	329 549 (59.2)	3270 (50.0)	7421 (55.4)	680 (50.3)
2012–2016	227 373 (40.8)	3272 (50.0)	5985 (44.6)	671 (49.7)
Baby sex				
Male	286 504 (51.4)	3437 (52.5)	6979 (52.1)	730 (54.0)
Female	270 210 (48.5)	3101 (47.4)	6421 (47.9)	621 (46.0)
Indeterminate or Unknown	208 (0.0)	–	6 (0.0)	–
Model of care~	N = 505 361	N = 6254	N = 12 612	N = 1303
Private obstetrician	164 142 (32.5)	4683 (74.9)	7433 (58.9)	1086 (83.4)
Hospital-based medical	119 069 (23.6)	639 (10.2)	2000 (15.9)	90 (6.9)
General practitioner	88 281 (17.5)	362 (5.8)	1394 (11.1)	57 (4.4)
Hospital-based midwives	203 659 (40.3)	874 (14.0)	2934 (23.3)	108 (8.3)
Independent midwife	1411 (0.3)	6 (0.1)	23 (0.2)	–
Not applicable	13 233 (2.6)	91 (1.5)	236 (1.9)	11 (0.8)

*Denominator = multiparous women.
**Condition recorded in hospital admission in the 4 years prior to pregnancy.
^Includes cardiac, renal, thyroid, asthma and chronic obstructive pulmonary disease, psychiatric and autoimmune conditions.
~Categories are not mutually exclusive.
–Values of five or less redacted for privacy reasons.

Table II Maternal and infant outcomes by Endometriosis (Endo) and ART use subgroups.

Outcomes	Group 1 No Endo + No ART N = 556 922 n (%)	Group 2 No Endo + ART N = 6542 n (%)	Group 3 Endo + No ART N = 13 406 n (%)	Group 4 Endo + ART N = 1351 n (%)
Maternal outcomes				
Pregnancy hypertension	50 231 (9.0)	766 (11.7)	1378 (10.3)	149 (11.0)
Placenta praevia	4378 (0.8)	183 (2.8)	307 (2.3)	59 (4.4)
Placental abruption	2805 (0.5)	49 (0.8)	100 (0.8)	11 (0.8)
Antepartum haemorrhage	14 308 (2.6)	265 (4.1)	477 (3.6)	64 (4.7)
Planned birth (IOL or CS)	289 695 (52.0)	4643 (71.0)	8554 (63.8)	939 (69.5)
Postpartum haemorrhage	51 505 (9.3)	611 (9.3)	1165 (8.7)	122 (9.0)
Maternal morbidity*	11 762 (2.1)	178 (2.7)	336 (2.5)	46 (3.4)
Maternal readmission within 42 days post-birth	20 676 (3.7)	286 (4.4)	641 (4.8)	57 (4.2)
Length of hospital stay for birth admission	Median 4 IQR 2–5	Median 5 IQR 4–6	Median 4 IQR 3–5	Median 5 IQR 4–6
Infant outcomes				
Preterm birth				
<33 weeks	8046 (1.4)	218 (3.3)	278 (2.1)	49 (3.6)
<37 weeks	34 357 (6.2)	695 (10.6)	1092 (8.2)	171 (12.7)
Spontaneous	15 575 (2.9)	385 (6.2)	581 (4.5)	93 (7.3)
Planned	18 773 (3.5)	310 (5.0)	509 (4.0)	78 (6.2)
Birthweight	N = 556 506	N = 6534	N = 13 397	N = 1348
Less than 2500 g	29 254 (5.3)	503 (7.7)	809 (6.0)	121 (9.0)
Small for gestational age	N = 553 593	N = 6485	N = 13 315	N = 1331
<3rd percentile	17 314 (3.1)	137 (2.1)	330 (2.5)	31 (2.3)
<10th percentile	60 518 (10.9)	580 (8.9)	1241 (9.3)	123 (9.2)
Large for gestational age	N = 553 593	N = 6485	N = 13 315	N = 1331
>90th percentile	48 194 (8.7)	661 (10.2)	1157 (8.7)	115 (8.6)
Apgar score at 1 min	N = 555 754	N = 6538	N = 13 397	N = 1351
Less than 4	14 779 (2.7)	220 (3.4)	416 (3.1)	59 (4.4)
Apgar score at 5 min	N = 555 848	N = 6538	N = 13 398	N = 1351
Less than 7	12 335 (2.2)	207 (3.2)	342 (2.6)	53 (3.9)
NICU/SCN admission	80 578 (14.6)	979 (15.1)	2061 (15.5)	235 (17.6)
Perinatal mortality (per 1000 births)	4389 (7.9)	81 (12.4)	123 (9.2)	27 (20.0)
Stillbirth (per 1000 births)	3339 (6.0)	57 (8.7)	88 (6.6)	19 (14.1)
Neonatal death (per 1000 live births)	1050 (1.9)	24 (3.7)	35 (2.6)	8 (6.0)

*Validated composite outcome measure.
IOL, induction of labour; CS, caesarean section; IQR, interquartile range; NICU/SCN, neonatal intensive care unit/special care nursery.

Mediation analysis showed that 4.2% of the endometriosis effect on preterm birth (<37 weeks) was mediated through ART use (Supplementary Table SIII).

Discussion

Main findings

We found placenta praevia, antepartum haemorrhage, planned birth and preterm birth were independently associated with endometriosis and with ART use. Placental abruption, low birthweight and maternal morbidity were associated with ART use but not endometriosis. For many of the adverse pregnancy outcomes, the magnitude of effect was larger for ART use than endometriosis. Furthermore, for women who had endometriosis and used ART, there appears to be an additive effect in the risk of having an adverse pregnancy outcome, however, many results did not reach statistical significance most likely due to small group size.

We found increased risk of placenta praevia among women who used ART as well as among women who had endometriosis, and while not statistically significant, our results suggest increased risk for women with endometriosis who used ART. These findings concur with studies among women who used ART that have consistently reported that

Table III Association between Endometriosis (Endo) status, ART use and maternal outcomes.

Maternal outcomes	Group 1 No Endo + No ART N = 556 922 aRR (99% CI)	Group 2 No Endo + ART N = 6542 aRR (99% CI)	Group 3 Endo + No ART N = 13 406 aRR (99% CI)	Group 4 Endo + ART N = 1351 aRR (99% CI)
Pregnancy hypertension	Ref	0.92 (0.70–1.20)	1.01 (0.87–1.18)	0.87 (0.42–1.79)
Placenta praevia	Ref	2.26 (1.42–3.60)	1.66 (1.18–2.33)	2.55 (0.90–7.20)
Placental abruption	Ref	2.36 (1.12–4.98)	1.36 (0.81–2.29)	1.12 (0.09–14.7)
Antepartum haemorrhage	Ref	1.99 (1.39–2.85)	1.31 (1.03–1.67)	2.69 (1.30–5.56)
Planned birth (IOL or CS)	Ref	1.08 (1.03–1.14)	1.11 (1.07–1.14)	1.07 (0.95–1.21)
Postpartum haemorrhage	Ref	1.28 (0.99–1.66)	0.90 (0.76–1.07)	1.13 (0.60–2.15)
Maternal morbidity*	Ref	1.67 (1.07–2.62)	1.06 (0.79–1.43)	1.68 (0.60–4.72)
Maternal readmission within 42 days post-birth	Ref	1.24 (0.83–1.86)	1.15 (0.91–1.45)	1.40 (0.57–3.42)

Endo, endometriosis; IOL, induction of labour; CS, caesarean section; Ref, reference.
Adjusted risk ratios (aRRs) are presented for Groups 2 to 4 compared to Group 1 (no endometriosis and no ART use).
Modified Poisson with robust variance models adjusted for: maternal age, year of birth, smoking, maternal country of birth, SES, remoteness, parity, previous CS, pre-existing hypertension, pre-existing diabetes and chronic conditions.
*Validated composite outcome.

Table IV Association between Endometriosis status, ART use and infant outcomes.

Infant outcomes	Group 1 No Endo + No ART N = 556 922 aRR (99% CI)	Group 2 No Endo + ART N = 6542 aRR (99% CI)	Group 3 Endo + No ART N = 13 406 aRR (99% CI)	Group 4 Endo + ART N = 1351 aRR (99% CI)
Preterm birth (<33 weeks)	Ref	1.76 (1.04–2.98)	1.38 (1.00–1.89)	1.72 (0.48–6.17)
Preterm birth (<37 weeks)	Ref	1.85 (1.46–2.34)	1.24 (1.06–1.44)	1.93 (1.11–3.35)
Spontaneous	Ref	1.81 (1.25–2.62)	1.23 (0.98–1.55)	2.51 (1.22–5.15)
Planned	Ref	1.91 (1.39–2.62)	1.25 (1.01–1.55)	1.48 (0.60–3.65)
Low birthweight (<2500 g)*	Ref	1.45 (1.09–1.93)	0.92 (0.75–1.14)	1.54 (0.70–3.39)
SGA (<3rd percentile)	Ref	0.73 (0.36–1.50)	0.93 (0.68–1.27)	1.00 (0.23–4.37)
SGA (<10th percentile)	Ref	0.74 (0.52–1.06)	0.93 (0.80–1.10)	0.94 (0.44–1.98)
LGA (>90th percentile)	Ref	1.00 (0.82–1.22)	0.83 (0.73–0.94)	0.79 (0.47–1.33)
Apgar score (<4 at 1 min)*	Ref	1.13 (0.73–1.74)	0.85 (0.66–1.08)	0.78 (0.29–2.11)
Apgar score (<7 at 5 min)*	Ref	1.13 (0.71–1.80)	0.81 (0.62–1.06)	0.83 (0.33–2.12)
NICU/SCN admission*,^	Ref	0.87 (0.72–1.05)	0.98 (0.88–1.09)	1.19 (0.82–1.72)
Perinatal mortality*	Ref	0.85 (0.44–1.65)	0.91 (0.67–1.24)	0.83 (0.46–1.48)
Stillbirth*	Ref	0.81 (0.40–1.66)	0.77 (0.52–1.13)	1.11 (0.59–2.09)
Neonatal death*,^	Ref	–	–	–

Ref, reference; NICU/SCN, neonatal intensive care unit/special care nursery; LGA, large for gestational age; SGA, small for gestational age.
Adjusted risk ratios (aRRs) are presented for Groups 2 to 4 compared to Group 1 (no endometriosis and no ART use).
Modified Poisson with robust variance models adjusted for: maternal age, year of birth, smoking, maternal country of birth, SES, remoteness, parity, previous CS, pre-existing hypertension, pre-existing diabetes and chronic conditions.
Chronic conditions include pre-existing cardiac, renal, thyroid, asthma and chronic obstructive pulmonary disease, psychiatric and autoimmune conditions.
*Additionally adjusted for gestational age at birth.
^Denominator excludes stillbirths.

those who also had endometriosis had increased risk of placenta praevia compared to those without endometriosis (Fujii *et al.*, 2016; Gasparri *et al.*, 2018; Jeon *et al.*, 2018; Lalani *et al.*, 2018; Horton *et al.*, 2019). Furthermore, a recent French cohort study reported increased odds of placenta praevia associated with endometriosis among spontaneous conceptions (Epelboin *et al.*, 2021). The mechanisms underlying these observations are not entirely clear, although factors related to ART have been implicated (Romundstad *et al.*,

2006). It has also been suggested that perturbed uterine peristalsis in women with endometriosis may influence the site of implantation and increase the risk of placenta praevia (Leone Roberti Maggiore et al., 2016; Kobayashi et al., 2020).

We found endometriosis and ART use, separately and together, were independently associated with increased risk of antepartum haemorrhage. This finding was partially supported by a meta-analysis of five studies that found increased odds of antepartum haemorrhage among women with endometriosis compared to those without endometriosis but further analysis among the subgroup of women who conceived using ART found no association between endometriosis and antepartum haemorrhage (Lalani et al., 2018). Suboptimal endometrial function and factors around the time of implantation have been suggested as possible explanations (Healy et al., 2010).

Our study found increased risk of planned birth (caesarean delivery or induction of labour) with both endometriosis and ART use independently and this may reflect the higher rates of placenta praevia in the endometriosis and ART groups. Meta-analyses have reported increased odds of caesarean delivery with endometriosis among women with spontaneous conceptions (Lalani et al., 2018). However, there are conflicting findings about the association between endometriosis and caesarean delivery among women who used ART (Lalani et al., 2018; Horton et al., 2019). Furthermore, other studies did not find an association between endometriosis and induction of labour; however, there was no accounting for ART use (Lalani et al., 2018).

Our study found increased risk of preterm birth associated with endometriosis as well as ART use. This concurs with a meta-analysis of nine cohort studies (including five population-based cohorts) that found increased risk of preterm birth in women with endometriosis compared to women without endometriosis in both spontaneous and ART pregnancies (Pérez-López et al., 2018). Inflammation has been suggested as a possible pathway between endometriosis and preterm birth (Petraglia et al., 2012), while the underlying causes of infertility and ART procedures have been found to be associated with adverse pregnancy outcomes (Qin et al., 2016).

While we found no association between endometriosis and placental abruption among non-ART pregnancies same as two meta-analyses (Gaspani et al., 2018; Lalani et al., 2018); we found increased risk of abruption with ART use similar to a cohort study using Nordic birth registry data (Romundstad et al., 2013). Consistent with a meta-analysis of 36 studies including ART and spontaneously conceived singletons, we found increased risk of low birthweight among women using ART (Qin et al., 2016). We found an association between ART use and increased risk of maternal morbidity in the birth admission with the most frequently occurring indication of morbidity being maternal blood transfusion. These findings concur with a large cohort study that reported higher rates of severe maternal morbidity among women who conceived using ART compared to fertile women (3.1% versus 1.1%) (Belanoff et al., 2016). We found decreased risk of having a large-for-gestational age infant for women with endometriosis, similar to findings from a large Korean population-based study (Yi et al., 2020). This could reflect increased levels of surveillance in this population of pregnant women. Reassuringly, stillbirth and neonatal death were rare outcomes, and we did not find a statistically significant association with endometriosis or ART use.

Strengths and limitations

One of the issues in studying the effects of endometriosis on pregnancy outcomes has been disentangling the effects of endometriosis and the effects of ART use. It can be argued that ART use is a mediator as it occurs sometime between the exposure and the outcome and is associated with both (Farland et al., 2020). The design of this large population-based study enabled us to assess the effect of endometriosis and ART use separately and jointly on maternal and infant outcomes.

However, the use of routinely collected data meant that some clinical information was unavailable. There was no information on stage or typology of endometriosis, therefore, we could not assess whether there were differences in the stage or typology between the ART and no ART groups and how potential differences may have affected the associations observed. Important information such as reason for planned birth were also unavailable. The diagnoses and procedure codes for ART did not differentiate between fresh and frozen/thawed embryos or oocyte donation; therefore, we were unable to assess the effect of these on pregnancy outcomes. As we utilized the data linkage to determine the timing of ART procedures relative to the pregnancy, there is the possibility of misclassification of spontaneous conceptions occurring following an ART procedure as ART conceptions. This would have the effect of biasing the results towards the null.

Endometriosis is known to be under-diagnosed and women with a history of hospital diagnosis are more likely to represent those with more symptomatic or severe disease. It is also likely that the effects of endometriosis on pregnancy may be greater for more severe disease than for milder disease; therefore, our results may over-estimate the effect of endometriosis on adverse pregnancy outcomes on a population level. There is also the potential for selection bias resulting from disparity in access to clinical treatment for endometriosis and endometriosis-related co-morbidities as well as disparity in access to ART for women with fertility issues. Women with endometriosis are more likely to have difficulty conceiving and maintaining a pregnancy up to 20 weeks (Saraswat et al., 2017; Zullo et al., 2017) and our study does not capture the experiences of these women.

Conclusion

Endometriosis and ART use are both independently associated with increased risk of preterm birth, antepartum haemorrhage, placenta praevia and planned birth (caesarean delivery or induction of labour), while ART use in the absence of endometriosis is associated with increased risk of placental abruption, low birthweight and maternal morbidity. These results suggest that women with endometriosis including those who used ART to achieve pregnancy are a higher-risk obstetric group requiring appropriate surveillance and management during their pregnancy.

Supplementary data

Supplementary data are available at *Human Reproduction* online.

Data availability

The data underlying this article cannot be shared publicly for privacy reasons. Approvals granted for the use of these data do not permit sharing of the data. Data can be obtained upon gaining appropriate approvals and clearances and upon request to the New South Wales Ministry of Health.

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Authors' roles

I.I., T.N., R.B. and S.T. conceived and designed the study. I.I. undertook the analysis. I.I., T.N., R.B. and S.T. interpreted the results. I.I. drafted the manuscript, which was revised by T.N., R.B. and S.T. I.I., T.N., R.B. and S.T. approved the final version of the manuscript. I.I., T.N., R.B. and S.T. agree to be accountable for all aspects of the work.

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Conflict of interest

The authors have no conflicts of interest to declare.

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