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Research paper

The association between conception history and subsequent postpartum depression and/or anxiety: Evidence from the Clinical Practice Research Datalink 1991–2013

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ABSTRACT

Background: Infertility, and fertility treatment, are associated with psychological distress that may influence subsequent mental health including postpartum depression and anxiety.
Methods: Data for women who had a livebirth between 1991 and 2013 were drawn from the Clinical Practice Research Datalink. Conception history prior to their first recorded birth was categorised as 'no fertility problems', 'untreated subfertility', ovulation induction (OI), and assisted reproductive technologies (ART). Depression and/or anxiety in the 12 months postpartum were identified using records of diagnoses, symptoms, and prescriptions. Prevalence was compared, and odds ratios estimated using multivariable logistic regression.
Results: Of 235,127 mothers, 31,947 (13.6%) had evidence of postpartum depression and/or anxiety. Mothers in the ART group had 22% lower odds of postnatal depression and/or anxiety compared to mothers in the fertile group (OR 0.78; 95% CI [0.70–0.86]; $p < 0.0001$). Accounting for prior mental health, lifestyle, sociodemographic and pregnancy-related factors reduced the strength of the association (aOR 0.87; 95% CI [0.78–0.97]; $p = 0.01$). There were no significant associations observed in the untreated subfertility or OI groups.
Limitations: As in any analysis of routine data, the quality of recording is important and some information was unavailable (e.g. education, social support).
Conclusions: Women with a history of subfertility, OI or ART treatment were not at increased risk of postpartum depression and/or anxiety compared to those with no fertility problems. It is important to explore whether women who underwent ART are less likely to experience depression/anxiety or do not seek help when needed, with implications for their health and care.

1. Introduction

While the impact of unsuccessful fertility treatment on women's mental health and relationships is well documented, there is a lack of consensus on the risk of postpartum depression or anxiety following successful treatment using assisted reproductive technologies (Chen et al., 2019). On one hand, a successful pregnancy could result in lower levels of anxiety and depression (Milazzo et al., 2016). On the other hand, the low self-esteem and the anxiety linked to the diagnosis of fertility problems could persist during pregnancy into the postpartum period, resulting in a higher risk of subsequent depression or anxiety (Hjelmstedt et al., 2004; Stewart et al., 2003). It is hypothesized that the long-term desire for a child creates an idealization of motherhood, which could cause feelings of guilt and low self-esteem should a mother find the postpartum period more difficult than expected (Hammarberg et al., 2008).

Evidence of an association between successful fertility has not been found in meta-analyses between infertility treatment and subsequent mental health (Chen et al., 2019; Gressier et al., 2015), however, these were based on individual studies that often have methodological limitations such as a low statistical power or selective clinic-based samples. Fertility history and risk factors were often assessed using self-reported

Abbreviations: ART, assisted reproductive technologies; CI, confidence intervals; OI, ovulation induction; OR, odds ratio.

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questionnaires with a possibility of recall bias, and postpartum depression ascertained using different screening tools, cut-offs and time periods, making it difficult to meaningfully combine the results (Chen et al., 2019; Gressier et al., 2015; Stewart et al., 2003).

To address these evidence gaps, this study was conducted using electronic medical records from primary care practices in England, aiming to describe the prevalence of postpartum depression or anxiety by conception history (no fertility problems, untreated subfertility, ovulation induction or ART); and to explore the association between conception history and postpartum depression and/or anxiety, accounting for potential confounders and mediators.

2. Methodology

2.1. Data source/setting

The Clinical Practice Research Datalink (CPRD) GOLD database collects anonymised medical records from GP practices across the UK and is deemed largely representative of the UK population (Herrett et al., 2015). As of 2nd July 2013, the dataset had data on over 11.3 million patients from 674 practices (Herrett et al., 2015). This study used CPRD's mother-baby link, a subset of the CPRD GOLD database, which matches children registered at the same general practice to mothers with a delivery date within 60 days of the child's birthday and who share a practice-specific family identifier (Padmanabhan, 2015). Clinical data are recorded by general practice staff using version 2 Read codes, a hierarchical clinical classification system containing over 96,000 codes (Chisholm, 1990). Prescriptions issued by the GP are recorded with a product name and British National Formulary code, alongside the dosage instructions and quantity (Herrett et al., 2015).

The study population included women who had a baby between 1st January 1991 and 31st December 2013, who were registered at a CPRD-reporting practice in England for 18 months prior to their baby's estimated date of birth (to allow identification of the exposure), and who remained registered for 12 months after the baby's birth (to allow identification of the outcome); and who had consent to linkage for deprivation and hospital admission data (Herbert et al., 2017). Where women had more than one child in the dataset, only the first recorded birth was selected, with a total of 235,127 mothers included in our main analysis. The study was approved by the CPRD Independent Scientific Advisory Committee (15_090R).

2.2. Study variables

2.2.1. Conception history (exposure variable)

The exposure of interest was conception history for the index (first recorded) pregnancy, based on medical codes and indicators from their GP records in the 18 months prior to that pregnancy. An assisted reproductive technology (ART) group comprised women who had records of treatment using ART such as in-vitro fertilization (IVF) or intracytoplasmic sperm injection (ICSI). An ovulation induction (OI) group constituted women who consulted for fertility concerns and conceived after receiving medications for ovulation stimulation or ovulation induction (such as clomiphene citrate), in the same time period. A sub-fertile group comprising women who consulted their GPs with fertility concerns but were not prescribed any fertility medications or referred for other treatment and therefore were considered to have conceived without intervention. The reference group was made up of women with no records of consultations or prescriptions for fertility problems.

2.2.2. Postpartum depression or anxiety (outcome measures)

Due to the common co-morbidity of depression and anxiety and the potential for misclassification or misdiagnosis of overlapping symptoms recorded in the primary care system, the main outcome was defined as women with evidence of depression and/or anxiety in their primary care records in the 12 months postpartum. Relevant codes for diagnoses, symptoms and medications for anxiety and depressive disorders were identified and reviewed by a clinical psychologist and psychiatrist, and were checked against published code lists (Baker et al., 2017). The finalised list was used to generate indicator variables for postpartum depression or anxiety following an algorithm. The algorithm, utilising diagnosis, symptom and medication codes and a history of ongoing treatment, was developed with input from a psychiatrist and a GP (Fig. 1), and takes the timing of the birth into account to classify the postpartum period. This triangulation approach to identify common mental health disorders in primary care records has been validated in the wider population for similar Welsh data (John et al., 2016a).

2.2.3. Potential confounding or mediating variables

Sociodemographic factors (maternal age, ethnicity, index of multiple deprivation (IMD), geographical region, and baby's year of birth), maternal lifestyle risk factors (smoking status and body mass index (BMI) before pregnancy), twin/higher order pregnancy and evidence of depression or anxiety *before* pregnancy were included as potential confounding factors or effect modifiers. Pregnancy-related factors such as low birthweight or preterm baby, and evidence of depression or anxiety *during* pregnancy were included as they were considered potential mediators. Variables were derived using the primary care data and augmented where missing with information from Hospital Episode Statistics (HES) which records hospital discharges.

2.3. Statistical analysis

The prevalence of postpartum depression or anxiety and the corresponding 95% confidence interval (CI) was calculated for each conception history group. Logistic regression models were used to estimate crude and adjusted odds ratios of the association between conception history and postpartum depression or anxiety. Multivariable regression models were initially built using a step-wise forward regression approach of individual variables, then in groups of confounders. Each independent variable remained in the model if it significantly improved the model fit, assessed by a likelihood ratio test ($p < 0.05$). Potential effect modification by evidence of depression or anxiety before pregnancy, baby's year of birth and multiple births were explored using a chi-squared test for homogeneity. Two-sided p-values < 0.05 were taken to indicate statistical significance. All data management and statistical analyses were carried out using Stata v15 (StataCorp LP, College Station, TX, USA).

2.4. Sensitivity analysis

A sensitivity analysis was performed to assess the effect of parity using all recorded births for women who had more than one baby during her registration period. Parity was poorly recorded in the primary care records, and so was drawn from HES birth records. Statistical considerations were made to allow for clustering by family, using robust standard errors. The effect in subsequent births and potential effect modification by birth order among mothers with more than one child was assessed.

2.5. Role of the funding source

The study is part of work conducted during an MRC Career Development Award held by CC (MR/L019671/1). The funder had no role in the study design, data collection, data analysis, data interpretation, and writing of the manuscript. CC, YL and FLT had full access to all data reported in the study and all authors had final responsibility for the decision to submit for publication.

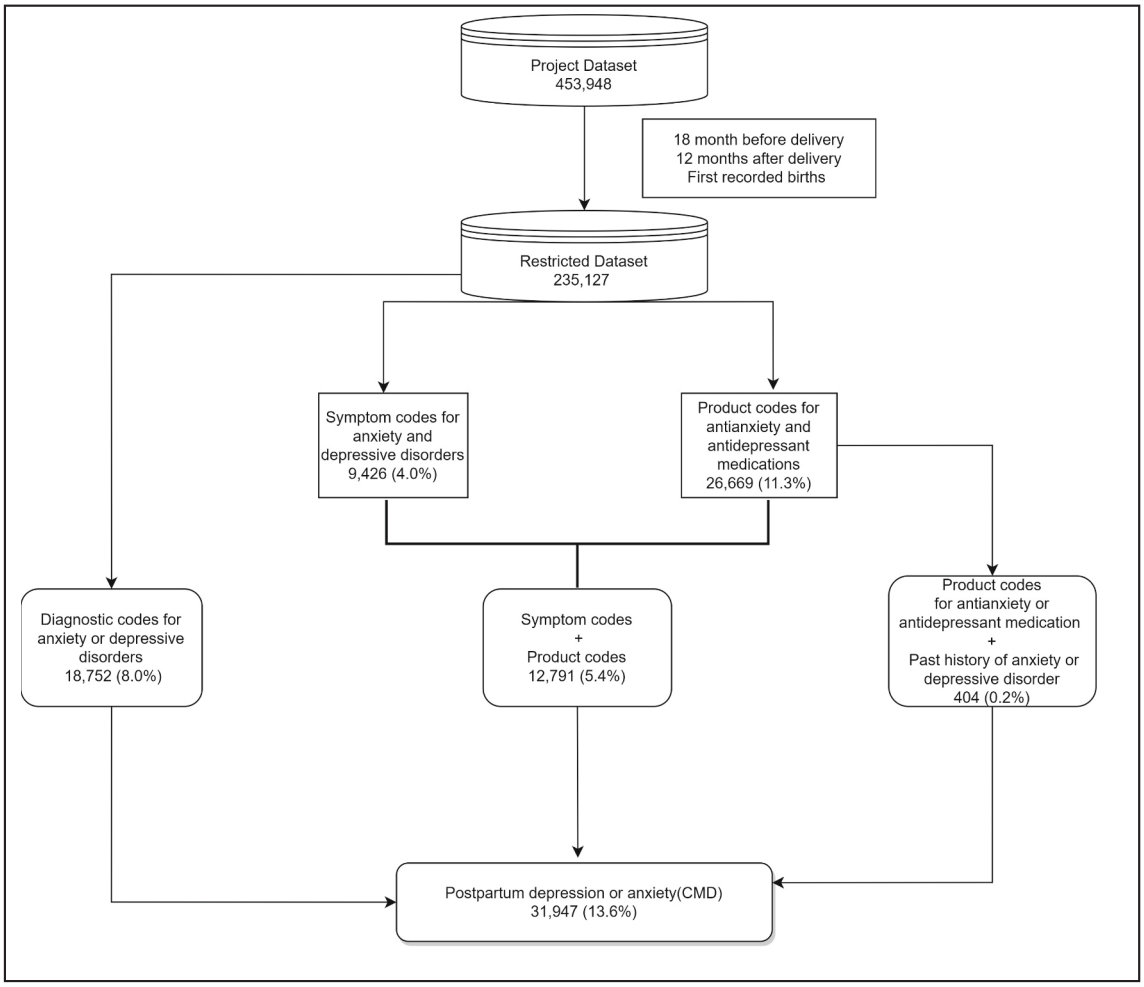

Fig. 1. Algorithm used in ascertaining evidence of postpartum depression or anxiety in women seeking primary healthcare in England.

3. Results

3.1. Characteristics of the study population

In total, 235,127 mothers with a live birth within the reference period, 1st January 1991–31st December 2013 were included; 220,334 (93.7%) were in the fertile group, 8043 (3.4%) in the sub-fertility group, 2314 (1.0%) in the OI group, and 4436 (1.9%) in the ART group. The overall mean age of the mothers was 29.5 years (SD 5.9), with the mothers in the ART group being on average older (34.0 years [SD 4.6]) and living in less deprived areas, compared to mothers in the other groups (Table 1). Mothers in the fertile group had a higher proportion of current smokers compared to mothers in the ART group (22.5% vs 13%) but a similar proportion of overweight/obesity (23.9% vs 25.8%). Mothers in the ART group had a higher proportion of low birth weight or preterm babies (11.9% vs 5.4%), and of twins or triplets (13.7% vs 1.3%), compared to mothers in the fertile group. The prevalence of anxiety and/or depression prior to pregnancy was higher among the women who experienced fertility problems than the comparison group (31.6%, 27.5% and 30.2% in untreated sub-fertile, OI and ART groups respectively, compared to 24.5%).

3.2. Patterns and prevalence of postpartum depression and/or anxiety

Overall, 31,947 mothers (13.6%) had evidence of postpartum depression and/or anxiety in their primary care records (Table 1). Mothers in the ART group had the lowest prevalence (11.2% [95% CI: 10.3–12.2]), with the proportion in the sub-fertility (14.5% [95% CI: 13.7–15.3]) and OI groups (13.4% [95% CI: 12.1–14.9]) being similar and slightly higher. Table 2 shows the patterns of diagnosis of postpartum depression and/or anxiety, and Fig. 1 shows how each indicator (diagnostic code, symptom, or treatment) contributed to the outcome variable.

3.3. Association between fertility history and postpartum depression and/or anxiety

There was no statistically significant association between fertility history and postpartum depression and/or anxiety for mothers in the sub-fertile group and in the OI group in the crude or fully adjusted models (Fig. 2). In the unadjusted model, mothers in the ART group had 22% lower odds of having postnatal depression or anxiety compared to mothers in the fertile group (OR 0.78; 95% CI [0.70–0.86]; $p < 0.0001$). After accounting for sociodemographic risk factors, lifestyle risk factors, multiple births and depression or anxiety before pregnancy, the effect reduced/attenuated an 18% (aOR 0.82; 95% CI [0.74–0.92]; $p = 0.0003$). There was no evidence of effect modification by baby's year of birth, multiple births, and depression or anxiety before pregnancy. After further adjustment for pregnancy-related factors (low birthweight babies or preterm birth, and depression or anxiety during pregnancy), mothers who conceived after ART treatment continued to show a 13% decrease in the odds of postpartum depression or anxiety compared to mothers in the fertile group (aOR 0.87; 95% CI [0.78–0.97]; $p = 0.01$).

Table 1
Descriptive statistics of women with their first recorded birth between 1st January 1991 and 31st December 2013, by fertility history. The proportions presented are the % of non-missing, except those shown in italics which are the % missing as a proportion of the total.

Characteristics	No fertility problems	Untreated sub-fertility	Ovulation induction	Assisted reproductive technology	Total	p-Value
	220,334 (93.7)	8043 (3.4)	2314 (1.0)	4436 (1.9)	N = 235,127	
Sociodemographic factors						
Mother's age	29.3 (5.9)	32.0 (5.2)	31.3 (4.6)	34.0 (4.6)	29.5 (5.9)	<0.0001
Mother's age in categories						<0.0001
<25	48,739 (22.1%)	694 (8.6%)	161 (7.0%)	110 (2.5%)	49,704 (21.1%)	
25–29	61,217 (27.8%)	1777 (22.1%)	674 (29.1%)	598 (13.5%)	64,266 (27.3%)	
30–34	67,632 (30.7%)	2910 (36.2%)	929 (40.1%)	1672 (37.7%)	73,143 (31.1%)	
35–39	34,231 (15.5%)	2104 (26.2%)	441 (19.1%)	1567 (35.3%)	38,343 (16.3%)	
≥40	8515 (3.9%)	558 (6.9%)	109 (4.7%)	489 (11.0%)	9671 (4.1%)	
Ethnicity						<0.0001
White	167,515 (91.0%)	6191 (86.5%)	1764 (91.4%)	3450 (89.9%)	178,920 (90.8%)	
BAME	16,520 (9.0%)	966 (13.5%)	166 (8.6%)	386 (10.1%)	18,038 (9.2%)	
Missing	*36,299 (16.5%)*	*886 (11.0%)*	*384 (16.6%)*	*600 (13.5%)*	*38,169 (16.2%)*	
Region						<0.0001
North	52,434 (23.8%)	1587 (19.7%)	511 (22.1%)	699 (15.8%)	55,231 (23.5%)	
Midlands	32,915 (14.9%)	944 (11.7%)	419 (18.1%)	708 (16.0%)	34,986 (14.9%)	
East	27,850 (12.6%)	1046 (13.0%)	265 (11.5%)	592 (13.3%)	29,753 (12.7%)	
South West	53,476 (24.3%)	1972 (24.5%)	604 (26.1%)	1045 (23.6%)	57,097 (24.3%)	
South East and London	53,659 (24.4%)	2494 (31.0%)	515 (22.3%)	1392 (31.4%)	58,060 (24.7%)	
Index of Multiple Deprivation						<0.0001
First (least)	47,892 (21.7%)	2215 (27.5%)	645 (27.9%)	1452 (32.7%)	52,204 (22.2%)	
Second	46,957 (21.3%)	1969 (24.5%)	579 (25.0%)	1127 (25.4%)	50,632 (21.5%)	
Third	43,151 (19.6%)	1490 (18.5%)	458 (19.8%)	831 (18.7%)	45,930 (19.5%)	
Fourth	45,268 (20.5%)	1440 (17.9%)	384 (16.6%)	669 (15.1%)	47,761 (20.3%)	
Fifth (most)	35,738 (16.2%)	900 (11.2%)	239 (10.3%)	338 (7.6%)	37,215 (15.8%)	
Missing	*1328 (0.6%)*	*29 (0.4%)*	*9 (0.4%)*	*19 (0.4%)*	*1385 (0.6%)*	
Year of birth						<0.0001
1991–1996	59,126 (26.8%)	584 (7.3%)	662 (28.6%)	685 (15.4%)	61,057 (26.0%)	
1997–2002	57,445 (26.1%)	1685 (20.9%)	676 (29.2%)	1068 (24.1%)	60,874 (25.9%)	
2003–2008	60,248 (27.3%)	3175 (39.5%)	635 (27.4%)	1255 (28.3%)	65,313 (27.8%)	
2009–2013	43,515 (19.7%)	2599 (32.3%)	341 (14.7%)	1428 (32.2%)	47,883 (20.4%)	
Maternal health status before pregnancy						
Smoking[a]						<0.0001
Non-smoker	109,235 (49.6%)	4746 (59.0%)	1415 (61.1%)	2820 (63.6%)	118,216 (50.3%)	
Ex-smoker	27,507 (12.5%)	1424 (17.7%)	296 (12.8%)	708 (16.0%)	29,935 (12.7%)	
Current smoker	49,573 (22.5%)	1386 (17.2%)	365 (15.8%)	578 (13.0%)	51,902 (22.1%)	
No record	34,019 (15.4%)	487 (6.1%)	238 (10.3%)	330 (7.4%)	35,074 (14.9%)	
Body mass index[b] (kg/m^2)						<0.0001
Underweight	7529 (3.4%)	280 (3.5%)	54 (2.3%)	152 (3.4%)	8015 (3.4%)	
Normal weight	96,450 (43.8%)	4188 (52.1%)	1086 (46.9%)	2408 (54.3%)	104,132 (44.3%)	
Overweight/Obese	52,612 (23.9%)	2376 (29.5%)	747 (32.3%)	1143 (25.8%)	56,878 (24.2%)	
No valid record	63,743 (28.9%)	1199 (14.9%)	427 (18.5%)	733 (16.5%)	66,102 (28.1%)	
Pregnancy related factors						
Mode of delivery						<0.0001
Normal	64,090 (29.1%)	2494 (31.0%)	525 (22.7%)	1025 (23.1%)	68,134 (29.0%)	
Instrument/emergency CS	35,940 (16.3%)	2174 (27.0%)	454 (19.6%)	1188 (26.8%)	39,756 (16.9%)	
Elective CS	8768 (4.0%)	538 (6.7%)	120 (5.2%)	399 (9.0%)	9825 (4.2%)	
Missing	111,536 (50.6%)	2837 (35.3%)	1215 (52.5%)	1824 (41.1%)	117,412 (49.9%)	
LBW or preterm births						<0.0001
No evidence	208,358 (94.6%)	7313 (90.9%)	2142 (92.6%)	3907 (88.1%)	221,720 (94.3%)	
Evidence of LBW or preterm birth	11,976 (5.4%)	730 (9.1%)	172 (7.4%)	529 (11.9%)	13,407 (5.7%)	
Multiple pregnancy						<0.0001
Single birth	217,438 (98.7%)	7800 (97.0%)	2227 (96.2%)	3830 (86.3%)	231,295 (98.4%)	
Multiple birth (twin/triplets)	2896 (1.3%)	243 (3.0%)	87 (3.8%)	606 (13.7%)	3832 (1.6%)	
Mental health outcomes						
Depression or anxiety before pregnancy						
No evidence	166,256 (75.5%)	5502 (68.4%)	1677 (72.5%)	3094 (69.8%)	176,529 (75.1%)	<0.0001
Evidence	54,078 (24.5%)	2541 (31.6%)	637 (27.5%)	1342 (30.2%)	58,598 (24.9%)	

(*continued on next page*)

Table 1 (*continued*)

Characteristics	No fertility problems	Untreated sub-fertility	Ovulation induction	Assisted reproductive technology	Total	p-Value
	220,334 (93.7)	8043 (3.4)	2314 (1.0)	4436 (1.9)	N = 235,127	
Depression or anxiety during pregnancy						
No evidence	210,046 (95.3%)	7628 (94.8%)	2224 (96.1%)	4277 (96.4%)	224,175 (95.3%)	<0.0001
Evidence	10,288 (4.7%)	415 (5.2%)	90 (3.9%)	158 (3.6%)	10,952 (4.7%)	
Postpartum depression or anxiety						
No evidence	190,358 (86.4%)	6879 (85.5%)	2003 (86.6%)	3940 (88.8%)	203,180 (86.4%)	<0.0001
Evidence	29,976 (13.6%)	1164 (14.5%)	311 (13.4%)	496 (11.2%)	31,947 (13.6%)	

BAME: Black, Asian and minority ethnic group CS: Caesarean section.
[a] Maternal smoking status before pregnancy.
[b] Maternal body mass index before pregnancy.

3.4. Sensitivity analysis

In the sensitivity analysis of a smaller sub-sample who had linked HES delivery records that included parity data (96,885 women with a total of 141,290 births), there was no statistically significant association between conception history and postpartum depression and/or anxiety after adjusting for all measured confounders including parity, although the pattern in the ART group remained the same (see Supplementary Table 1). The findings were similar for first recorded births and for subsequent births with no evidence of effect modification by parity (Supplementary Tables 2 and 3).

4. Discussion

This study, based on routinely collected medical records from primary care and hospitalisations for over 235,000 women in England, indicates that women who became mothers after subfertility, ovulation induction or ART were not at increased risk of depression and/or anxiety in the 12 months postpartum, compared to mothers who have no history of fertility problems. Overall, 13.6% of women with one or more pregnancies in their GP records had evidence of postpartum depression and/or anxiety after their first recorded birth. The prevalence varied by fertility history, with the highest prevalence in the untreated subfertility group (14.5%) and lowest in the mothers who had ART (11.2%). The small OI group was similar to those with no records of fertility difficulties (13.4% and 13.6%, respectively). After adjusting for socioeconomic indicators, lifestyle, and pregnancy-related factors, the apparent decrease in the odds of depression and/or anxiety among ART mothers remained (OR 0.87 (0.78–0.97)).

A systematic review including 20 papers in this area suggested that women who conceived after IVF had either the same or fewer symptoms of depression, compared to women who conceived naturally (Gourounti, 2016), which aligns with the findings of the present study. However, this review was restricted to those with an outcome assessed in person using a validated instrument, such as the State-Trait Anxiety Inventory, and therefore all studies were relatively small (many <100 ART mothers). Studies using routine data are rare; a large analysis of Finnish registry data also reported an IVF-achieved pregnancy was associated with a lower risk of postpartum depression (PPD) but was restricted to occurrence in the first 4–6 weeks postpartum (Raisanen et al., 2013) yet many women who develop postpartum depression and anxiety do so in the subsequent months after giving birth.

Mothers who conceive after ART may perceive their pregnancies as more rewarding and satisfactory than the women who conceived naturally, in part because they had to invest so much in becoming pregnant, resulting in more positive attitudes to the pregnancy or greater resilience when experiencing the challenges of early motherhood. These could have a protective effect against depressive symptoms in the postpartum period (Gourounti, 2016). Another explanation for this finding could be a differential underreporting of symptoms. There is evidence that mothers who conceive after ART are more willing to adjust to pregnancy demands and are more likely to idealize parenthood, hence a higher tendency to focus on parenting challenges and raising the child, while repressing negative emotions resulting in an underreporting of symptoms of depression. Furthermore, the stigma of mental health problems especially the fear of losing the custody of their child could be an extra motive to underreport symptoms of depression (Dolman et al., 2013). It is also plausible that women who conceive after ART may have a low sense of entitlement to complain and seek help, and that they should be 'grateful' after having fulfilled their long-term desire for a baby (Covington and Burns, 2006; Fisher et al., 2005).

Higher anxiety in the perinatal period could be considered normal when women are adjusting to their new role as a parent, but becomes problematic when it becomes extreme or persistent (Harrison and Alderdice, 2020). During the perinatal period concerns about maternal wellbeing, as well as those of her child, could be sources of maternal anxiety (Kiani et al., 2020), which may be more common in women who experienced infertility. Review evidence suggests that mothers in the ART group have equal or lower anxiety concerns about the child's health compared to mothers that conceived naturally (Gourounti, 2016). After going through an IVF procedure, women may feel the transferred embryo is a tested embryo and therefore has no defects (Gourounti, 2016). Furthermore, mothers who have ART may feel they are 'owed' an effortless birth or a healthy child, having suffered infertility and undergone the long and uncertain process of fertility treatment (Covington and Burns, 2006).

It is also important to consider the potential for selection among ART mothers, which may contribute to the observed relationship. Some studies report that anxiety and stress during treatment may adversely impact clinical pregnancy rates (Matthiesen et al., 2011), and that while major depression does not influence the chances of a successful IVF livebirth, treatment with antidepressants might increase pregnancy loss (Evans-Hoeker et al., 2018). These effects could remove some women who may have been more likely to show symptoms postpartum from the ART group, thus generating an apparent 'protective' effect for postpartum depression and/or anxiety.

The relative affluence of women in the ART group compared to the fertile group, suggests they may have had other beneficial experiences such as more stable socioeconomic circumstances, an established relationship and more social support. These may have had a protective effect against depression and anxiety, however area deprivation (IMD) was used as a proxy for socioeconomic status (SES) and the results were not materially changed after adjustment. In addition the stress and uncertain nature of the process of infertility treatment may have resulted in some degree of resilience among mothers who conceived after ART treatment (An et al., 2011; Lynch and Prasad, 2014). The women who experienced challenges on their journey to parenthood may have developed an ego-defence mechanism which could be protective against

Table 2
Patterns of indicator variables for depression and anxiety in the postpartum in the dataset.

Indicator Variables	Total 235,127
Depression or anxiety diagnosis (D)	18,752 (8·0%)
Symptoms and medications (S+M)	27,788 (11·8%)
Medications and history of depression or anxiety (M+Phx)	9,611 (4·1%)
Continued medication use (Mc)	7,856 (3·3%)

D	S+M	M+Phx	Mc	Frequency	Percentage	Cum %
○	○	○	○	203,180	86·41	86·41
●	○	○	○	3,696	1·57	87·98
○	●	○	○	7,514	3·20	90·18
●	●	○	○	8,766	3·73	94·91
○	○	●	○	404	0·17	95·08
●	○	●	○	59	0·03	95·11
○	●	●	○	1,169	0·50	95·61
●	●	●	○	2,483	1·06	96·67
○	○	○	●	0	0	96·67
●	○	○	●	0	0	96·67
○	●	○	●	1,460	0·62	97·29
○	○	●	●	0	0	97·29
●	○	●	●	0	0	97·29
●	●	○	●	900	0·38	97·67
○	●	●	●	2,648	1·13	98·80
●	●	●	●	2,848	1·20	100

Note: Black circles indicate the presence of data, white the absence, so that the top line with all white means no evidence of anxiety and/or depression while the next line indicates evidence of a diagnosis only.

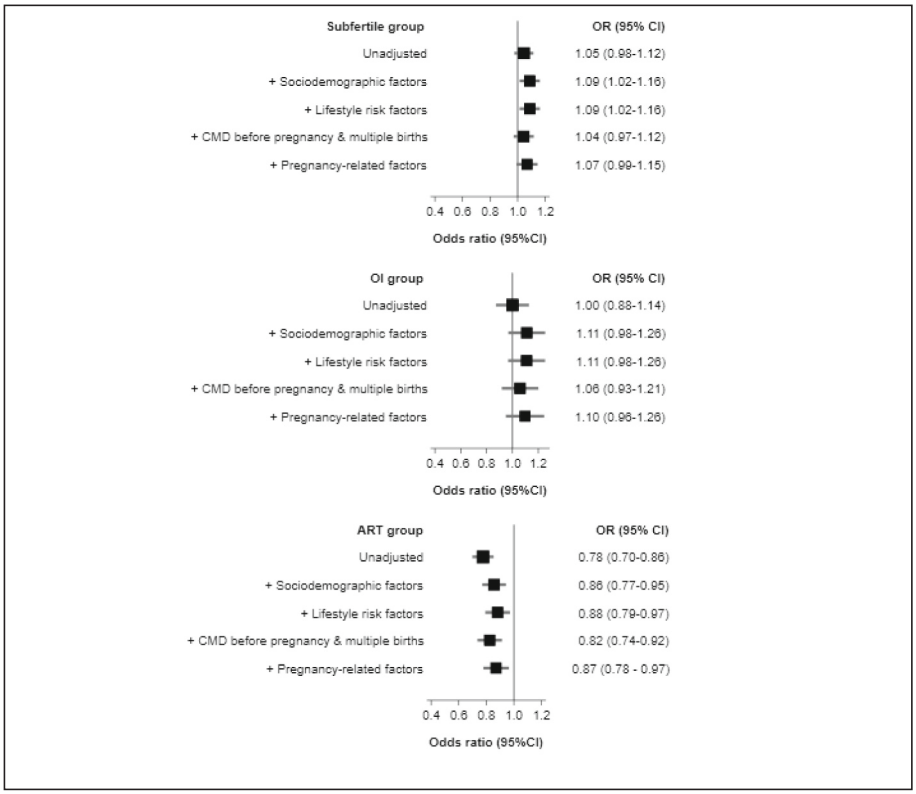

Fig. 2. Forest plots showing the change in adjusted odds ratio of the association between fertility history and postpartum depression or anxiety (compared to no fertility problems), following sequential adjustment for confounders and mediators.

the low moods and the feeling of helplessness associated with mental health disorders (Pasch et al., 2012; Repokari et al., 2005).

This is the largest population-based study to date in which the association between fertility history and postpartum depression and/or anxiety has been studied. In addition, the strict definition of our exposure groups, and rigorous ascertainment of the outcomes underscores the validity of our findings. The use of electronic medical records removes the risk of recall bias, and the possibility of obtaining evidence of previous episodes of depression or anxiety lowered the risk of residual confounding by mental health history – a factor often overlooked in studies of PPD and anxiety. Our findings are broadly generalisable to all mothers in England, and they could be extrapolated to other high-income settings.

However, it is important to interpret the findings from this study within the context of the study limitations. Women in the study population had to be registered at their GP practices for a minimum of 18 months prior to childbirth, and 12 months after. This may have excluded women with less stable lives, who may also be more likely to experience postpartum depression and anxiety. There was a possibility of misclassification of the exposure, particularly across the fertile and untreated sub-fertile groups where women would not have a record if they did not consult their GP. The 'fertile' comparison group, by definition, includes women who experienced an unplanned or unwanted pregnancy, which is a recognised risk factor for PPD (Hall et al., 2018). This may artificially inflate the difference between the ART and the comparison group, as we were unable to account for pregnancy planning or desire for a child (Carson et al., 2010). While GPs are the main access point for health care in England, it is possible that some women may have sought help from other sources such as private psychological treatment or peer support from third sector organisations. If this is more common in women who had ART it may underestimate depression and/or anxiety in this group, as we cannot reliably identify in this type of care in the records.

Similarly, given the diagnostic challenges around postpartum depression and anxiety, misclassification of the outcome variable must be considered. We considered a combined outcome of depression and/or anxiety, as symptoms overlap, are often co-morbid, and rapid diagnosis in a primary care setting is likely to conflate the two conditions. Meta-analyses found a pooled prevalence of 10–15% for depression, and 9.9% for anxiety disorders in the postpartum period (Dennis et al., 2018); this suggests that the prevalence in the present study may be slightly low. However, there is substantial overlap between the two conditions with another meta-analysis suggesting an estimated prevalence of 7.9% for clinically diagnosed co-morbid anxiety and depression. It is suggested that in comorbid cases the more common diagnosis is depression, even in the presence of substantial anxiety symptoms which may lead to an underestimate (and therefore under-treatment) of anxiety (Falah-Hassani et al., 2017). The triangulation approach to identify the outcomes has been validated in the general population, which indicated that the inclusion of symptom codes improved sensitivity (John et al., 2016b). As the symptom codes are often ambiguous these were used in combination with prescribing data on medications, however, this ensures improved specificity at the cost of some sensitivity.

In our sensitivity analysis, the same pattern of results was seen across the groups, but was no longer statistically significant after considering all recorded births and adjusting for parity. However, this analysis used a smaller sample of women who had longer follow-up and more than one birth recorded; as such the results should be interpreted with caution and the impact of parity requires further exploration. Finally, we were unable to adjust for other recognised predictors of postpartum depression or anxiety such as social support and sources of maternal stress, opening a possibility of residual confounding that cannot be explored in the routine data.

In conclusion, we found that women who had a history of subfertility, OI or ART treatment were not at increased risk of postpartum depression and/or anxiety compared to those with no history of fertility

problems. Among first births in the CPRD record, women who had ART pregnancies were significantly less likely to have a record of a diagnosis or treatment for depression or anxiety in the 12 months after childbirth. While broadly reassuring, further work is required to explore whether this is a true effect or indicates a group of women who are less likely to seek help when needed.

Data sharing

This study is based on data from the Clinical Practice Research Datalink obtained under licence from the UK Medicines and Healthcare products Regulatory Agency. The data is provided by patients and collected by the NHS as part of their care and support. Copyright © 2021, re-used with the permission of The Health & Social Care Information Centre. All rights reserved.

The interpretation and conclusions contained in this study are those of the author/s alone.

The authors do not have the right to share these data, and therefore enquiries regarding access should be made to the CPRD (enquiries@cprd.com). Details of code lists are available on request from the corresponding author.

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CRediT authorship contribution statement

CC developed the original proposal and secured funding. FLT, YL, FA, MAQ, JJK, CB had input into the design of study. CC secured the data. FLT conducted the analysis and composed the original manuscript. YL, FA, and CC supported data analysis. FLT, YL, FA, MAQ, JJK, CB, and CC contributed to the interpretation, drafts and composition of the final manuscript. All authors have read and approved the final version of the manuscript.

Declaration of competing interest

The authors declare no competing interests.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jad.2022.04.138.

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