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The impact of pregnancy on future health in Rheumatoid Arthritis: A systematic review of the literature

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ABSTRACT

Objectives: To assess whether obstetric history predicts future rheumatoid arthritis (RA) diagnosis, severity, and/or maternal health beyond the immediate postpartum period.
Methods: A systematic literature search was conducted on 01/07/24 (PubMed, Embase); PROSPERO ID CRD42024559893. Primary research examining health outcomes in RA-affected females, stratified on obstetric history pre- or post-RA onset, were selected for inclusion. Studies of overlapping cohorts were included if differing exposures/outcomes reported.
Results: Out of 3333 articles screened, 95 studies were selected. Future health outcomes analysed included RA diagnosis (n = 66 studies), severity (n = 11), cardiovascular disease (n = 2), immunity (n = 9), and microchimerism (n = 7). Parity/gravidity (n = 67), infertility (n = 7), and pregnancy loss (n = 22) were not reliable predictors of subsequent RA. High parity (n = 2) was linked to increased cardiovascular disease risk in RA-affected females. Both pre-eclampsia (n = 4) and delivery of a low birthweight infant (n = 2) were associated with RA diagnosis/severity. A trend suggested increased RA risk after preterm birth (n = 3) and severe hyperemesis gravidarum (n = 3), but not for gestational diabetes (n = 1). No significant differences in post-translational modification of serum proteins were noted beyond 6 months postpartum, though persistent differences in anti-HLA antibodies and microchimerism were observed.
Conclusions: Research indicates that parity, gravidity, infertility, and pregnancy loss do not adversely affect RA development. Conversely, low birthweight delivery was associated with RA diagnosis and severity, while pre-eclampsia correlated with subsequent RA diagnosis. Differences in immune responses, as indicated by anti-HLA and microchimerism, may indicate immune sensitisation relevant to RA pathogenesis. The predictive impact of pre-eclampsia and gestational diabetes on cardiovascular health in RA-affected females remains unstudied.

1. Introduction

Rheumatoid arthritis (RA) is a chronic autoimmune disease affecting ~1 % of adults with synovitis, joint erosions, and extra-articular manifestations (e.g., rheumatoid nodules, accelerated atherosclerosis) [1]. There is a 2–3:1 female-to-male ratio in RA, and RA incidence peaks during menopause and after pregnancy [2,3].

Historically, approximately 60 % of people experienced disease amelioration during pregnancy, and almost half flared postpartum [4]. With modern treat-to-target strategies, however, up to 90 % of RA-affected females can achieve remission or low disease activity by the 3rd trimester [5]. Pregnancy in RA is associated with an increased risk of adverse pregnancy outcomes (APOs), including pre-eclampsia, pregnancy-induced hypertension (PIH), preterm birth and small for gestational age (SGA) [6]. The risk of APO increases further with active RA [7].

In the general population, it is well-established that pregnancy offers a window into future maternal health. Pre-eclampsia quadruples an

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individual's lifetime risk of hypertension, and gestational diabetes mellitus (GDM) increases the risk of type 2 diabetes 10-fold [8,9]. Given the combined endothelial, metabolic and immunologic mechanisms underpinning healthy pregnancy and APOs, authors have explored the role of pregnancy in predicting or unmasking subclinical immune dysfunction in diverse fields, including transplantation, where females with a history of pregnancy are more likely to be allosensitised, experience delays to transplant, and have an increased risk of acute cellular rejection [10,11].

Previous systematic reviews have explored the impact of various female-specific factors on subsequent RA diagnosis, including oral contraceptives (no effect) and lactation (reduced risk) [12,13]. To our knowledge, there are no previous reviews of APO on future RA development, severity and immunity. Therefore, this systematic review will explore the impact of obstetric history on RA beyond the immediate postpartum to evaluate whether obstetric history predicts future maternal health and/or diagnosis/severity of RA.

2. Methods

The protocol for this systematic review was registered with PROSPERO on 01/07/24 (ID: CRD42024559893). A systematic review of Pubmed (within title/abstract) and Embase was conducted from inception to 01/07/2024 as follows: (pregn* OR reproduct* OR parity) AND rheumatoid AND (onset OR risk OR progression OR severity OR disability OR subsequent). Inclusion criteria: English language, original research only, humans only; reporting on RA outcomes in females stratified on obstetric history ≥6 months postpartum, APOs, or infertility. Exclusion criteria: case reports, pre-prints, and conference abstracts.

BG performed the searches, removed duplicate papers, removed those meeting exclusion criteria and cross-checked relevant conference abstracts for full-text peer-reviewed articles. All remaining studies were then considered for inclusion in the review. Four independent reviewers screened the titles and abstracts of articles from the searches, and then two reviewers examined the full texts of relevant studies, selecting articles that met the inclusion criteria. Two reviewers performed data extraction. Disagreements arising during screening and extraction were resolved by group discussion, with involvement of a third reviewer when necessary.

Quality assessment of case-control and cohort studies was performed using the Newcastle-Ottawa score by two reviewers allocating a maximum score of nine across three categories: selection (maximum points four), comparability (maximum points two which required, at minimum, controlling/matching for age and smoking), and exposure/outcome (maximum points three) [14].

Terms in this review have been defined as per the European Alliance of Associations for Rheumatology (EULAR) core data set for pregnancy registries in rheumatology [15]. Papers included in this review have sometimes defined these terms differently and these discrepancies are highlighted where relevant.

Results are presented where possible as odds ratios (OR), relative risks (RR) or hazard ratios (HR) with a 95 % confidence interval (CI). The result is either extracted directly from the original publication, or if not provided, calculated based on raw data in the original article or supplementary data.

3. Results

The literature review identified 95 studies for inclusion (Fig. 1), including 59 studies with participants from Europe [16–74], 30 from North America [75–104], two from Asia [105,106], one from South America [107] and one with international participants [108]. Two were systematic reviews and meta-analyses of existing studies [109,110]. No articles with participants from Africa or Oceania were identified. Only eight of 93 studies included an author with an Obstetrics, Gynaecology

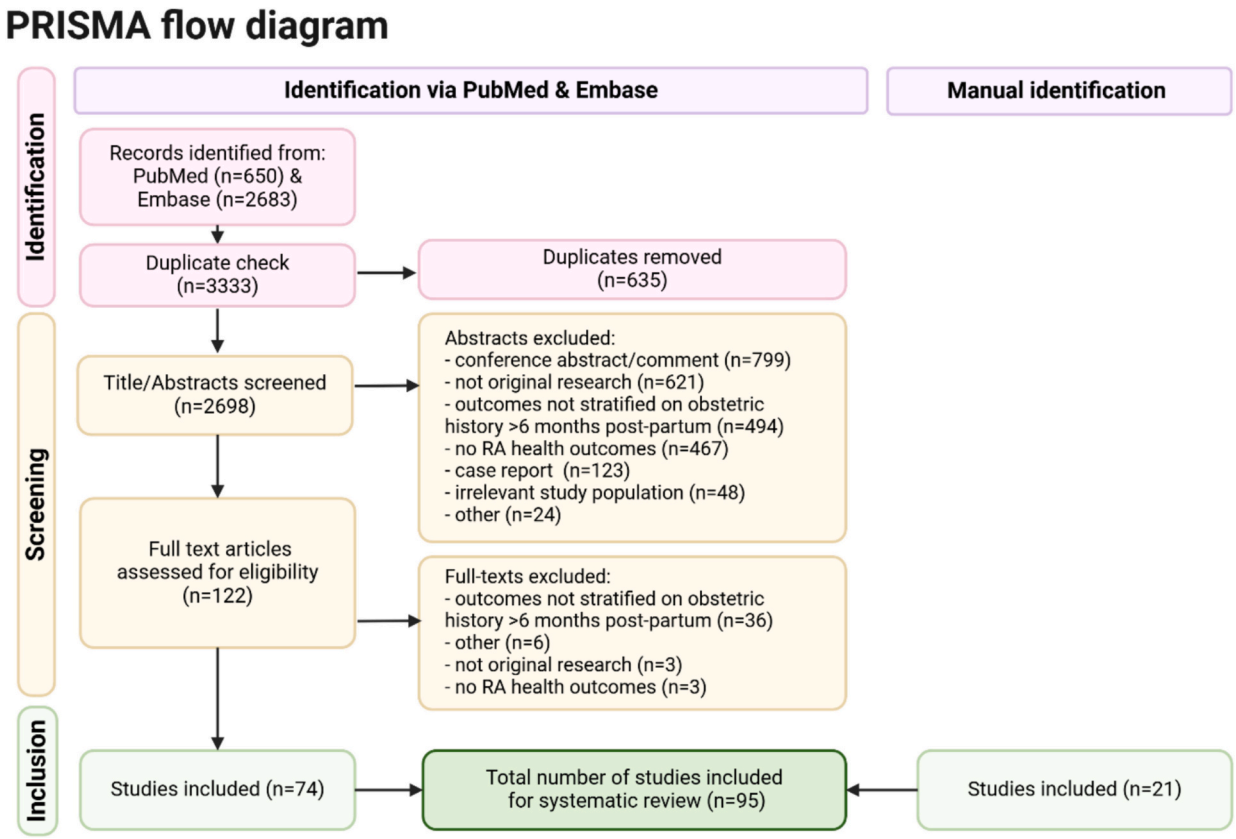

Fig. 1. Preferred Reporting Items for Systematic review and Meta-Analysis (PRISMA) flowchart of search results.

or Women's Health affiliation [25,32,43,50,79,82,95,105].

The outcome of Newcastle-Ottawa scoring of case-control and cohort studies is summarised in *Tables 1, 2* and *3*.

Numerous studies included overlapping cohorts: 11 with cases and/or controls from King County and Seattle in the USA [75,78–80,82,84,86,87,89,90,98], seven from linked Danish registers (including Danish Civil Registration System, Danish National Patient Registry, Danish Medical Birth Registry) [25,28–30,50,65,74], seven from the Dutch Pregnancy induced Amelioration of RA (PARA) study [19–22,69–71], five from the United Kingdom's (UK) Norfolk Arthritis Register (NOAR) [27,31,33,39,59], five from the Swedish Epidemiological Investigation of RA (EIRA) study [38,45,55,56,96], four from the University of Leiden Medical Centre [18,24,32,35], four from the American Nurses' Health Study [83,85,96,99], three from the American Mother-Child Immunogenetic Study (MCIS) [91,92,103], three from the American Rochester Epidemiology Project [93,100,104], two from the French Étude épidémiologique auprès des femmes de la mutuelle générale de l'Éducation nationale (E3N) cohort [16,36], two from the same East London Rheumatology clinics [44,51], two from the UK Biobank [73,108], and two from the American National Health and Nutrition Examination Survey (NHANES) [95,102].

Obstetric exposures could be grouped into five themes, including parity/gravidity ($n = 85$), pregnancy loss ($n = 20$), infertility (n = 8), placental insufficiency (e.g., pre-eclampsia, low birth weight infant; $n = 7$) and other APOs (e.g., GDM, hyperemesis gravidarum, preterm birth; n = 7). Five distinct themes in health outcomes >6 months postpartum were identified – RA diagnosis ($n = 66$), RA severity ($n = 11$), cardiovascular disease (CVD) in RA (n = 2), female immunity in RA ($n = 9$), and microchimerism (Mc) in RA (n = 7). This information is summarised in Fig. 2.

3.1. Parity/gravidity and RA

3.1.1. Parity/gravidity and future RA diagnosis

Of the two existing systematic reviews and meta-analyses exploring RA diagnosis stratified on pre-onset parity and/or gravidity - neither found a significant association between pregnancy and subsequent diagnosis of RA [109,110]. In Ren et al.'s review (searches up to April 2016), the RR of subsequent RA diagnosis in parous compared to nulliparous females was 0.90 (95 % CI 0.79–1.02) [109], whilst Chen et al. report an OR for gravidity and future RA of 0.86 (95 % CI 0.46–1.62) and for parity of 0.91 (95 % CI 0.80–1.04) (searches up to January 2018) [110]. Studies suggesting an effect were often of case-control design, occasionally used problematic outcome measures (e.g., RA diagnosis ascertained from death certificate) or failed to account for key confounders (e.g., smoking). Due to heterogeneity in groupings of parity/gravidity, not all identified papers were included in the pooled analyses of Chen et al.'s review, and only the most recent studies from each cohort were selected.

Since Ren et al. and Chen et al.'s reviews, a further five studies have examined the impact of parity/gravidity, predominantly in relation to post-menopausal onset RA [16,36,73,105]. Their findings are largely in keeping with Chen et al., including results from a large prospective cohort of 223,526 females from the UK biobank that found no impact of gravidity on RA risk (HR 1.04; 95 % CI 0.94–1.16) [73].

Chen et al. also explored whether new diagnoses of RA increased within the first year postpartum. They provided a descriptive analysis of six case-control studies with conflicting results, albeit suggesting that RA is increased immediately postpartum. Chen et al. did not, however, include the outcome of a large Danish cohort of 1011 individuals who developed RA among 403,958 females with a singleton live birth [74]. The incidence of International Classification of Diseases (ICD) coding of incident RA in this study was decreased during the pregnancy itself, rose following delivery to a peak at 6–9 months, and then declined to baseline by 1–2 years postpartum. Assuming a delay between first symptoms to secondary care referral, investigation and diagnosis, the original onset for many is likely to occur within, rather than beyond, six months postpartum.

Unaccounted for in the above research is whether maternal genotype at RA risk loci influences the impact of parity/gravidity. A specific amino acid sequence called the shared epitope (SE), within the β chain of human leukocyte antigen (HLA) DR4 (encoded by HLA-DRB1), is the strongest genetic risk factor for RA, whilst an alternative HLA-DRB1 sequence, DERAA, is protective against RA [111]. Three case-control studies which explored the impact of parity/gravidity on subsequent RA diagnosis had varying degrees of tissue type information for participants, thereby allowing genotype sub-analyses to be performed [24,54,79]. In work by Hazes et al., parity was associated with a reduced

Table 1
Infertility and risk of subsequent Rheumatoid Arthritis outcomes.

Author (year)	Location	Study design	Study quality*	Population	Pregnancy variable of interest	RA risk
McHugh NJ et al., 1989 [52]	UK	CC	3 (2/0/1)	117 ♀ RA, 100 ♀ population controls	Infertility (>2 years)	Infertility RR 0.43 (0.08–2.28)
Nelson JL et al., 1993 [86]	USA (King County)	CC	5 (3/1/1)	259 ♀ RA, 1258 ♀ age matched controls	Infertility (>12 months)	**Infertility OR 1.44 (1.10–1.91)**
Brennan P et al., 1994 [46]	UK	CC	5 (3/1/1)	35 monozygotic ♀ twin discordant for RA, 31 dizygotic ♀ twin pairs discordant for RA, with age matched ♀ control twin pairs and 160 ♀ population controls	Infertility ("ever consulted a doctor regarding infertility") Miscarriage	Infertility OR 2.00 (0.18–22.1) (monozygotic) Infertility OR 2 (0.18–22.1) (dizygotic) **Infertility OR 4.09 (1.07–15.7) (cases vs population controls)**
Pope JE et al., 1999 [94]	Canada	CC	6 (3/1/2)	34 ♀ RA, 68 ♀ age & marital status matched controls	Infertility (>6 months)	Infertility OR 0.7 (0.3–1.7)
Merlino LA et al., 2003 [97]	USA	Co	6 (3/1/2)	158 post-menopausal ♀ RA, 31336 post-menopausal ♀ controls	Infertility (>12 months)	Infertility RR 1.09 (0.72–1.66)
Van Dunné FM et al., 2004 [32]	Netherlands	Co	6 (4/0/2)	113 ♀ RA	Subfertility (TTP >12 months)	TTP <3 months cf. 4–12 months cf. >12 months no difference in mmSS, p > 0.05
Salliot C et al., 2021 [36]	France	Co	8 (3/2/3)	698 ♀ RA among 78,452 ♀ participants born between 1925 and 1950	Infertility ("ever taken hormonal treatment for infertility")	Infertility HR 0.8 (0.5–1.3)

CC = case control study, cf. = compared to, Co = cohort study, HR = hazard ratio, OR = odds ratio, RR = relative risk, TTP = time to pregnancy, * = Newcastle-Ottawa grading system; **statistically significant values highlighted in bold.**

Table 2
Pregnancy loss and risk of subsequent Rheumatoid Arthritis outcomes.

Author (year)	Location	Study design	Study Quality*	Population	Pregnancy variable of interest	RA risk
Kay A et al., 1965 [47]	UK	CC	4 (4/0/0)	209 ♀ RA (98 pre- & 111 post-menopausal), 209 ♀ age/social status matched controls	Miscarriage Stillbirth	Pre-menopausal onset RA: Miscarriage OR 1.2 (0.6–2.3) Stillbirth OR 3.1 (0.3–30.0)
Linos A et al., 1983 [93]	USA	CC	7 (4/1/2)	229 ♀ RA, 458 ♀ age matched controls	Miscarriage	≥2 miscarriages (cf <2) RR 0.7 (0.3–1.4)
Kaplan D et al., 1986 [81]	USA	CC	4 (3/0/1)	96 ♀ RA, 113 ♀ OA & non-inflammatory musculoskeletal diseases	Miscarriage TOP	**Miscarriage OR 2.6 (1.5–4.7)** **TOP OR 0.13 (0.04–0.46)**
Siamopoulou-Mavridou A et al., 1988 [53]	Greece	CC	4 (3/1/0)	69 ♀ RA, 98 ♀ age, marital & social status matched healthy controls	Miscarriage Stillbirth	Miscarriage OR 1.42 (0.83–2.43) Stillbirth OR 0.69 (0.20–2.33)
Silman A et al., 1988 [34]	UK	CC	4 (2/1/1)	40 ♀ RA, 67 unaffected ♀ relatives	Perinatal death (stillbirth & neonatal) Miscarriage	**Perinatal death RR 12.4 (1.6–91.1)** Miscarriage RR 1.2 (0.5–2.9)
McHugh NJ et al., 1989 [52]	UK	CC	3 (2/0/1)	117 ♀ RA, 100 ♀ population controls	Pregnancy loss (miscarriage & stillbirth)	Pregnancy loss RR 0.80 (0.42–1.54)
Hazes JM et al., 1990 [24]	Netherlands	CC	6 (2/2/2)	135 ♀ RA, 378 ♀ soft tissue rheumatism (e.g. bursitis, OA, fibromyalgia)	Pregnancy loss (any loss <25 weeks)	**Parous RR 0.49 (0.27–0.91)** but when pregnancy loss included became non-significant (RR 0.73 (0.50–1.07))
Spector T et al., 1990 [44]	UK	CC	5 (3/1/1)	195 ♀ RA, 462 controls (233 ♀ OA, 229 ♀ population controls)	Ectopic & miscarriage Stillbirth TOP	**Ectopic & miscarriage OR 0.6 (0.4–0.9)** Stillbirth OR 1.5 (0.7–3.4) TOP OR 1.7 (0.8–3.4)
Nelson JL et al., 1992 [80]	USA (King County)	CC	5 (3/1/1)	144 ♀ RA, 605 ♀ age matched controls	Ectopic Miscarriage Stillbirth TOP	Ectopic OR 1.1 (0.4–3.5) Any miscarriage OR 0.9 (0.6–1.4) ≥2 miscarriages OR 0.7 (0.3–1.5) Stillbirth OR 0.9 (0.3–2.7) TOP OR 1.7 (0.9–3.2)
Deighton CM et al., 1993 [54]	UK	CC	2 (2/0/0)	98 ♀ RA, 98 ♀ matched discordant sisters	Pregnancy loss (miscarriage, stillbirth, TOP)	Pregnancy loss mean 0.3 in RA & 0.3 in controls
Brennan P et al., 1994 [46]	UK	CC	5 (3/1/1)	35 monozygotic ♀ twin discordant for RA, 31 dizygotic ♀ twin pairs discordant for RA, with age matched ♀ control twin pairs and 160 ♀ population controls	Miscarriage	Miscarriage OR 0.67 (0.11–3.99) (monozygotic) Miscarriage OR 0.5 (0.05–5.51) (dizygotic) Miscarriage OR 0.16 (0.02–1.35) (cases vs population controls)
Symmons DPM et al., 1997 [59]	UK (NOAR)	CC	6 (4/1/1)	69 ♀ RA, 69 ♀ age matched controls	Miscarriage	Miscarriage OR 2.17 (0.86–5.49)
Pope JE et al., 1999 [94]	Canada	CC	5 (3/1/1)	34 ♀ RA, 68 ♀ age & marital status matched controls	Miscarriage TOP	Miscarriage OR 0.8 (0.3–2.5) TOP OR 0.9 (0.2–4.0)
Carette S et al., 2000 [33]	UK (NOAR/ EPIC)	nCC	4 (2/1/1)	43 ♀ RA, 129 ♀ age matched controls	TOP	**TOP OR 3.74 (1.4–9.9)**
Merlino LA et al., 2003 [97]	USA	Co	6 (3/1/2)	158 post-menopausal ♀ RA, 31336 post-menopausal ♀ controls	Miscarriage Stillbirth	≥2 miscarriages RR 0.99 (0.54–1.80) Stillbirth RR 1.36 (0.69–2.68)
Van Dunné FM et al., 2004 [32]	Netherlands	Co	6 (4/0/2)	113 ♀ RA	Miscarriage	**≥1 miscarriage ↑ mmSS at 2 years (24 (95 % CI 15–32)) cf. to 0 miscarriage who had mmSS 16 (10−23), $p < 0.05$))**
Berglin E et al., 2010 [42]	Sweden	nCC	5 (3/1/1)	70 ♀ RA who had donated blood pre-symptom onset, 280 ♀ control blood donors	Pregnancy loss (miscarriage, TOP)	Pregnancy loss OR 1.03 (0.54–1.94)
Khashan AS et al., 2011 [25]	Denmark	Co	7 (4/1/2)	1709 ♀ RA among 1,035,639 ♀ born 1962–1992	TOP (as outcome of 1st pregnancy)	TOP RR 0.93 (0.74–1.18)
Jørgensen KT et al., 2012 [30]	Denmark	Co	7 (4/1/2)	6404 ♀ RA among 1,564,567 ♀ born in 1955–1993 who's pregnancy history was subsequently analysed	Miscarriage Stillbirth TOP	Miscarriage RR 1.06 (0.97–1.15) Stillbirth RR 0.88 (0.61–1.22) TOP RR 1.03 (0.97–1.10)
Camacho EM et al., 2012 [31]	UK (NOAR)	Co	7 (3/2/2)	1586 ♀ inflammatory polyarthritis (75 % in NOAR ultimately have RA)	Miscarriage Stillbirth	**≥3 stillbirth/miscarriage ↑ HAQ (mean difference 0.23; 0.02–0.43) & DAS28 ↑ 0.98; 0.23–1.74)**
Nathan NO et al., 2020 [50]	Denmark	Co	7 (4/1/2)	19,991 pregnancies among ♀ RA among 3,276,127 pregnancies between 1977 and 2014	Miscarriage	♀ <35: Miscarriage within 5 years pre-RA Δ OR 1.06 (0.93–1.22)
Pan D et al., 2020 [75]	USA (King County)	Co	8 (4/2/2)	156 ♀ gravid prior to RA onset, 48 ♀ nulligravid prior to RA onset	Live births only (cf. Nulligravid cf. Gravid with history of miscarriage/stillbirth)	Overall live births only cf. nulligravid - **severe JC RR 0.55 (0.33–0.92)**, no difference in x-ray or HAQ; ♀ with 0 cf. 1+ copies of the shared epitope - **erosion score RR 0.26; 95 % CI 0.09–0.89 & JC RR 0.28 95 % CI 0.09–0.87)**
Boman A et al., 2022 [37]	Sweden	Co	7 (3/2/2)	64 post-menopausal ♀ RA with CVD after RA onset, 700 post-menopausal ♀ without CVE after RA onset	Pregnancy loss (miscarriage & TOP)	Pregnancy loss RR for CVD 0.79 (0.47–1.32)

CC = case control study, cf. = compared to, Co = cohort study, CVD = cardiovascular disease, EPIC = European Prospective Investigation of Cancer, g = grams, HAQ = health assessment questionnaire, HR = hazard ratio, JC = joint count, mmSS = mean modified sharp score, nCC = nested case-control, NOAR = Norfolk Arthritis Registry, OA = osteoarthritis, OR = odds ratio, RA = rheumatoid arthritis, RF = rheumatoid factor, RR = relative risk, * = Newcastle-Ottawa grading system; **statistically significant values highlighted in bold.**

Table 3
Other APO and risk of subsequent Rheumatoid Arthritis outcomes.

Author (year)	Location	Study design	Study quality*	Population	Pregnancy variable of interest	RA risk
Siamopoulou-Mavridou A et al., 1988 [53]	Greece	CC	4 (3/1/0)	69 ♀ RA, 98 ♀ age, marital & social status matched healthy controls	Preterm birth	Preterm birth OR 1.40 (0.19–10.04)
Pope JE et al., 1999 [94]	Canada	CC	5 (3/1/1)	34 ♀ RA, 68 ♀ age & marital status matched controls	PET	PET OR 0.9 (0.2–3.4)
Jørgensen KT et al., 2010 [29]	Denmark	Co	6 (3/1/2)	1648 ♀ hospitalised with RA among 1,387,186 ♀ born in 1955–1989 (subsequent pregnancies analysed)	HG PET PIH	**HG RR 1.70 (1.06–2.54)** **PET RR 1.42 (1.08–1.84)** **PIH RR 1.49 (1.06–2.02)**
Salliot C et al., 2010 [57]	France	Co	6 (4/0/2)	275 ♀ RA, 18 ♀ other rheumatic disease, 275 ♀ undifferentiated arthritis	Preterm birth	Preterm birth OR 1.7 (0.9–3.2)
Jørgensen KT et al., 2012 [30]	Denmark	Co	7 (4/1/2)	6404 ♀ RA among 1,564,567 ♀ born in 1955–1993 (subsequent pregnancies analysed)	HG PET & PIH	**HG RR 1.35 (1.09–1.64)** **PIH & PET RR 1.18 (1.05–1.31)**
Jørgensen KT et al., 2014 [28]	Denmark	Co	8 (4/2/2)	169 ♀ RA among 55,752 ♀ born 1996–2002	HG PET PIH	HG HR 0.86 (0.50–1.49) **PET HR 1.96 (1.06–3.63)** PIH HR 1.18 (0.73–1.91)
Ma KK et al., 2014 [82]	USA (King County)	CC	6 (3/2/1)	202 ♀ RA, 1102 ♀ controls	Birthweight (absolute birthweight & <10th for gestational age) Preterm birth	*For RA*: ≤1500 g RR 2.4 (0.9–6.3) **≤1000 g RR 3.7 (1–13.2)** Preterm birth RR 1.4 (0.9–2.0) <10th centile RR 0.8 (0.5–1.1) *For RF positive RA*: **≤1500 g RR 4.0 (1.3–11.4)** **≤1000 g RR 5.5 (1.4–22.5)** Preterm birth RR 0.9 (0.5–1.7) <10th centile RR 1.1 (0.7–1.91)
Nagase T et al., 2022 [106]	Japan	Co	4 (3/0/1)	11 ♀ RA (15 pregnancies) combined with 4 JIA patients (5 pregnancies)	Low birth weight	ΔmTSS from delivery-1 year PP 13.4 ± 2.1 in those with LBW infant vs. 7.0 ± 2.5 in those with NBW infant, p = 0.06
Mao Y et al., 2022 [102]	USA	Co	6 (3/2/1)	834 ♀ RA, 11997 ♀ without RA	GDM	GDM OR 1.04 (0.69–1.57)

CC = case-control, cf. = compared to, Co = cohort, CS = cross-sectional, g = grams, GDM = gestational diabetes, LBW = low birth weight, mTSS = modified total sharp score, NBM = normal birth weight, NOAR = Norfolk Arthritis Register, PP = postpartum TTP = time to pregnancy, * = Newcastle-Ottawa grading system; **statistically significant values highlighted in bold.**

risk of RA in the presence of HLA-DR4 (OR 0.25; 95 % CI 0.08–0.71), but if HLA-DR4 was absent, parity did not affect RA risk (OR 0.59; 95 % CI 0.24–1.41) [24]. Deighton et al. examined HLA type, parity, and RA risk in a study of familial RA - reporting that sibling discordancy for class I HLA types did not modify the impact of parity [54]. Finally, in an American study, the reduction in RA risk seen with parity was most significant in those with the risk-enhancing SE (RR 0.42; 95 % CI 0.22–0.79) and who lacked the protective DERAA sequence (RR 0.44; 95 % CI 0.26–0.74) [79].

Others have considered whether the interrelationship between maternal and fetal-paternal genotypes influenced pregnancy-associated RA risk [67,91,92]. Brennan et al. identified no increased risk of RA following pregnancy with an HLA-DR1 or -DR4 haplocompatible partner/child, whilst Cruz et al. reported an increased risk of RA in parous females who had given birth to a child haplocompatible at two HLA class II alleles (DPB1: OR 1.8; 95 % CI 1.2–2.6 and DQB1: OR 1.8; 95 % CI 1.2–2.7), as well as at the class I HLA: HLA-B (OR 1.9; 1.2–3.1) [91]. In a subsequent study by Cruz et al., RA risk was not significantly modified in SE-negative mothers who had given birth to SE-positive children (OR 1.7; 95 % CI 0.8–3.7), but DERAA-negative mothers with children positive for DERAA had an increased risk of RA (OR 1.7; 95 % CI 1.0–2.7) [92].

3.1.2. Parity/gravidity and future health in RA

Investigators have also studied whether obstetric history predicts or influences RA severity (e.g., Health Assessment Questionnaire (HAQ), disease activity scores (DAS)) [18,26,27,37,38,41,75,76]. Among three cohort studies stratified on parity prior to RA onset, one reported reduced HAQ scores following ≥3 versus ≤1 pregnancy ($n = 132$, $p = 0.05$) [18]. A second cohort study which compared ≥1 pregnancy to nulliparity found no significant difference in erosion scores, joint space narrowing, joint counts or HAQ scores ($n = 222$, all $p > 0.05$) [75]. Thirdly, in the EIRA study, it was only a subset of anti-cyclic citrullinated peptide (anti-CCP) negative individuals ($n = 103$ of 1237 participants in total) in whom parity was associated with worse outcomes when they later developed RA (mean difference in DAS28: 1.17; 95 % CI 0.65 to 1.68, mean difference in HAQ: 0.43; 95 % CI 0.20 to 0.66) [38].

A single study explored the impact of post-onset parity – reporting a beneficial effect of pregnancy after a diagnosis of RA (HAQ: mean difference − 0.16; 95 % CI −0.25 to −0.06), and in contrast to the EIRA study, the 10 anti-CCP positive participants in this study had worse outcomes than anti-CCP negative individuals (HAQ: mean difference + 0.31; 95 % CI 0.05 to 0.56) [27]. Changes in treatment related to pregnancy and lactation were not accounted for in this study, but baseline RA activity was similar between groups [27].

Finally, two prospective analyses examined the risk of future CVD stratified by parity. Among 600 RA-affected females, 205 subsequently developed CVD, with an HR among those with any prior pregnancy of 0.96 (95 % CI 0.68–1.33; adjusted for age) [104]. In 803 postmenopausal females with RA, CVD was more common in parous individuals (HR 1.84; 95 % CI 1.35–2.52), and these risks remained significant even when adjusted for smoking, hypertension, diabetes, body mass index and age [37]. In both studies, CVD risk was highest for those with high parity (≥3 children (HR 5.67; 95 % CI 2.15–15.00) [37]).

3.2. Infertility and RA

3.2.1. Infertility and future RA diagnosis

A total of six studies explored risk of RA diagnosis in relation to a history of infertility [36,46,52,86,94,97] (Table 1). The World Health Organisation (WHO) defines infertility as a failure to achieve pregnancy after 12 months of regular unprotected sex. Of those studies reporting on

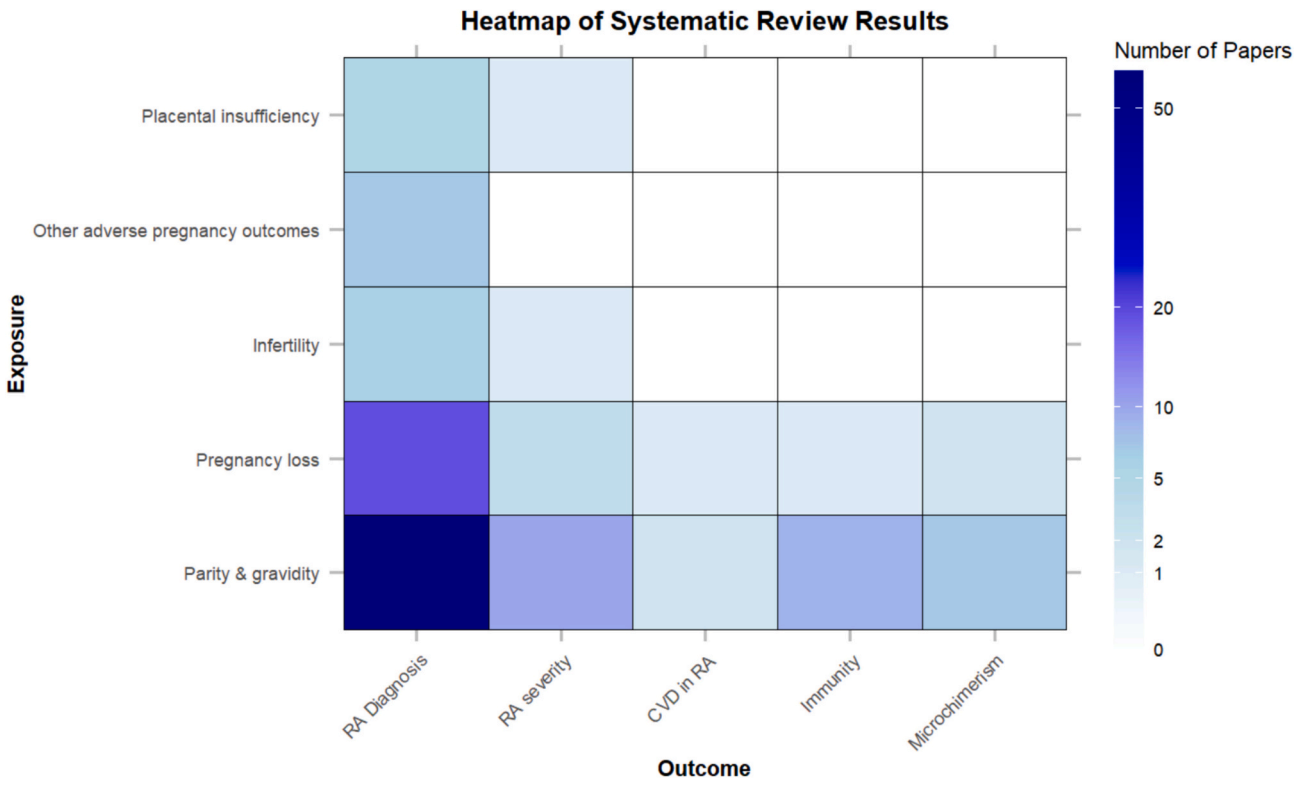

Fig. 2. Heatmap of search results.
CVD = cardiovascular disease; Other adverse pregnancy outcomes = gestational diabetes mellitus, hyperemesis gravidarum, preterm birth; Placental insufficiency = pre-eclampsia, low birthweight; RA = Rheumatoid Arthritis.

infertility - three utilised a WHO-like definition [32,86,97], one reduced this to >6 months [94], one lengthened it to >2 years [52], whilst Brennan et al. defined it as "ever consulted a doctor regarding fertility" [46] and Salliot et al. as "ever taken hormonal treatment for infertility" [36].

Among the included studies, infertility was not consistently associated with a subsequent diagnosis of RA. Only two studies, by Nelson et al. and Brennan et al., identified a statistically significant effect [46,86]. In age-adjusted analyses, Nelson et al. reported an OR for pre-onset infertility of 1.44 in RA compared to controls (95 % CI 1.10–1.91); but with similar numbers of absolute infertility between the two groups (i.e., those *never* managing to conceive) and a latency of >20 years between the episode of infertility and RA diagnosis for >70 % of cases [86]. Brennan et al. identified a 4-fold increased risk of preceding infertility (OR 4.09; 95 % CI 1.07–15.7, unadjusted for smoking) in RA cases compared to controls. Brennan et al. used a self-administered postal questionnaire to identify participants who had consulted a doctor regarding infertility; RA cases may have therefore been more likely to answer in the affirmative due to their increased healthcare contact, rather than due to a true increase in infertility [46].

3.2.2. *Infertility and future health in RA*

A single study considered whether more severe RA was seen in those with a history of infertility (Table 1) [32]. Van Dunné et al. compared radiographic progression in RA stratified by a history of conception within 3 months, within 4–12 months, and > 12 months. There was no significant difference across groups in joint damage measured using a mean modified sharp score (unadjusted for age or smoking) [32].

3.3. *Pregnancy loss and RA*

A total of 20 studies reported on risk of RA diagnosis in relation to a previous pregnancy loss, with 18 including data on miscarriage [24,30,34,42,44,46,47,50,52–54,59,80,81,93,94,97,108], 10 on stillbirth [24,30,34,44,47,52–54,80,97], nine on termination of pregnancy (TOP; induced abortion) [25,30,33,42,44,54,80,81,94], and three on ectopic pregnancy [30,44,80]. The results of these studies are summarised below and in Table 2.

3.3.1. *Miscarriage and RA diagnosis*

As miscarriage may occur prior to contact with healthcare services and may not require medical care, most studies relied on patient recall in single-centre cohorts. Of the 13 case-control studies, 10 reported no effect of miscarriage on future RA. Exceptions included one retrospective analysis reporting a reduced risk of RA (composite of miscarriage and ectopic pregnancy: OR 0.6; 95 % CI 0.4–0.9 [44]) and one unadjusted analysis suggesting miscarriage increased the risk of RA (OR 2.6; 95 % CI 1.5–4.7) [81]. Even when recurrent miscarriage is considered, there was no significant increase in incident RA in those with ≥2 miscarriages compared to those with ≤1 miscarriage (OR 0.7; 95 % CI 0.3–1.5 [80]; RR 0.7; 95 % CI 0.3–1.4 [93]; RR 0.99; 95 % CI 0.54–1.80 [97]).

Two large cohort studies using Danish registries incorporating ICD coding of miscarriage from hospital records supported the trend of no effect. Jørgensen et al. examined RA diagnoses in individuals with and without a history of miscarriage (RR 1.06; 95 % CI 0.97–1.15) [30], whilst Nathan et al. additionally considered the impact of age at miscarriage and RA diagnosis (for females <35 years old experiencing miscarriage within the preceding 5 years: OR 1.06; 95 % CI 0.93–1.22) [50]. Furthermore, no effect was seen in a Mendelian randomisation study using miscarriage as an exposure ($p > 0.05$) [108]. Finally, despite the relationship between smoking and both RA and miscarriage, only one of 17 studies adjusted for this confounder (adjusted RR for RA diagnosis in this study following pregnancy <25 weeks gestation: 0.73; 95 % CI 0.50–1.07) [24].

3.3.2. Ectopic pregnancy and RA diagnosis

Two studies reported on ectopic pregnancy alone - a large Danish registry study (ectopic RR 1.05; 95 % CI 0.9–1.2) [30] and an American case-control study (ectopic OR 1.1; 95 % CI 0.4–3.5) [80]. A further study presented a pooled estimate of miscarriage and ectopic pregnancy, but it is unclear how many ectopic pregnancies were included to understand its relevance [44]. Overall, there was no indication that an ectopic pregnancy predicted incident RA.

3.3.3. Stillbirth and RA diagnosis

10 studies reported on pre-onset stillbirth and risk of subsequent RA diagnosis. Most were limited by a low number of stillbirths, leading to low power ($n < 10$ in cases in all but one study), but overall there was no indication of an association between stillbirth and future RA [24,30,44,47,52–54,80,97]. The only outlier was a small British study of 40 females with RA and 67 of their unaffected female relatives in which those with RA were significantly more likely to have experienced a stillbirth or neonatal death before RA diagnosis (RR 12.4; 95 % CI 1.6–91.1; n = 7 stillbirths among RA participants vs 1 among controls) [34]. The largest included study, from the Danish-linked registers, examined 6404 RA-affected females, of whom 33 had a history of pre-onset stillbirth, and found no relationship between stillbirth and subsequent RA diagnosis (RR 0.88; 95 % CI 0.61–1.22) [30].

3.3.4. Termination of pregnancy and RA diagnosis

In general, authors found no association between TOP and RA [25,30,34,42,44,54,94] with only one small, low-quality study supporting an increased risk of RA following TOP (OR 3.74; 95 % CI 1.4–9.9) [33] and one suggesting TOP reduced the risk of RA (OR 0.13; 95 % CI 0.04–0.46 – OR calculated using raw data) [81]. The authors did not address this reduced risk, and participants in this study would have been of childbearing age during the legalisation of abortion in the state (New York) in 1970. As an outlier to other studies, their findings may be an artefact of a small sample group (three TOPs among 93 RA patients vs 22 TOPs among 113 controls). Alternatively, it may reflect inaccuracies in self-reporting to healthcare staff by patients compared to controls in response to the social context of the time. This contextual information serves as a reminder that TOP differs from other forms of pregnancy loss in its varied legal standing and ongoing stigmatisation [112] – both of which may impact the validity of self-reporting. Only two studies were able to control for this impact by examining data from the Danish registries with medical record-linked confirmation of TOP among a population of over one million individuals [25,30]. Neither showed a significant effect of TOP on future RA diagnosis (RR if 1st pregnancy ended in TOP 0.93; 95 % CI 0.74–1.18 [25]; RR for any history of TOP 1.03; 95 % CI 0.97–1.10 [30]).

3.3.5. Pregnancy loss and future health in RA

Three papers reported on other future health outcomes in RA (e.g., HAQ scores, joint counts, radiographic progression, CVD) stratified on pregnancy loss (Table 2). All three included data on miscarriage [31,32,37], with two also including pooled data incorporating stillbirth [31] and TOP [37]. An additional paper primarily reported on pre-onset parity but performed analyses sub-stratified to exclude those with any history of pregnancy loss [75].

A history of miscarriage predicted more rapid radiographic progression in Van Dunné et al.'s single centre cohort (using modified sharp scores) [32]. However, whilst the two groups (miscarriage vs no miscarriage) had similar radiographic scores at baseline, those with prior miscarriage had higher C-reactive protein and DAS – both established predictors of radiographic progression, and analyses were not adjusted for smoking or age. Additionally, Camacho et al. studied individuals with inflammatory polyarthritis (IP; 50 % of whom went on to meet 1987 ACR criteria for RA); comparing females with live births only against those with a history of miscarriage and/or stillbirth [31]. Those with ≥3 pregnancy losses before the onset of IP subsequently had worse HAQ and DAS28 scores during follow-up (mean difference in HAQ: 0.23 (95 % CI 0.02 to 0.43); mean difference in DAS28: 0.98 (95 % CI 0.23 to 1.74)). This adverse effect persisted after multiple adjustments, including for age and smoking, and despite similar baseline activity. Pan et al. found no impact of pre-onset parity alone on future health outcomes, but in a small subgroup, excluding those with any history of pregnancy loss and sub-stratifying to those without the SE, pregnancy protected against severe RA (erosion score RR 0.26; 95 % CI 0.09–0.89; joint count RR 0.28; 95 % CI 0.09–0.87; age-adjusted) [75].

The single study investigating future CVD risk in RA following pregnancy loss observed no significant association (miscarriage/TOP RR for CVD 0.79; 95 % CI 0.47–1.32) [37].

3.4. Other adverse pregnancy outcomes and RA

Papers exploring the impact of APOs other than infertility and pregnancy loss on future RA were also identified – including the impact of PIH, pre-eclampsia, low birthweight, preterm birth, hyperemesis gravidarum and GDM. The results are summarised in Table 3.

3.4.1. Hypertensive disorders of pregnancy and subsequent RA

The spectrum of gestational hypertensive disorders includes PIH and pre-eclampsia [113,114]. The relationship between pre-eclampsia and subsequent RA risk was first explored in a small retrospective case-control study by Pope et al.(OR 0.9; 95 % CI 0.2–3.4) [94]. The definition of pre-eclampsia has evolved over the years, but Pope's study did not provide a formal definition. Information was obtained retrospectively from a postal questionnaire, and no raw data on the number of individuals who developed pre-eclampsia was provided to determine the ascertainment rate.

Since then, three studies using the Danish linked registers have identified a positive association between pre-eclampsia and subsequent RA diagnosis [28–30]. These three studies varied in the timeframe covered and inclusion criteria. The most recent iteration in 2014 provided the most complete dataset, albeit in a smaller cohort of 169 females with RA among 55,752 participants in the Danish National Birth Cohort [28]. This study included both inpatient and outpatient consults for RA and additional capture of pregnancy complications not resulting in hospitalisation, unlike the two earlier studies [28]. The 2014 study reported a significant HR for pre-eclampsia of 1.96 (95 % CI 1.06–3.63) but not for PIH (HR 1.18; 95 % CI 0.73–1.91); both analyses were age-adjusted, and smoking adjustment did not modify the estimates. No study stratified risk in relation to timing of pre-eclampsia (i.e., term versus preterm pre-eclampsia).

3.4.2. Infant birthweight or gestational age at delivery and subsequent RA

Two studies considered infant birth weight [82,106]. A case-control study from the USA of 202 parous RA patients and 1102 controls reported a progressive increase in risk in those with lighter pre-RA onset birthweight infants (≤1500 g RR 2.4; 95 % CI 0.9–6.3 cf. ≤1000 g RR 3.7; 95 % CI 1.0–13.2) particularly if they were rheumatoid factor (RF) positive (≤1500 g RR 4.0; 95 % CI 1.3–11.4 cf. ≤1000 g RR 5.5; 95 % CI 1.4–22.5) [82]. However, the rates of these complications were low for those with very low birthweight (LBW) infants, particularly when sub-stratified based on serology (e.g., only three RF-positive individuals with infant weight ≤ 1000 g). The rates presented are unadjusted for confounders, but the authors state that adjusting for smoking did not modify the result.

Meanwhile, Nagase et al. considered radiographic progression following delivery of an LBW infant (definition not provided) among a small number of individuals with either RA or JIA. Those with an LBW infant subsequently had more progressive disease than those with a normal birthweight (NBW) infant (mean modified sharp score: mean difference 13.4 ± 2.1 in those with LBW infant vs. 7.0 ± 2.5 in those with NBW infant, $p = 0.06$) [106]. A Mendelian randomisation study examined single nucleotide polymorphisms (SNPs) associated with poor

fetal growth in the offspring as an exposure but found no causal association with maternal RA ($p > 0.05$) [108].

Three studies reported on incident RA stratified on a history of preterm birth [53,57,82]. There was a trend in favour of an increased risk in the studies by Salliot et al. (OR 1.7; 95 % CI 0.9–3.2) and Ma et al. (RR 1.4; 95 % CI 0.9–2.0). Findings were not meaningfully altered by two studies which specifically analysed in reference to being seropositive for either RF [82] or anti-CCP [57].

No studies were identified that examined maternal CVD risk in RA in relation to pre-eclampsia, infant birthweight or preterm birth despite these being risk factors in the general population.

3.4.3. Hyperemesis gravidarum and subsequent RA

Three studies used Danish-linked registers to investigate hyperemesis gravidarum [28–30]. Whilst the 2010 and 2012 studies by Jørgensen et al. suggested an increased risk of RA following a diagnosis of hyperemesis (RR 1.70; 95 % CI 1.06–2.54 [29] and RR 1.35; 95 % CI 1.09–1.64 [30]), this was no longer the case in the 2014 study in which hyperemesis not resulting in hospitalisation was included (HR 0.86; 95 % CI 0.50–1.49) [28].

3.4.4. Gestational diabetes and subsequent RA

A single American prospective cohort study of 11,997 females explored the risk of RA stratified on a history of GDM [102]. No effect was seen (OR 1.04; 95 % CI 0.69–1.57) despite multiple adjustments, including for smoking and body mass index, but both GDM and RA diagnoses were self-reported. No studies were identified that considered the risk of CVD in relation to GDM history in RA-affected females.

3.5. Physiological changes of pregnancy and impact on future RA

3.5.1. Immunologic change in pregnancy and future RA

Nine papers explored female immunity in RA stratified on obstetric history [19–22,69–71,103,107], (Table 4). Those investigating mannose-binding lectin (MBL) levels and galactosylation of immunoglobulin G and other serum proteins showed no persisting impact of pregnancy on these parameters beyond 6 months postpartum [19–22,69–71,107].

Jackman et al. described higher class I and II anti-HLA antibodies in parous females with RA than either male RA patients, nulliparous female RA patients or parous healthy controls [103]. These differences in anti-HLA frequency between parous and non-parous females with RA appeared more marked than in SLE patients, particularly for class II HLA. Anti-HLA antibodies in parous females with RA were mostly alloreactive.

3.5.2. Microchimerism and future RA

Microchimerism (Mc) describes the bidirectional trafficking of maternal and fetal cells across the placenta resulting in infants being born with maternal-Mc (i.e., non-inherited maternal antigens (NIMA)) and postpartum females having detectable fetal-Mc [115]. Seven studies examined differences in Mc in RA [48,49,68,87–90], see Table 5. Papers varied in their attempts at ascertaining the source of Mc. Pregnancy (e.g., miscarriage), blood transfusion, organ transplantation, NIMA and acquisition from an older sibling in-utero are all potential sources.

Compared to healthy controls, RA-affected females were generally more likely to have detectable Mc and higher concentrations of Mc in peripheral blood [48,49,87,89,90]. Whilst the presence of Mc cells was partly explained by obstetric history, high parity in patients and controls were reported in many studies, and other sources of Mc were contributory. Among RA-affected females, concentrations of male-Mc were higher in those with a history of TOP than those who were nulliparous, parous or had a history of miscarriage [89]. The impact of APO other than pregnancy loss were not considered in any study. Overall, Mc results were not meaningfully influenced by the use of DMARDs, seropositivity, or radiographic damage [49,89], and the concentration of Mc fluctuated over time in individual patients [48].

Two studies considered whether pregnancy could lead to the acquisition of risk alleles such as the SE not present in the maternal genome [48,90]. Yan et al. found that among SE-negative females, SE-Mc was more common in RA-affected females than controls (OR 4.1; 95 % CI 1.6–10) [90]. Rak et al. considered both SE- and non-SE-Mc in

Table 4
Pregnancy and changes to maternal immunity assessed ≥6 months post-partum.

Author (year)	Location	Population	Variable of interest	Sample	Outcome
Van de Geijn FE et al., 2009 [71]	Netherlands (PARA study)	148 ♀ RA, 32 ♀ controls	IgG glycosylation	Serum	Increased IgG1 & IgG2 galactosylation in pregnancy, peaking in 3rd trimester before declining by 26+ weeks postpartum
Van de Geijn FE et al., 2011 [70]	Netherlands (PARA study)	216 ♀ RA, 31 ♀ controls	MBL genotype	Peripheral blood	No association between MBL genotype and disease activity or IgG galactosylation levels at 26+ weeks postpartum
Bondt A et al., 2013 [22]	Netherlands (PARA study)	219 ♀ RA, 32 ♀ controls	IgG Fc glycosylation	Serum	Increased IgG1, IgG2/3 & IgG4 Fc glycosylation in pregnancy, peaking in 3rd trimester, before declining towards pre-conception levels by 26+ weeks postpartum
Bondt A et al., 2016 [19]	Netherlands (PARA study)	33 ♀ RA, 32 ♀ controls	IgG Fab glycosylation	Serum	Increased IgG Fab glycosylation in pregnancy, peaking in 3rd trimester, before declining towards pre-conception levels by 26+ weeks postpartum
Bondt A et al., 2017 [21]	Netherlands (PARA study)	252 ♀ RA, 32 ♀ controls	IgA glycosylation	Serum	Similar changes to IgG glycosylation but IgA bisection increases from 1st trimester until 6 weeks postpartum, then decreases to 26+ weeks postpartum
Reiding KR et al., 2017 [69]	Netherlands (PARA study)	253 ♀ RA, 32 ♀ controls	Protein N-glycosylation	Serum	Increased galactosylation, glycan branching & sialylation in pregnancy, peaking in 3rd trimester but reverts to normal by 26+ weeks postpartum
Bondt A et al., 2018 [20]	Netherlands (PARA study)	112 ACPA positive ♀ RA, 101 ACPA negative ♀ RA	ACPA IgG glycosylation	Serum	Increased ACPA IgG glycosylation in pregnancy, peaking in 3rd trimester, before declining towards pre-conception levels by 26+ weeks postpartum
Cieslinski JZ et al., 2017 [107]	Brazil	177 ♀ RA total (146/177 history of pregnancy, 54/146 history of miscarriage or stillbirth)	MBL levels	Serum	♀ with at least one previous miscarriage or stillbirth had similar MBL levels to those without a history of pregnancy loss (median 886 ng/ml cf. 625 ng/ml; $p > 0.05$).
Jackman RP et al., 2018 [103]	USA (MCIS study)	250 ♀ RA (48 nulliparous, 202 parous), 1996 ♀ controls	Antibodies against class I and II HLA	Serum or plasma	Parous ♀ with RA had higher titres of anti-HLA antibodies than either non-parous ♀ with RA or parous ♀ controls ($p < 0.0001$)

ACPA = anti-cyclic citrullinated peptide antibodies, cf. = compared to, MBL = mannose-binding lectin, MCIS = Mother-Child Immunogenetic Study, PARA = Pregnancy induced Amelioration of Rheumatoid Arthritis.

Table 5
Pregnancy, the acquisition of microchimerism assessed ≥6 months post-partum.

Author (year)	Location	Primary variable of interest	Variable of interest	Method of identification	Outcome	Other variables considered
Yan Z et al., 2005 [89]	USA (King County)	Male mc in the mother	71 ♀ RA, 49 ♀ controls	DYS14 qPCR of PBMCs	Male mc in RA (cf. HC): 12 % (0 %) parous only with daughters, 20 % (23 %) miscarriage, 55 % (58 %) TOP, 9 % (13 %) nulligravid; OR for male mc in ♀ with RA with TOP cf. no TOP: OR 9.1 (2.2–37.8); concentrations of male mc ↑ in RA than HC (no *p*-value provided)	Parity Organ transplantation Pregnancy loss
Hromadnikova I et al., 2008 [68]	Prague	Male mc in the mother	19 ♀ RA	SRY qPCR of synovial cells or skin fibroblasts	Male mc in 38 % synovial & 40 % skin samples in ♀ with a son; no male mc in nulliparous ♀/♀ only with daughters	TOP
Rak JM et al., 2009 [48]	France	SE mc in the mother	♀ genotype negative for DRB1*01 (33 RA, 46 HC) & DRB1*04 (48 RA, 64 HC); + testing of family members	DRB1*01 & DRB1*04 qPCR of PBMCs	↑ prevalence & concentration of DRB1*01/04 mc in RA vs HC despite similar parity & rates of pregnancy loss ($p < 0.05$ for all), no significant differences in non-SE related mc	Blood transfusion Parity Pregnancy loss NIMA Older male sibling
Yan Z et al., 2011 [90]	USA (King County)	SE mc in the mother	♀ genotype negative for the shared epitope (52 RA, 34 controls)	DRB1*0401 (QKRAA), DRB1*0101/0404/0405/0408 (QRRAA) qPCR of PBMCs	↑ prevalence & concentration of DRB1*0401/0101 mc in RA vs HC ($p < 0.05$ for all) but overall similar parity among mc positive & negative ♀	Parity
Chan WFN et al., 2012 [88]	Canada	Male mc & SE mc in the mother	30 ♀ RA; + genotype testing of participants mothers & children for 13 ♀ RA	DRB1, DQA1, DQB1, DYS14 qPCR of rheumatoid nodules	21 % (6/29) had rheumatoid nodules positive for male mc; 23/29 were parous, 19/23 had at least one son On SE testing, 54 % (7/13) had fetal Mc in their rheumatoid nodule	Blood transfusion Parity Pregnancy loss NIMA Older male sibling
Kekow M et al., 2013 [49]	Germany	Male mc in the mother	♀ with at least one son: 72 RA, 54 HC	DYS14 qPCR of PBMCs	↑ prevalence of male mc in RA (18 %; 13/72) RA cf. HCs (4 %; 2/54), $p < 0.05$; RA with ≥2 sons more likely to have male mc than those with one son, $p > 0.05$)	Parity Excluded individuals with history of blood transfusion & pregnancy loss
Kanaan SB et al., 2019 [87]	USA	DERAA epitope mc in the mother	♀ genotype negative for DERAA (70 RA, 65 HC)	DERAA specific qPCR of PBMCs	↑ prevalence & concentration of DERAA mc in RA (53 %) cf. HC (6 %), $p < 0.05$, but no correlation with parity	Parity

cf. = compared to, HC = healthy controls, mc = microchimerism, NIMA = non-inherited maternal antigens, OR = odds ratio, SE = shared epitope, TOP = termination of pregnancy.

SE-negative females [48]. In their study, the higher prevalence and concentration of Mc in RA-affected females compared to controls was specifically for SE-Mc. Non-SE-Mc were not differentially present between RA and controls [48]. Testing of participants' own mothers and children allowed them to confirm that the source of Mc was fetal-Mc or NIMA in most cases. For those with no identified offspring or maternal source, there was often a history of early pregnancy loss or transfusion.

Given previous work suggesting RA risk was highest among DERAA-negative mothers with offspring who were DERAA-positive [92], a further study from King County specifically examined DERAA-Mc in DERAA-negative mothers [87]. This study found 53 % of the RA-affected females, compared to 6 % of healthy controls, to have DERAA-Mc (OR 17.1; 95 % CI 5.7–46.9). DERAA-Mc was more common in recent-onset RA (<2 years) than in those with established disease (>2 years) and inversely correlated with disease severity indicators (i.e., pain score, HAQ, modified sharp score). Still, there was no association with age of RA onset, seropositivity, or DMARD use. In this study, SE-Mc or non-SE/non-DERAA-Mc was present in 50–56 % of RA-affected females but also in ~28 % of controls, and thus relatively common in both groups compared to the significant difference reported for DERAA-Mc.

Synovial samples and healthy skin from RA-affected females have also been examined for male-Mc. In RA-affected females with sons, male-Mc was identified at similar frequency within affected and non-affected tissue (38.5 % of diseased synovial samples, 40 % of healthy skin fibroblast samples) but was absent in samples from nulliparous RA patients or those who had only ever had daughters [68]. Within rheumatoid nodules, 6/29 (21 %) RA-affected females had nodules containing male-Mc among a population in which 20/29 (69 %) had had a son [88].

4. Discussion

4.1. Summary

The role of pregnancy in predicting future maternal health in RA beyond 6 months postpartum was the focus of this review. We found that whilst existing research has almost exclusively investigated the impact of parity, gravidity, subfertility and pregnancy loss, these metrics do not significantly modify the risk of incident RA. In contrast, conditions like pre-eclampsia and delivery of a low birthweight infant may indicate susceptibility to RA, although they remain understudied. Additionally, there is limited research on whether pregnancy and APO predict future CVD in individuals with RA. Few studies have explored immune responses stratified on obstetric history, and the influence of Mc and allosensitisation needs further investigation, particularly given the differences observed between RA-affected females and controls.

Whilst parity and gravidity have been widely studied, from an immunological and cardiometabolic perspective, these are arguably crude measures of maternal health. An individual may be parous following term delivery of a well-grown infant following an uncomplicated pregnancy without any gestational syndromes (e.g., GDM, pre-eclampsia, hyperemesis). Conversely, they may be parous but have delivered an infant with severe growth restriction or had any number of complicating gestational syndromes. This nuance is evidently important in considering future cardiometabolic health in the general population, and it is plausible that the same is true from an immunological standpoint.

The apparent absence of a relationship between incident RA and pregnancy loss or subfertility is likely to be multifactorial. Shared immunological dysfunction is one plausible link between these events

and RA, but approximately 50 % of miscarriages are estimated to occur secondary to chromosomal defects within the fetus, and a couple may be subfertile due to female anatomical abnormalities (e.g., loss of a fallopian tube following ectopic pregnancy) or male factor infertility (e.g., azoospermia) [116–118].

Multiparity was identified as a possible risk factor for CVD among RA-affected females [37,104]. Data from the general population suggest the impact of multiparity on CVD is partly environmental and also seen, albeit to a lesser degree, in fathers [119]. It is striking that no papers were identified examining CVD risk in relation to pre-eclampsia, infant birthweight or GDM, all of which now appear in major clinical guidelines for female-specific CVD-risk prediction [120]. Despite CVD being a leading cause of death among RA-affected females and the poor performance of traditional risk scores in RA – gestational syndromes remain absent from the prevailing discourse on CVD in this population [121–123].

Our systematic review highlights the possible association between pre-eclampsia and infant birthweight with future RA diagnosis and severity [28–30,82,106]. Since our searches concluded, a Canadian study of over 1.7 million singleton births has been published, supporting this finding. RA risk was increased following a pre-eclamptic pregnancy or delivery of an SGA infant (<5th centile), with a peak in the adjusted HR 4–12 years following delivery [124].

Whilst established hypertension, renal disease and diabetes increase the risk of pre-eclampsia (and other placental insufficiency syndromes, e.g., SGA), so too do the use of an egg or sperm donor, use of barrier contraception before pregnancy, and in the case of a subsequent pregnancy, a change in male partner or long inter-pregnancy interval [114]. In addition, pre-eclampsia is increased in a diverse range of autoimmune disorders, including RA. Together, these findings indicate that the development of pre-eclampsia is related both to maternal endothelial function – of relevance to future CVD – but also to maternal immunity [114].

In the setting of RA, whether pre-eclampsia could itself prime an aberrant immune response or represent the temporary unmasking of pre-existing immune dysfunction remains to be determined. Regulatory T cell (Treg) abnormalities are reported both in RA and in individuals with pre-eclampsia [114,125,126], and a single study, by Förger et al., of Tregs in RA pregnancy demonstrated an inverse correlation between Treg number and RA activity [127]. Pre-eclampsia has also been associated with upregulation of HLA-DRB1 within maternal switched memory B cells [128] and aberrant placental expression of HLA-DRB1 [129,130]. Given the differences in Mc seen in RA-affected females, it is also notable that investigations in the general population find higher concentrations of fetal-Mc in individuals with pre-eclampsia [131].

Mc is more prevalent in RA-affected females than controls but is detectable in both affected and non-affected tissues, fluctuates over time and correlates poorly with RA activity and DMARD use. Mc may, therefore, be an epiphenomenon of inflammation and autoimmunity rather than being directly pathogenic. However, fetal-Mc containing RA-risk alleles distinct from the mother's genome may contribute to immune sensitisation of relevance to RA pathogenesis [87]. DERAA-negative mothers have an increased risk of RA if they have DERAA-positive children or if they acquire DERAA-Mc [87,92]. The DERAA sequence is found not only within HLA-DRB1 but also within the cytoskeletal protein vinculin and various pathogens. Maternal genotype-encoded DERAA is considered protective as it leads to the negative thymic selection of DERAA-reactive T-cells [132]. Individuals without the DERAA sequence, and thus with DERAA-reactive T-cells, can develop cross-reactive immune responses to vinculin during infections thereby contributing to autoimmunity of relevance to RA. The work of Kanaan et al. and Cruz et al. suggest that pregnancy, too, can lead to DERAA exposure and sensitisation in DERAA-negative mothers via fetal-Mc [87,92]. Additional murine work suggests fetal-Mc encoding differing RA risk alleles to the maternal genotype may also contribute to RA development through Mc cells themselves producing autoantibodies, including anti-CCP, although this has not been examined in humans [133].

4.2. Limitations

The populations studied are overwhelmingly European and North American, and authorship lists rarely included an obstetrician. Analyses of specific sub-groups of interest, for example, based on seropositivity for RF/anti-CCP or susceptibility alleles, were generally only available within small sub-analyses of case-control studies, limiting statistical power and generalisability. Furthermore, terminology within the included papers was heterogenous (e.g., differing definitions of infertility), sometimes imprecise (e.g., interchangeably using gravidity and parity), and outcomes were frequently presented as pooled analyses of pathophysiologically distinct events (e.g., groupings of miscarriage, ectopic pregnancy, and TOP). Furthermore, the tendency to use binary measures (e.g., parous or nulliparous) means the control group in many studies could still include individuals with significant APOs (e.g., the inclusion of individuals with pre-eclampsia in parous groups). Use of birthweight rather than birth centile may also dilute effect sizes by incorporating constitutionally small and preterm infants rather than specifically measuring for growth restriction caused by placental insufficiency. Confounders were often poorly accounted for, including for well-characterised exposures such as smoking, which displays a clear and independent association with rheumatoid arthritis, as well as with miscarriage, stillbirth and infertility [134–136]. In the future, accurate and standardised reporting would benefit from greater cross-speciality collaboration with obstetricians and the use of the EULAR core data set for pregnancy registries in rheumatology [15].

Specific questions within this review were potentially more difficult to answer than others. For example, analyses which stratified on post-RA onset pregnancy were more complex in terms of understanding causation due to the confounding effect of avoiding pregnancy due to severe disease at baseline or stopping medications during pregnancy [137]. The outcomes presented may have therefore reflected accumulated damage during a period of uncontrolled disease caused by medication withdrawal rather than a biological effect of pregnancy itself. The ongoing uncertainty for the impact of other female-specific life events/interventions (e.g., menopause, menstruation, hormonal contraception) further complicates analyses and speaks to the need for a life-course approach to reproductive health in RA from menarche to menopause and beyond.

4.3. Conclusions

Existing work in RA fails to incorporate well-known associations between APO and future cardiometabolic health and understudies the role of specific gestational syndromes. There is, however, emerging evidence for pre-eclampsia and low infant birthweight heralding RA, and for differing impacts of Mc dependent on maternal-fetal genotype interactions. Finally, despite sex-specific differences in RA, pregnancy-induced amelioration and the postpartum predisposition to incident RA and RA flare, little is known about the persisting impact of pregnancy on female immunity in RA.

Pregnancy can be considered a stress test for life, offering a unique window into future maternal health through the temporary unmasking or persistent priming of pathological immune responses and endothelial damage. We propose a future research agenda for studies in this field to measure the predictive role of APO on cardiometabolic health in RA, delineate the causative relationship (if any) between placental syndromes (e.g., pre-eclampsia) and the development of RA, and explore how female immunity is shaped by pregnancy and modified by maternal-fetal genotype interactions.

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Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Dr. Bethan Goulden reports financial support was provided by Versus Arthritis. Dr. Bethan Goulden reports a relationship with GSK that includes: speaking and lecture fees. Professor Ian Giles reports a relationship with UCB Inc. that includes: consulting or advisory, funding grants, and speaking and lecture fees. Professor Ian Giles reports a relationship with MGP Ltd. that includes: consulting or advisory. Professor Radboud Dolhain reports a relationship with ReumaNederland that includes: funding grants. Professor Radboud Dolhain reports a relationship with Netherlands Organisation for Health Research and Development that includes: funding grants. Professor Radboud Dolhain reports a relationship with UCB Inc. that includes: funding grants and speaking and lecture fees. Professor Radboud Dolhain reports a relationship with Galapagos that includes: funding grants. Professor Radboud Dolhain reports a relationship with Roche that includes: consulting or advisory and speaking and lecture fees. Professor Radboud Dolhain reports a relationship with AbbVie Inc. that includes: consulting or advisory and speaking and lecture fees. Professor Radboud Dolhain reports a relationship with genzyjme that includes: consulting or advisory and speaking and lecture fees. Professor Radboud Dolhain reports a relationship with Novartis that includes: consulting or advisory and speaking and lecture fees. Professor Radboud Dolhain reports a relationship with AstraZeneca that includes: consulting or advisory and speaking and lecture fees. Professor Radboud Dolhain reports a relationship with Eli Lilly and Company that includes: consulting or advisory and speaking and lecture fees. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

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