THE ASSOCIATION BETWEEN GRAVIDITY, PARITY AND THE RISK OF DEVELOPING RHEUMATOID ARTHRITIS: A SYSTEMATIC REVIEW AND META-ANALYSIS

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ABSTRACT

Objective: to establish if gravidity and parity associate with the development of rheumatoid arthritis (RA), and to establish if this effect is influenced by the time elapsed since pregnancy/childbirth, the number of pregnancies/childbirths, and serological status, through systematically reviewing the literature and undertaking a meta-analysis.

Methods: we searched Medline/EMBASE (from 1946-2018) using the terms "rheumatoid arthritis.mp" or "arthritis, rheumatoid/" and "pregnancy.mp" or "pregnancy/" or "parity.mp" or "parity/" or "gravidity.mp" or "gravidity/" (observational study filter applied). Case-control/cohort studies that examined the relationship between parity/gravidity and the risk of RA in women were included. Studies reporting effect size data for RA in ever vs. never parous/gravid women as ORs/RRs with 95% confidence intervals were included in a meta-analysis. Other relationships (i.e. risk by pregnancy/childbirth numbers) were analysed descriptively.

Results: twenty studies (from 626 articles) met our inclusion criteria, comprising 14 case-control (4,799 cases; 11,941 controls) and 6 cohort studies (8,575 cases; 2,368,439 individuals). No significant association was observed in the meta-analysis of studies reporting the risk of RA in ever vs. never parous women (OR 0.91; 95% CI 0.80-1.04) and ever vs. never gravid women (OR 0.86; 95% CI 0.46-1.62). No consistent evidence of a relationship between the number of pregnancies/childbirths and RA risk was seen. No significant association was observed between being pregnant, or in the immediate post-partum period, and the risk of developing RA.

Conclusion: our systematic review does not support the concept that gravidity and parity are associated with the risk of RA development.

Key Words: Arthritis, Rheumatoid; Parity; Gravidity; Meta-Analysis

1. INTRODUCTION

Rheumatoid arthritis (RA) is a complex disease, resulting from a range of gene-environment risk factors (1). The main environmental RA risk factor is cigarette smoking, demonstrated across various studies to increase the risk of RA development, particularly seropositive disease (2). Alcohol consumption may reduce the risk of RA, although this association has generally been reported in case-control studies subject to recall bias (3). The roles of other environmental risk factors, including periodontitis (4,5) and caffeine intake (6,7), are less well-established with positive associations often not replicated across studies. The increasing interest in identifying people at a high-risk of RA (8) in whom preventative strategies could be evaluated, means it is vital to accurately define risk factors contributing to RA development.

Previous research suggests pregnancy (gravidity) and childbirth (parity) have a complex relationship with RA. A recent systematic review by Jetwha et al (9) has confirmed the observation first made by Hench in 1938 that disease activity often reduces during pregnancy and flares in the post-partum period (10). A broad range of studies have also evaluated whether gravidity and parity are risk factors for the development of RA. The general trend appears to be that the risk of RA development is reduced during pregnancy (11,12), increases in the post-partum period (11,12), and is subsequently reduced in those that have previously been pregnant or given birth (13–15). The "protective effect" of previous pregnancy and childbirth has not, however, been replicated across all studies (16–18), and its precise impact on RA susceptibility remains uncertain. To date, one systematic literature review and meta-analysis has been undertaken in this area, reporting an inverse relationship between parity and RA risk (19). This review did not, however, evaluate risk by gravidity or childbirth timing, and included results from different analyses undertaken in the same patient groups (including two publications from the Nurses' Health Study, and two from a case-control population in Seattle, USA) (16,20–22).

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We have, therefore, undertaken a systematic literature review of observational studies evaluating the association between gravidity and parity, and the risk of developing RA. Our primary aim was to examine the risk of developing RA in previously gravid/parous women compared to non-gravid/parous women, by testing the hypothesis that previous gravidity/parity influenced the likelihood of RA development. Our secondary aims were to examine: (1) the risk of developing RA during the partum and immediate post-partum periods; (2) the risk of developing RA by the number of pregnancies/childbirths; (3) if these risks are different for seropositive and seronegative disease.

2. METHODS

2.1 Reporting and Data Extraction

We followed the Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines for the reporting of our review (23). The literature search, and study quality assessments were performed separately by two authors (WYMC/SS). Data extraction was undertaken by one author (WYMC), and checked for accuracy by a second author (SS). Discrepancies were resolved by discussion, with involvement of a third researcher (ICS) if necessary. Inclusion criteria/analytical methods (detailed below) were pre-specified. The review was registered on PROSPERO (ID 92723) (24).

2.2 Search Strategy

The literature search was conducted using the Ovid platform in January 2018 using Medline (1946 to January 2018) and Embase Classic and Embase (1947 to January 2018). The following search terms were used: "rheumatoid arthritis.mp" or "arthritis, rheumatoid/" and "pregnancy.mp" or "pregnancy/" or "parity.mp" or "parity/" or "gravidity.mp" or "gravidity/". The Scottish Intercollegiate Guidelines Network (SIGN) observational study filter was applied (25), and the search limited to "humans". Citations were exported to the EndNote programme. Duplicates were removed. Articles were further removed by screening titles and/or abstracts. Additional articles were included from reference lists of identified papers, if they fulfilled inclusion criteria.

2.3 Selection Criteria

We included observational studies that (1) were case control/cohort design; (2) examined the relationship between gravidity and/or parity and the risk of RA development in women. Studies reporting effect size data for RA development in ever vs. never gravid or ever vs. never parous women as odds ratios (ORs) or relative risks (RRs) with 95% CIs were included in a meta-analysis.

We excluded (1) studies evaluating the same cohort (including the most comprehensive and recent); (2) unpublished studies (conference abstracts); (3) other study designs (case-reports/series, systematic reviews); (4) studies evaluating other risk factors.

2.4 Data Extraction

The following were extracted: publication year; author names; location; design; sample size; if risk was reported by parity, gravidity, number of pregnancies/childbirths, or serological status;

method of assessing parity/gravidity; effect size data; adjustment factors; RA definition; age range; *P*-value for trend (between number of pregnancies/childbirths and RA risk).

2.5 Study Quality

The Newcastle-Ottawa Scale (NOS) assessed study quality. This comprises a "star system" judging studies on three domains: (1) selection of study groups; (2) comparability of groups; (3) ascertainment of exposure/outcome of interest. A maximum of 9 stars indicates the highest quality study (26).

2.6 Statistical Analysis

2.6.1 Meta-Analysis of RA Risk in Ever vs. Never Gravid Women or Ever Vs. Never Parous Women

The OR is considered a good estimate of the population RR when the disease/outcome prevalence is <10% (27). As the UK adult RA prevalence is ~0.81% (28), ORs and RRs were used interchangeably (29). This approach is consistent with meta-analyses of other RA risk factors (2,3,30)). In studies where OR/RR were reported using ever-pregnant as the reference group, the reciprocal was taken, to obtain an OR/RR using never-pregnant as the reference group. A random-effects model based on DerSimonian and Laird's approach was used, due to heterogeneity across studies (31). Cohort and case-control study data were analysed both together and separately, with pooled ORs/RRs reported in both instances. The most adjusted ORs/RRs from each study were included in the meta-analysis. *P*-values <0.05 were considered statistically significant.

2.6.2 Heterogeneity Assessment

Between study heterogeneity was assessed using Cochran's Q-test and the I^2-statistic. The former tests the null hypothesis that homogeneity exists between the sample estimates of the population parameter across studies, and any variation between them is a result of sampling error (32). The latter describes the percentage of total variation across studies due to heterogeneity rather than chance. It ranges from 0% (no heterogeneity) to 100% (high heterogeneity) (33).

2.6.3 Publication Bias

Publication bias was looked for by constructing funnel plots and using the "trim-and-fill" method. This data augmentation technique estimates the number of studies missing from a meta-analysis due to suppression of the most extreme results on one side of the plot, and augments the observed data, delivering a more symmetrical plot (34).

2.6.4 Analysis of Other Risk Types

Other risk periods or influences, such as the risk of RA in the partum, or post-partum period, and risk by the number of childbirths/pregnancies, or serological status were analysed descriptively. This is because of the heterogeneity between studies in (a) their definition of the post-partum period (with risk reported in the first 3 months (12), first 12 months (35), and many years post-partum (20)); (b) their categorisation of number of childbirths/pregnancies by which risk was reported, or (c) the small numbers of studies assessing these issues (e.g. only 2 studies reported risk by serological status (18,36)).

2.6.5 Programme Used

Meta-analysis and funnel plots were undertaken using R, version 3.5.0. (R Foundation for Statistical Computing, Vienna, Austria), and the package "Metafor" (37).

3. RESULTS

3.1 Studies Identified

626 articles were screened. All identified abstracts were published in English; we did not identify any studies in non-English languages fulfilling our inclusion criteria from abstract review. 604 were excluded (by abstract/title), providing 22 articles for full text review (Figure 1). Of these, 9 were excluded for the following reasons: 2 evaluated the same cohort (22,38); 3 were conference abstracts (39–41), 3 were review articles (42–44), and one was a meta-synthesis of a range of RA risk factors (45). 7 studies were added from the reference lists of included articles (12,15,35,46–48).

20 studies meeting our inclusion criteria were included in the analysis; 6 were cohort, and 14 case-control studies (Table 1). 14 studies reported the risk of RA in relation to being ever-gravid or ever-parous (13–16,18,20,35,36,42,48–53), 11 reported the risk of RA in relation to the number of previous pregnancies or childbirths (13,16,18,20,46,48–51,54,55), 9 reported the risk of RA in relation to the timing of pregnancy (11,12,14,17,20,35,36,46,47), and 2 reported the risk in relation to serological status (18,36).

3.2 Cohort Studies

3.2.1 Overview

The six cohort studies included 8,575 incident RA cases from a total population size of 2,368,439 individuals (Table 1). Two were undertaken in North America and four in Europe.

Publication year ranged from 1995 to 2014. Four studies attained information on gravidity/parity by questionnaire, one by interview and one using registry data.

3.2.2 Study Quality

Four cohort studies had Newcastle-Ottawa scores of 7, and two studies had scores of 6 (Table 1). Five studies lost one star for not mentioning follow-up rates (18,49,50,54,55). Four studies lost one star for "ascertainment of exposure" due to using self-reported questionnaires (16,18,50,54), and three studies lost one star for not demonstrating the outcome (RA) was absent at the study start (49,54,55). One study lost one star for "comparability" for only adjusting risk for age (50). One study lost one star for the "exposed cohort" being a selected group of individuals (nurses) (16).

3.3 Case-Control Studies

3.3.1 Overview

The 14 case-control studies totalled 4,799 cases and 11,941 controls. Four were undertaken in North America, and 10 in Europe. Publication year ranged from 1989 to 2014. Seven studies attained information on gravidity/parity by questionnaire, two from medical records, and five by interview.

3.3.2 Study Quality

One study had a Newcastle-Ottawa score of 5, eleven studies had scores of 6, and one study had a score of 7 (Table 1). One study contained insufficient data to undertake a quality assessment (14). All studies with data available to assess quality lost one star for "non-response rate" as they failed to show an equal non-response rate in cases and controls, or response rates were not described, and lost one star for "ascertainment of exposure" as they either used non-

blinded interviews or self-reported questionnaires. One study lost one star for "adequacy of case definition" as it used record linkage to identify cases (51). One study lost one star for "case representativeness" as cases were twins (35). Three studies lost one star for "control selection" as hospital population controls were used (12,13), or controls were unaffected first and second-degree relatives (46). Seven studies lost one star for "control definition" as they did not explicitly state controls had no history of RA (15,20,35,36,47,48,53). One study lost one star for "comparability" due to not demonstrating adjustment for additional confounders (52).

3.4 Risk of RA by Previous Parity and Gravidity Status

3.4.1 Meta-Analysis

Eleven studies reported RA risk in ever vs. never parous women (Table 2). Two studies reported a significantly reduced risk of RA; the remaining studies reported no significant association. Combining these in a meta-analysis (Figure 2) showed no significant association between ever vs. never-parity and RA (OR 0.91; 95% CI 0.80-1.04). No significant association was seen when the analysis was restricted to cohort (OR 0.96; 95% CI 0.89-1.03) and case-control (OR 0.81; 95% CI 0.61-1.08) studies. Low-to-moderate heterogeneity levels were observed (I^2=38.4%; P=0.09).

Four studies reported RA risk in ever vs. never gravid women (Table 2). One study reported a significantly reduced risk of RA, one reported a reduced OR without providing data on its significance, and two reported no significant association. Combining the three studies with 95% CI data in a meta-analysis (Supplementary Figure 1) showed no significant association between ever vs. never-gravidity and RA (OR 0.86; 95% CI 0.46-1.62). Moderate-to-high heterogeneity levels were seen (I^2=58.7%, P=0.09).

One study reported RA risk in both ever-parous vs. nulligravid women (significant risk reduction seen) and ever-gravid but nulliparous vs. nulligravid women (trend towards increased risk seen) (20). Due to different parity and gravidity groupings to the other studies it was not included in the meta-analysis.

3.4.2 Individual Study Influences

Excluding individual studies from our meta-analysis did not result in an overall significant association between ever-parous status and RA risk (Supplementary Table 1).

3.4.3 Publication Bias

There was some evidence of funnel plot asymmetry (Figure 3), with two medium precision studies favouring a reduced risk of RA in ever vs. never-parous women, and an absence of similar medium precision studies with effect sizes in the opposing direction (shown as white circles in the funnel plot).

3.5 Risk of RA by Number of Childbirths or Pregnancies

Nine studies reported RA risk by number of childbirths. Risk was reported using a variety of birth number groupings/reference groups, making these data unsuitable for meta-analysis (Table 2). Six studies reported no significant dose-risk trend between the number of childbirths and RA risk. Three studies reported some evidence of a dose-risk trend. Firstly, Jørgensen et al reported a significantly reduced risk of RA in women having 2 (RR 0.84; 95% CI 0.78-0.90) or 3 births (RR 0.83; 95% CI 0.77-0.91) but not ≥4 births (RR 0.89; 95% CI 0.80-1.00) relative to 1 childbirth (no *P*-trend data) (49). Secondly, Lahiri et al reported a significantly increased risk of RA for ≥2 births (hazard ratio [HR] 2.55; 95% CI 1.19-5.48), but not 1 birth (HR 1.10; 95% CI 0.40-3.01) relative to nulliparity (54). Thirdly, Peschken et al reported a significantly

reduced risk of RA in females with ≥6 births (OR 0.43; 95% CI 0.21-0.87) and 3 births (OR data not provided), but not 4-5 births (OR data not provided) compared with 1-2 births (*P*-trend=0.046) (46).

Two studies reported the risk of RA stratified by the number of pregnancies (13,50). Hazes et al reported a greater risk reduction in women with ≥3 pregnancies (OR 0.44; 95% CI 0.22-0.88) than 1-2 pregnancies (OR 0.53; 95% CI 0.28-0.99) when compared with nulliparity (no *P*-trend data). Merlino et al reported no increased risk by number of pregnancies, using women with 1 pregnancy as the reference group and excluding nulligravid women (*P*-trend 0.30) (50).

3.6 Risk of RA during Pregnancy and Immediate Post-Partum Period

Four studies reported RA risk during pregnancy (Table 3). One study reported a reduced OR for RA, without providing 95% CI data or information on significance (14). In the remaining three studies, no significant association was observed, with Brennan et al (35), Lansik et al (12), and Silman et al (11), reporting ORs of 0.95 (95% CI 0.19-4.70), 0.64 (95% CI 0.13-3.21), and 0.3 (95% CI 0.04-2.6), respectively. Combining these within a meta-analysis (Supplementary Figure 2) showed no significant association between being pregnant and developing RA (OR 0.63; 95% CI 0.23-1.70; I^2=0.0%).

Six studies reported the risk of RA during the 12-month post-partum period (Table 3). Brennan et al reported no significant association with RA (OR 1.02; 95% CI 0.33-3.16) (35). Del Junco et al reported an increased RR (4.67) but did not provide CI or significance data (14). Lansink et al reported a trend towards an increased risk <3 months' post-partum (OR 3.37; 95% CI 0.86-13.11) and trend towards a reduced risk 3-12 months' post-partum (OR 0.67; 95% CI 0.13-3.55) (12). Orellana et al reported a trend towards a reduced risk of ACPA-positive RA

(OR 0.8; 95% CI 0.4-1.6) and increased risk of ACPA-negative RA (OR 2.1; 95% CI 0.9-4.8) (36). Peschken et al reported a significantly increased risk of RA (OR 3.8; 95% CI 1.45-9.93) using >15 years post-partum as the reference group (46). Finally, Silman et al reported an increased risk of RA 0-3 months post-partum (OR 5.6; 95% CI 1.80-17.6), and a trend towards an increased risk 3-12 months post-partum (OR 2.6; 95% CI 0.8-7.9) (11).

In addition, Rodriguez et al reported the risk of incident RA (over a 12-month period) in women that had been pregnant in the previous 12-months (potentially encompassing both the pregnant and post-partum period), with a significantly reduced risk of RA seen (OR 0.22; 95% CI 0.06-0.77) (47).

Two studies reported RA risk in the longer-term post-partum period. Guthrie et al reported a marked risk reduction in females 1-5 years post-partum, which was lesser in magnitude at 5-15 years post-partum, and not significant at >15 years post-partum (20). In contrast, Jørgensen et al reported no relationship between the risk of RA, and the time since birth of the most recent child (using time categories spanning 0-2 years to >20 years) (17).

3.7 Risk of RA by Serological Status

Two studies reported RA risk stratified by serological status. Heliövaara et al reported risk for RF-positive vs. RF-negative RA by parity status, with no significant association observed with either disease subtype (age adjusted RR of RF-positive and RF-negative RA in ever vs. never parous women of 1.26 (95% CI 0.82-1.92) and 0.80 (95% CI 0.48-1.32), respectively) (18). Orellana et al reported risk for ACPA-positive vs. ACPA-negative RA by parity status, stratified by age (36). In women aged 18-44 years an increased risk for ACPA-negative (OR 2.1; 95% CI 1.4-3.2) but not ACPA-positive RA (OR 0.9; 95% CI 0.7-1.2) in ever vs. never-

parous women was reported (adjusting for age and residential area). In women aged 45-70 years no association was seen (ACPA-negative RA OR 0.9 (95% CI 0.7-1.3); ACPA-positive RA OR 1.0 (95% CI 0.8-1.2)).

4. DISCUSSION

Our systematic review provides a comprehensive summary of research exploring the association between parity, gravidity and the risk of developing RA in women. It has three main findings. Firstly, no significant association was seen between being ever-parous or ever-gravid and the risk of developing RA in women, when published study results were combined in a meta-analysis. Secondly, no clear dose-risk relationship existed between the number of childbirths a woman has experienced and their risk of developing RA. Thirdly, no significant association was observed between being pregnant, or in the immediate post-partum period and the risk of developing RA. When considered together, these findings do not support the concept that pregnancy and childbirth are associated with the risk of developing RA in women.

It is notable that the only studies reporting a significant association between RA and parity/gravidity were of case-control design. Whilst case-control studies can provide important findings at relatively little time and monetary costs in comparison to cohort studies, they are susceptible to a range of biases influencing their reliability (56). Schulz et al recommended that good quality case-control studies require: (1) controls that are disease-free and representative of the population at risk; (2) data gatherers trained to capture information from cases and controls in a similar manner, and blinded to case-control status; (3) confounding to be addressed (56). All of the four case-control studies reporting a significantly reduced risk of RA according to parity/gravidity (13,15,20,53) did not adhere to at least one of these concepts. Hazes et al (13) used controls with musculoskeletal conditions attending the rheumatology

department, and did not blind interviewers to case-control status; Reckner-Olsson et al (15) and Spector et al (53) obtained information by questionnaire; Guthrie et al (20) captured data via non-blinded interviewers.

There are several complexities when considering the relationship between gravidity and parity and RA risk that merit discussion. Firstly, patients with RA appear to be less fertile than people without RA (57). This was demonstrated in two large Scandinavian cohort studies, one of which showed that women with RA take longer to conceive and are more likely to be treated for infertility (58), with the other showing that women with RA have smaller families and longer inter-pregnancy intervals (59). Consequently, higher infertility rates in RA could provide the appearance in case-control studies that pregnancy/childbirth reduces RA risk. Secondly, breast-feeding has been reported to be significantly associated with a lower risk of RA (60). As only parous women will be able to breastfeed, any relationship between parity and RA risk could be mediated by breastfeeding.

It is noteworthy that only two of the studies identified in this review reported risk by serological status; this meant we could make no conclusions on whether serological status affected the impact of parity or gravidity on the risk of developing RA. It is established that the genetic architectures of ACPA-positive and ACPA-negative RA differ, with contrasting associations observed at the HLA locus (61,62). Similarly, the environmental factors, smoking and alcohol, have been shown to have stronger associations with seropositive RA (2,3). The failure of most studies to stratify their analysis by serological status could have affected their findings, with the inclusion of a serologically heterogeneous population reducing their power to detect significant associations with one of the RA serological subsets.

As discussed in our introduction, Ren et al have previously systematically reviewed the relationship between parity and the risk of RA in women (19). Our systematic review builds on their earlier work, by evaluating the association between both parity and gravidity and the risk of RA, examining the impact of serology on RA risk, and assessing if risk differs during pregnancy, and the post-partum period. We decided to examine the impact of the numbers of childbirths and pregnancies on the risk of RA descriptively, primarily because different studies used different reference groups when reporting risk, precluding their inclusion in a meta-analysis. Although Ren et al undertook a dose-response meta-analysis, reporting a significant J-shaped relationship between the number of childbirths and RA risk, their meta-analysis included (a) two studies examining the effect by the number of pregnancies and not childbirths (13,50); (b) two pairs of studies assessing the relationship between RA and parity in the same cohorts (with Hernandez Avilla et al (22), and Karlson et al (16) both reporting data from the North American Nurses' Health Study; and Guthrie et al (20), and Ma et al (21) both reporting data from the same case-control study conducted in the Seattle area); (c) the mortality rate ratio reported by Brun et al for death from RA by number of childbirths (55). Overall, we consider that these issues have the potential to affect the accuracy of their findings.

Our analysis has several limitations. Firstly, two cohort studies used documentation of RA on the death certificate (55) or hospital admission episode (49) to identify cases; this is likely to miss many RA cases. Secondly, the included studies were of variable quality, with the majority capturing information on patients' gravidity and pregnancy status retrospectively using questionnaires, increasing the chances of recall bias, which could be a risk for multigravid women. Thirdly, all studies were undertaken in North America/Europe, with none performed in developing nations, limiting the generalisability of our findings. Fourthly, there was some evidence of publication bias in studies reporting risk by ever-parous status.

In conclusion, our systematic review does not support the concept that gravidity and parity are associated with the risk of RA development. Further research is needed, ideally using prospective cohort studies that evaluate risk by serological status and account for key confounders such as smoking, to better define environmental risk factors for RA.

5. FUNDING

6. CONFLICT OF INTEREST

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Table 1. Overview of Included Studies

Study (Year)	Design	Area	Gravidity/Parity Assessment	RA diagnosis	Size	Age Range	Quality
Brun et al (1995) (55)	Cohort	Norway	Interview	Death certificate	355 RA; 62,735 no RA	32-74	7 (3/2/2)
Heliövaara et al (1995) (18)	Cohort	Finland	Questionnaire	Drug registry	269 RA; 15,172 no RA	≥30	7 (3/2/2)
Jørgensen et al (2010) (49)	Cohort	Denmark	Registry	Hospital admissions	7,017 RA; 2,133,039 no RA	15-69	7 (3/2/2)
Karlson et al (2004) (16)	Cohort	USA	Questionnaire	ACR 1987	674 RA; 103,968 no RA	30-55	7 (2/2/3)
Lahiri et al (2014) (54)	Cohort	UK	Questionnaire	ACR 1987	102 RA; 13,772 no RA	40-79	6 (2/2/2)
Merlino et al (2003) (50)	Cohort	USA	Questionnaire	ACR 1987	158 RA; 31,178 no RA	55-69	6 (3/1/2)
Brennan et al (1994) (35)[a]	Case-control	UK	Questionnaire	ACR 1987	60 RA; 160 controls	16-45	5 (2/2/1)
Del Junco et al (1989) (14)	Case-control	USA	Medical records	Clinician	324 RA; 324 controls	-	-[c]
Guthrie et al (2010) (20)	Case-control	USA	Interview	ACR 1987	310 RA; 1,418 controls	18-64	6 (3/2/1)
Hazes et al (1990) (13)[b]	Case-control	Netherlands	Interview	ARA 1958	135 RA; 378 controls	20-50	6 (3/2/1)
Lansink et al (1993) (12)[b]	Case-control	Netherlands	Interview	ARA 1958	135 RA; 378 controls	20-50	6 (3/2/1)
Reckner-Olsson et al (2001) (15)	Case-control	Sweden	Questionnaire	ARA 1987	179 RA; 259 controls	25-75	6 (3/2/1)
Orellana et al (2014) (36)	Case-control	Sweden	Questionnaire	ACR 1987	2,035 RA; 2,911 controls	18-70	6 (3/2/1)
Pedersen et al (2006) (48)	Case-control	Denmark	Interview	ACR 1987	366 RA; 478 controls	18-65	6 (3/2/1)
Peschken et al (2012) (46)	Case-control	Canada	Questionnaire	ACR 1987	168 RA; 400 controls	15->45	7 (4/2/1)
Pikwer et al (2009) (51)	Case-control	Sweden	Questionnaire	ACR 1987	136 RA; 544 controls	44-74	6 (3/2/1)
Pope et al (1999) (52)	Case-control	Canada	Questionnaire	ACR 1987	34 RA; 68 controls	18-44	6 (4/1/1)
Rodriguez et al (2009) (47)	Case-control	UK	Medical records	Clinician	559 RA; 4,234 controls	20-79	6 (3/2/1)
Silman et al (1992) (11)	Case-control	UK	Interview	ACR 1958	88 RA; 144 controls	18-40	6 (4/2/1)
Spector et al (1990) (53)	Case-control	UK	Questionnaire	ARA 1958	270 RA; 245 controls	35-70	6 (3/2/1)

Study quality was assessed using the Newcastle-Ottawa Score, which provides a total score, and in brackets its individual component breakdown (selection/comparability/exposure or outcome); a=Brennan et al included only twins with RA; b=Hazes et al and Lansink et al evaluated different issues in the same case-control dataset (one evaluated risk by pregnancy, and the other by timing of pregnancy); c=insufficient data given to assess study quality; ACR=American College of Rheumatology; ARA=American Rheumatism Association.

Table 2. Risk by Previous Parity and Gravidity Status and by Number of Pregnancies or Childbirths

Study	Risk by Parity and Gravidy Status	Risk by Number of Pregnancies or Childbirths
Brennan et al (35)	OR in ever vs. never parous women 2.33 (0.80-6.67)[a]	-
Brun et al (55)	-	No significant increased risk (of mortality with RA reported on death certificate) by number of childbirths (*P*-trend 0.66; no depature from linear trend)
Heliövaara et al (18)	RR in ever vs. never parous women 1.06 (0.77-1.46)	No significant increased risk by number of childbirths (*P*-trend RF-positive RA 0.14; RF-negative RA 0.76; no evidence of departure from linear trend)
Jørgensen et al (49)	RR in ever vs. never parous women 0.96 (0.89-1.04)	Using 1 live birth as reference group, significantly reduced risk of RA with 2 and 3 births, but not ≥4 births (no *P*-trend reported)
Karlson et al (16)	RR in ever vs. never parous women 0.77 (0.53-1.11)[a]	No significant increased risk for 1, 2, 3 or ≥4 births (nulliparous as reference group; no *P*-trend reported)
Lahiri et al (54)	-	Increased risk for ≥2 births vs. no births (HR 2.55; 95% CI 1.19-5.48) but not 1 birth vs. no births (no *P*-trend reported)
Merlino et al (50)	OR in ever vs. never parous women 1.14 (0.63-2.05) OR in ever vs. never gravid women 1.15 (0.62-2.12)	Using 1 pregnancy as reference group and excluding nulligravid women no increased risk for 2-3, 4-5 or >5 pregnancies (*P*-trend 0.30)
Del Junco et al (14)	OR in ever vs. never gravid women 0.32 (no CI data)	-
Guthrie et al (20)	OR in ever-parous vs. nulligravid women 0.61 (0.43-0.86) OR in ever-gravid & nulliparous vs. nulligravid women 1.2 (0.72-2.00)[a]	Using 1 birth as reference group no increased risk for 2, 3, or ≥4 births (*P*-trend not reported but written "not significant")
Hazes et al (13)	OR in ever-gravid vs. nulligravid women 0.49 (0.27-0.91)	Greater risk reduction in women with ≥3 pregnancies than 1-2 pregnancies relative to nulligravid (*P*-trend not reported, both pregnancy categories significantly associated with reduced risk)
Reckner-Olsson et al (15)	OR in ever vs. never parous women 0.5 (0.3-0.9)	-
Orellana et al (36)	OR in ever vs. never parous women aged 18-44 years 1.1 (0.9-1.5) and aged 45-70 years 1.0 (0.8-1.2)	-
Pedersen et al (48)	OR in ever vs. never parous women 0.87 (0.57-1.32)	No significant risk reduction for 1,2,3, or ≥4 live births (0 live births as reference group; *P*-trend 0.15)
Peschken et al (46)	-	Significant risk reduction in women with ≥6 births and 3 births, but not 4-5 births, compared with women who had 1-2 births. *P*-trend=0.046.
Pikwer et al (51)[b]	OR in ever vs. never parous women 0.75 (0.45-1.24)	OR 1.00 (95% CI 0.78-1.27) per number of childbirths (*P*-trend not reported)
Pope et al (52)	OR in ever vs. never parous women 0.71 (0.26-2.0)[a] OR in ever vs. never gravid women 1.3 (0.5-3.3)	-
Spector et al (53)	OR in ever vs. never parous women 0.55 (0.31-0.97)[a]	-

Risk data reported as odds ratios (ORs) or relative risks (RRs) unless otherwise stated; a=risk recalibrated as reported in paper using never vs ever-parous; b=risks reported as risk of parity in cases vs. controls, which is equivalent to RA risk in ever-parous vs. nulliparous women; RF=rheumatoid factor.

Table 3. Risks in Relation to Pregnancy Timing

Study	Risk Reported
Brennan et al (35)	Reported risk during pregnancy (OR 0.95; 95% CI 0.19-4.70) and during 12-month post-partum period (OR 1.02; 95% CI 0.33-3.16) (reference group not described).
Del Junco et al (14)	Reported risk during pregnancy (RR 0.31) and 12 months post-partum (RR 4.67). No CI data given.
Guthrie et al (20)	Limited data given in manuscript text, with risk reported by duration since last given birth (nulliparous women as reference group): last given birth 1-5 years previously RR 0.29 (*P*<0.001; CI data not given); last given birth 5-15 years previously RR 0.51 (*P*<0.001; CI data not given); last given birth >15 years previously RR 0.76 (*P*=0.18; CI data not given).
Jørgensen et al (17)	Stratified risk by time in years since birth of last child: 0 to <2 years RR 0.99 (95% CI 0.86-1.14); 2-4 years RR 0.95 (95% CI 0.83-1.08); 5-9 years RR 1.02 (95% CI 0.91-1.13); 10-14 years RR 1.00 (reference); 15-19 years RR 1.06 (95% CI 0.96-1.18); >20 years RR 1.09 (95% CI 0.98-1.21).
Lansink et al (12)	Risk compared to time period other than pregnancy and the post-partum year: during pregnancy OR 0.64 (95% CI 0.13-3.21); <3 months post-partum OR 3.37 (95% CI 0.86-13.11); 3-12 months post-partum 0.67 (95% CI 0.13-3.55).
Orellana et al (36)	Assessed risk of RA according to post-partum period for last delivered child (analysis restricted to women aged 18-44 years and stratified by ACPA status; time is in years between last delivered child and index year; nulliparous is the reference group): • ACPA positive RA - 0 years OR 0.8 (95% CI 0.4-1.6); 1 year OR 0.8 (95% CI 0.4-1.5); 2 years OR 0.6 (95% CI 0.3-1.3). • ACPA negative RA - 0 years OR 2.1 (95% CI 0.9-4.8); 1 year OR 1.4 (95% CI 0.6-3.6); 2 years OR 0.8 (95% CI 0.2-2.3).
Peschken et al (46)	OR for RA in 12-months post-partum year was 3.8 (95% CI 1.45-9.93) compared with >15 years post-partum as the reference group.
Rodriguez et al (47)	OR for incident RA in women pregnant in previous 12 months 0.22 (0.06-0.77)
Silman et al (11)	Reported risk during and 12-months after pregnancy (using outside the post-partum period as the reference group): during pregnancy OR 0.3 (95% CI 0.04-2.6); 0-3 months post partum OR 5.6 (95% CI 1.80-17.6); 3-12 months post partum OR 2.6 (95% CI 0.8-7.9)

RR=relative risk; OR=OR; CI=confidence interval

Figure 1. Search Strategy

Figure 2. Forest Plot of Risk of Rheumatoid Arthritis in Ever Vs Never Parous Women

The 95% confidence interval data presented in the Forest plot differs slightly from that reported in several studies due to using standard errors to derive 95% confidence intervals; RE=random effects model; OR=odds ratio; CI=confidence interval; Q=Cochran's Q-test.

Figure 3. Funnel Plot of Studies Included in Meta-Analysis, Augmented Using the "Trim and Fill" Method

The 11 black circles show the observed effect sizes for the 11 studies; the 2 white circles show the augmented "missing" studies of medium precision reporting an increased risk associated with being ever-parous.