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Is pregnancy a risk factor for rheumatic autoimmune diseases?

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Abstract

Purpose of review—To review the association of pregnancy with the risk of subsequent development of rheumatic autoimmune diseases in women, including rheumatoid arthritis, systemic lupus erythematosus, and scleroderma.

Recent findings—There is a small but growing literature related to the risk of autoimmune rheumatic disease in association with pregnancy history. However, results conflict both in terms of the direction and magnitude of risk of disease in relationship to prior pregnancy history. Although anecdotal evidence tends to favor the premise that pregnancy is protective against certain diseases, such as rheumatoid arthritis, the heterogeneity of results precludes the ability to confirm an association in either direction. There is indication that time elapsed since pregnancy may influence risk, with the postpartum year being of particular relevance.

Summary—To date, a clear pattern has not emerged regarding pregnancy and the future risk of autoimmune rheumatic diseases. This topic requires greater study, and given the strong female preponderance of these diseases, future research efforts should seek to resolve this important issue.

Keywords

autoimmune disease; rheumatic disease; rheumatoid arthritis; systemic lupus erythematosus; scleroderma; pregnancy

INTRODUCTION

Autoimmune diseases in general affect women at a disproportionately higher rate than men(1). The majority of rheumatic autoimmune diseases such as systemic lupus erythematosus (SLE), scleroderma (SSc) and rheumatoid arthritis (RA), are far more prevalent among women. For example, recent population based incidence and prevalence

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estimates for SLE reveal that the disease affects women at a rate of 9:1 compared to men(2). Furthermore, the peak incidence of these diseases is well into the menopausal transition, suggesting that in addition to female gender, events over the course of a women's reproductive history likely contribute to disease expression(3)(4)(5)(6). The immunologic effects of sex hormones including estrogen, progesterone, and other pregnancy and postpartum related hormones may have significant roles as epigenetic modifiers in the induction and elaboration of autoimmunity in a susceptible host. As such, reproductive history, including age of menarche, pregnancies, oral contraceptive use and development of menopause play complex roles in autoimmune diseases and continue to be the focus of extensive research. This review covers current research related to pregnancy and the development of rheumatic autoimmune diseases in women (Table 1).

PREGNANCY AND AUTOIMMUNITY

It is useful to examine autoimmune diseases as a group in order to appreciate patterns that may not be discernable when these diseases, many of which are individually rare, are considered as separate entities.

Autoimmune diseases as a group

Certain combinations of autoimmune diseases have been demonstrated to cluster among individuals and within families, supporting the premise of shared environmental and/or genetic risk factors across autoimmune diseases.

A population-based study from Denmark including 1,035,639 women born between 1960 and 1992 examined the development of autoimmune disease following first pregnancies, including following pregnancies terminated by induced abortion (7). Their composite autoimmune disease outcome included a group of thirty well-recognized autoimmune diseases. During the overall follow-up period, future risk of autoimmune disease was significantly lower in women who had a first pregnancy that ended with vaginal delivery, compared to nulliparous women, after adjusting for confounders including maternal age and calendar year [RR 0.91(95% CI 0.84, 0.99)]. No association was detected for the overall follow-up interval among women whose first pregnancy ended with cesarean section or induced abortion. When dividing the follow-up interval according to length of time since end of pregnancy, a more nuanced pattern emerged. In the first year of follow-up after pregnancy, in comparison to nulliparous women, the risk of autoimmune disease was significantly increased among women with either vaginal or cesarean deliveries [RR 1.15 (95% CI 1.03, 1.28) and RR 1.30 (95% CI 1.10, 1.55), respectively], but risk significantly decreased in the year following induced abortion [RR 0.70, (95% CI 0.56, 0.88)]. In contrast, from 12 months onward following end of first pregnancy, there was a trend toward reduced risk of future autoimmune disease for women with a vaginal delivery (RRs ranging from 0.84–0.95, but only reaching statistical significance for the 3–10 year post-pregnancy interval), and no association from 12 months onward for women with cesarean delivery or induced abortion. A significant limitation of this study was that only the first, but not subsequent pregnancies, was analyzed. Thus, the potential cumulative effects of number and timing of pregnancies among multiparous women could not be assessed. However, the results of this study highlight the complexity of the issue of pregnancy and risk of

autoimmune disease, and are compatible with anecdotal evidence that the postpartum year is a specialized window of susceptibility.

A complementary Danish study, examining a similar group of 31 autoimmune diseases among persons born from 1935 to 1993, examined number of live births in association with autoimmune disease (8). They further grouped autoimmune diseases according to those that were female predominant, defined as having a female to male ratio of greater than 2 in the general Danish population, and those that did not meet this definition of female predominance. They found that compared to nulliparous women, women with at least one live born child had an increased risk of developing a female predominant autoimmune disease, after adjusting for confounders [RR 1.07 (95% CI 1.04, 1.10)], though when assessing number of births, this trend only remained significant for women with 1 live birth and women with 4 or more live births. For women with 2 or 3 births, risk of female predominant disease was similar to that for nulliparous women. Conversely, when assessing the other (non-female predominant) autoimmune diseases, the risk of disease was reduced for women with at least one child [RR 0.94 (95% CI 0.91, 0.97)], and was likewise significantly reduced for women with 2, 3, or 4+ live births (RRs ranging from 0.88 to 0.92) compared to nulliparous women. Curiously, for both female predominant and other autoimmune diseases, the patterns observed among women were similar among men who had fathered children, leading to speculation that there may be sociodemographic or lifestyle factors involved rather than direct biologic effects of pregnancy. Further analyses based on individual autoimmune diseases revealed that for six diseases there were significant associations between parity and risk of among females but not males (reduced risk of SLE, and increased risk of Hashimoto thyroiditis, Graves' disease, erythema nodosum, psoriasis, and sarcoidosis), making the case for an association between pregnancy and future risk of disease most compelling for this subset of autoimmune disorders.

Rheumatoid arthritis

Rheumatoid arthritis (RA), a systemic autoimmune disease associated with symmetric small joint inflammatory arthritis and characteristic autoantibodies (rheumatoid factor and antibodies against citrullinated proteins (37)(38), is 2–3 more times more prevalent in women than men(39). A significant improvement in RA symptoms has been well described during pregnancy in as many as 75% of patients, with subsequent flare in disease often occurring 2–3 months postpartum(40). In general this is attributed in part to the shift during pregnancy from a Th-1 to Th2 anti-inflammatory cytokine milieu induced by increased levels of estrogen, progesterone and cortisol (40)(41).

Thus, much interest has focused on whether pregnancy affects a women's subsequent risk of developing RA. Several retrospective and prospective case control studies have found a decreased risk of RA among women who had ever been pregnant compared with nulliparous women(9, 10, 12, 13). One such study from the UK reported results of a health questionnaire sent to 270 women with RA aged 35–70, 292 osteoarthritis controls and 245 population based controls (12). Information about RA diagnosis date and other medical history was obtained from records and from patient report. The percentage of nulliparous women was found to be significantly higher in the RA group than in the OA or population control groups

(26.3% vs 17.8% and 13.5% respectively; $p < 0.05$). Adjusted OR for developing RA was higher in this population for nulliparous women in comparison to both OA controls (OR 1.82; 95% CI 1.09–3.03) and population controls (OR 1.83; 95% CI 1.03–3.26). Other risk factors for RA were assessed, including HLA-DR4 antigen, family history of RA or use of oral contraceptives, and were not found to be associated with subsequent risk of developing RA. There was a trend towards further risk reduction among women with multiple pregnancies vs only one or two pregnancies, and a trend towards decreased RA risk with younger age at first pregnancy, which was significant when adjusted for year of birth ($p < 0.005$). These findings are supported by a similar retrospective case control study from the Netherlands in which reproductive history questionnaire data and historical records were also compared in 135 women with RA and 378 controls with OA or soft tissue rheumatism (10). A lower OR of developing RA was seen among parous and multiparous women vs controls (OR 0.53; 95% CI 0.28–0.99).

Another large US population based prospective case control study of women aged 18–64 enrolled in a large health plan also found association between pregnancy and RA risk among patients (13). In this study, the date and the diagnosis of RA for 301 cases was confirmed by board certified rheumatologists via physical exams and abstraction of records, and RA specific HLA genotyping of RA cases was performed. 1418 controls were selected randomly from the health plan database. Compared to nulliparous women in the study, parity of any number was significantly associated with a lower RA risk (adjusted RR 0.61, 95% CI 0.43–0.86, $p = 0.005$). Interestingly, gravidity without parity was not associated with a decreased risk for RA. The risk was lowest among women 1–5 years from their last birth, but risk reduction lessened as time elapsed from last birth. Risk reduction imparted by parity was also not observed in women 45 years and older, nor was RA risk significantly associated with age at first birth or with total numbers of births. Additionally, among RA cases with 2 copies of RA-associated HLA alleles, significantly fewer were parous vs nulliparous ($p = 0.02$). In a follow up study involving these 310 RA cases and 571 different controls, for whom HLA genotyping was available, the investigators found relationships between women's parity and HLA-genotype, raising the question of whether HLA disparate fetal microchimerism in pregnancy may be affecting risk.(42) Furthermore, among RA cases with two copies of the HLA alleles, 18% were parous vs 29% nulliparous, and those negative for the allele 36% were parous vs 27% nulliparous ($p = 0.02$), supporting the authors' hypothesis that parity is especially beneficial for women at greatest genetic risk for RA.

Follow up studies in this study population also revealed an association between complicated pregnancies, in particular delivery of extremely low birth weight infant (ELBW), and subsequent risk of maternal RA (RR 3.7, 95% CI 1.0–12.2)(15). Other studies, including a Danish national cohort study, have also found associations between pregnancy complications and increased RA risk, including hyperemesis (RR 1.70; 95% CI 1.06 to 2.54), gestational hypertension (RR 1.49; 95% CI 1.06 to 2.2) and preeclampsia (RR 1.42; 95% CI 1.08 to 1.84)(16). Unlike the previously cited case control studies, these authors found no association between nulliparity and RA risk in their study population comprised of 7017 women and 3041 men with RA admitted to hospital from 1977–2004. These authors did, however, note that compared with one-child mothers, women with two or three children were at reduced RA risk (RR 0.84; 95% CI 0.78 to 0.90; RR 0.83; 95% CI 0.77 to 0.91

respectively). Younger age at the birth of the first child was inversely associated with the risk of RA in both women and men (p for trend <0.001), raising the question of environmental, socioeconomic or epigenetic factors playing a role in clinical disease manifestation. Another large cohort study using prospectively collected data from the Nurses' Health Study found no association between parity and the development of RA, nor an association with the age at first child's birth among 217 incident cases of RA from 1976–1982(17). A subsequent 2004 Nurses' Health Study analysis, reflecting a longer follow up period, included 674 incident cases of self-reported RA among women followed from 1976 to 2002. Neither parity nor age at first birth were associated with subsequent development of RA in this study (18). Furthermore, a study of incident cases of RA among a large Finnish cohort found parity increased, not decreased, RA risk, among 176 seropositive and 93 seronegative RA cases identified (19). Compared to nulliparous women, the age adjusted RR of parous women in this study who went on to develop RF positive RA was 1.26 (95% CI 0.82 to 1.92). In general, these and other population based cohort studies(20)(21) have not found association between pregnancy or parity and risk of RA that has been observed with more frequency in case control studies as described above, possibly reflecting differences in study methodology, including heterogeneity of case ascertainment methods and the definition of outcome measures (e.g. pregnancies vs parity).

Systemic lupus erythematosus

Systemic lupus erythematosus (SLE), an antibody mediated autoimmune disease characterized by heterogeneous manifestations, is associated with a higher obstetric risk, in particular among those women with active disease or with associated antiphospholipid antibodies(22). Whether parity increases the risk of SLE is currently unknown, as high quality studies on large data sets have produced conflicting results. One large population based Danish cohort study identified 1,614 women through a health registry with an ICD-9 diagnosis of SLE(43), and found that women with one or more child had a 25% reduced risk of SLE compare to those women who were nulliparous (RR 0.74; 95% CI 0.64–0.86). The risk of developing SLE decreased further for those with women with two or more children. Increased SLE risk in this study was observed for women with idiopathic pregnancy losses, perhaps reflecting early, pre-clinical immunologic derangement that would ultimately result in clinical SLE. As referenced in the section on autoimmune diseases in general, another Danish study found SLE to be one of 6 autoimmune diseases for which having at least one child was significantly associated with reduced risk among women [RR 0.76 (95% CI 0.66, 0.88)], but not men (8). Moreover, the reduced risk of SLE was most pronounced in the year following most recent birth, in which odds of SLE were reduced by 30% compared to 10 to 14 years after childbirth [OR 0.69 (95% CI 0.52, 0.92)].

Another population-based case control study of hormonal effects in 240 SLE patients compared to 321 controls from the Carolina Lupus Study collected data on reproductive historical events prior to SLE diagnosis and found no association between the risk of developing SLE and parity, including both live births and number of pregnancies (23). Similarly, data on 262 incident cases of SLE from the Nurses' Health Study found no association between parity or age at first birth and subsequent development of SLE(26).

Smaller case control studies of SLE patients identified through record reviews have not demonstrated an association between parity and subsequent development of SLE(27)(29).

Scleroderma (systemic sclerosis, SSc)

SSc is another rheumatic autoimmune disease with clear female preponderance, with a female to male ratio of 4.6 to 1 based on prevalence data(3). SSc is characterized by diffuse fibrotic skin changes and vasculopathy, with excess morbidity and mortality associated with cardiopulmonary, renal and gastrointestinal manifestation. The risk of developing scleroderma peaks after the reproductive years in women, with peak incidence during the 45–54 year age range among black females, and 65–74 years among white females(3).

Several studies have examined the question of whether pregnancy is associated with future risk of developing SSc, with conflicting results. Prior pregnancy was reported to be associated with a reduced risk of SSc in two European studies. The first was an Italian study including 46 cases and 153 controls: when adjusted for age, parous compared to nulliparous females had a reduced risk of scleroderma [RR 0.3 (95% CI 0.1, 0.8)], which on further examination pertained only to women with 2 or more children(31). The overall history of any pregnancy, including completed and abortive pregnancies, was associated with a reduced risk of SSc after adjusting for age [OR 0.3 (95% CI 0.1–0.7)]. The inverse association persisted when also including women with a history of abortive pregnancy. The second study finding an inverse association between parity and SSc was a Swedish study of including 2,149 SSc cases and 9,879 matched controls born between 1964 to 1999. Results from this case-control study were that nulliparous women had an increased risk of scleroderma [OR 1.37 (95% CI 1.22, 1.55)], with risk decreasing with increased number of births(33).

In contrast, a US study including 172 SSc cases and 256 non-SSc sisters, found suggestion of a positive association between a history of one or more pregnancies and SSc [OR 2.8 (95% CI not reported)]. In a subset of 39 cases and 40 unaffected sisters, history of at least one live birth and at least one pregnancy loss was reported to be associated with SSc [OR 3.27 (95% CI 1.62, 6.6)](34). An Australian study including 387 SSc cases and 457 controls, found that while SSc cases were more likely to be multiparous compared to controls [OR 1.8 (95% CI 1.1, 2.98)], there were neither significant differences in number of pregnancies nor age of first pregnancy between cases and controls(36). Finally, the largest study assessing pregnancy and risk of SSc was one of the population-based Danish studies cited previously. This study found no evidence for an association with SSc among women with at least one child compared to nulliparous women, adjusting for confounders [RR 0.90 (95% CI 0.71, 1.15)](8).

CONCLUSION

Current literature regarding pregnancy as a risk factor for rheumatic autoimmune diseases is conflicting. This may in part reflect the difficulty of case ascertainment and validation of rheumatic diseases, and the challenges of identifying date of disease onset, which is subject to recall bias. The existing studies are furthermore not uniform in how reproductive status

was assessed, including whether the outcome of interest was parity or pregnancy, and whether the use of exogenous hormones and family planning issues were considered.

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Key points

- In general, there remains conflicting evidence regarding an association between pregnancy and risk of rheumatic autoimmune diseases
- Certain autoimmune diseases seem to be more likely than others to be associated with pregnancy based on large registry studies
- To advance the understanding of the true role of pregnancy in the risk of autoimmune diseases, and to clarify windows of vulnerability such as during the postpartum year, detailed assessment is needed of reproductive factors across the lifespan, in conjunction with genetic factors and environmental exposures.

Table 1
Summary of studies evaluating association between pregnancy and risk of subsequent rheumatic autoimmune diseases (AID)

Author (Ref.) Year published	Study design	Study population	Disease; diagnostic criteria or method	No. AID pts	No. Contr ols	Pregnancy measure	Association
Khashan (7) 2011	Retrospective cohort	(n=1,035,639)1960–1992	AID: ICD codes Seropositive RA	n/a	n/a	Method of delivery	Not known Vag RR 0.72(0.55, 0.96) CS/Section (RR=1.17, [95% CI: 0.88, 1.55]) abortion (RR=0.93, [95% CI: 0.74, 1.18])
Jørgensen (8) 2012	Retrospective cohort	Denmark; Danish Natl Registry (45.4 million person yrs)	AID: ICD codes	n/a	n/a	Parity	Nulliparity vs parous RR = 1.04 (1.02–1.06) for any AIDs, 1.11 (1.08– 1.14) for female predominant and 0.97 (0.95–1.00) for other AIDs
Del Junco (9) 1988	Retrospective case control	USA; Olmstead county, MN	RA: Record review	324	324	Gravidity	Decreased RR=0.31 (95% CI not reported)
Hazes (10) 1990	Retrospective case control	The Netherlands; Leiden University Hospital in Leiden	RA: 1958 ARA(11)	135	378	Parity	Decreased (RR 0.49 [95% CI] 0.27–0.91)
Spector (12) 1990	Retrospective case control	UK; London outpatient rheumatology clinics	RA: 1958 ARA(11)	150	337	Parity	Decreased nulliparity (age-adjusted OR= 1.82 [95% CI]1.09– 3.03)
Guthrie (13) 2010	Prospective case control	USA; Seattle based health plan	RA: 1987 ACR(14)	310	1418	Gravidity and parity	Decreased (RR 0.61 [95% CI] 0.43–0.86)
Ma (15) 2013	Prospective case control	USA; Seattle based health plan	RA: 1987 ACR(14)	202	1102	Birth weights (extremely low birth weight)	Prior delivery of an infant with ELBW a/w RA (RR 3.7 [95%CI] 1.0–13.2)
Jørgensen (16) 2010	Retrospective cohort	Denmark; Danish Natl Registry (88.8 million person yrs)	RA: ICD codes	7017	n/a	Parity	NS [†]
Hernandez (17) 1990	Prospective cohort	USA Nurses' Health Study (n=121,700)	RA: 1987 ACR(14)	217; 115 Definite RA 102	n/a	Parity	NS

Author (Ref.) Year published	Study design	Study population	Disease; diagnostic criteria or method	No. AID pts	No. Contr ols	Pregnancy measure	Association
				"undifferentiated polyarthritis"			
Karlson (18) 2004	Prospective cohort	USA: Nurses' Health Study (n=121,700)	RA: 1987 ACR(14)	674	n/a	Parity	NS
Heliövaara (19) 1995	Prospective cohort	Finland: Helsinki Prospective population cohort (n= 15,441)	Self-report	269	n/a	Parity	NS
Brun (20) 1995	Prospective cohort	Norway: Bergen Population based cohort (1,485,400 person-yrs)	RA: ICD codes	335	n/a	Parity	NS
Merlino (21) 2003	Prospective cohort	USA: Iowa Iowa Women's' Health Study (n=31,336)	RA: 1987 ACR(14)	158	n/a	Parity	NS
Ulf-Møller (22) 2009	Prospective cohort	Denmark; Danish Natl Registry (n= 88.9 million person yrs)	SLE: ICD codes	1614	n/a	Gravidity and parity	Decreased: women with at least one live born child decreased risk vs nulliparous women (RR 0.74; [95% CI] 0.64–0.86)
Cooper (23) 2002	Retrospective case control	USA; Carolina Lupus Study	SLE: ACR criteria(24,25)	240	321	Gravidity and parity	NS
Costenbader (26) 2009	Prospective cohort	USA Nurses' Health Study I & II (n=238,308)	SLE: Self report, record review	262	n/a	Parity	NS
Bengtsson(27) 2002	Retrospective case control	Sweden Lund University Hospital, (n=92,962)	SLE: multisystem disease diagnoses(28)	85	205	Gravidity and parity	NS
Grimes (29) 1985	Retrospective case control	USA: Atlanta, GA Emory University Hospital	SLE: 1971 ARA(30)	109	109	Parity	NS
Pisa (31) 2002	Retrospective case control	Italy: Verona University Hospital Verona	SSc: LeRoy(32)	46	153	Parity	Decreased (Age-adjusted OR 0.3 [95% CI] 0.1– 0.8)
Lambe (33) 2004	Retrospective population based case control	Sweden Stockholm Inpatient Registry	SSc: ICD codes	2149	9879	Parity	Decreased: Nulliparity (OR 1.37[95% CI] 1.22–1.55)

Author (Ref.) Year published	Study design	Study population	Disease; diagnostic criteria or method	No. AID pts	No. Contr ols	Pregnancy measure	Association
Cockrill (34) 2010	Case sibling	USA: Scleroderma Family Registry	SSc: Leroy, 1980 ACR(32,35)or 3/5 CREST features	974 sibships	n/a	History of 1 pregnancy	OR 2.8 (95% CI not reported)
Russo (36) 2013	Retrospective case control	Australia South Australian Scleroderma Registry	SSc: ARA(35), 2/5 CREST features+ sclerodactyly	387	457	Parity	Increased: SSc cases more likely to be multiparous compared to controls (OR 1.8 [95% CI] 1.1, 2.98)

1, NS= Significant association not detected