

## Review

## The Role of Pregnancy in the Course and Aetiology of Rheumatoid Arthritis

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**Summary** The aetiology of rheumatoid arthritis (RA) is unknown, although being female is generally recognized as the most important independent risk factor, the disease being 2 to 3 times more frequent in females than in males. The dramatic effect of pregnancy in rheumatoid arthritis has been documented for over 50 years. This review examines the evidence and possible mechanisms by which pregnancy modifies the disease process and may alter predisposition to the development of RA in later life.

## EFFECT OF PREGNANCY ON EXISTING RA

First reported by Hench in 1938 (1), the ameliorating effect of pregnancy on the activity of rheumatoid arthritis has been repeatedly confirmed. In a personal series and review of the literature, Persellin (2) reported improvement or remission of RA in 74% of 274 individual pregnancies. The few prospective studies have demonstrated, together with symptomatic relief, a marked decrease in objective measurements of synovitis, disability and even extra-articular features of RA, like lymphadenopathy and rheumatoid nodules (3-5). These effects enable the vast majority of patients to reduce or even to completely interrupt the use of slow acting drugs and NSAIDs (3,4).

Symptomatic relief is apparent from the first trimester in the majority of cases reported and tends to become more pronounced as pregnancy progresses. The reported case series have been combined in Table I. Two-hundred ninety-one individuals have been studied in 12 studies with fairly consistent findings. Overall 77% of cases went into remission (range 54% - 95%). Unfortunately, the remission is not long lasting: most of the patients experiencing partial or complete remission during pregnancy will experience relapse in the post-partum period. Of the 189 cases involved in the 6 series that examined disease activity at three months, 81% had relapsed (range 62% - 100%). Over 60% of the patients will have relapsed within 8 weeks of delivery and almost

all before the sixth month (15). Patients will need to return to medication and the level of disease activity is similar to the one that preceded pregnancy (8,14).

## MECHANISMS

The understanding of the mechanisms involved in these phenomena would certainly be of paramount importance to our knowledge of the pathogenesis of RA and offer new approaches to therapy. There are, however, important gaps in our knowledge. Predictive factors of the response of RA during pregnancy are inconsistent. No relation has been found with factors like parity, duration of disease, maternal age, rheumatoid factor, functional class or sex of the fetus (3,16). Some authors have reported marked elevations of prior IgG and IgM as being predictive of gestational remissions, although these observations remain unconfirmed (5). The only consistent predictor appears to be the response in a previous pregnancy (2,8,16). A recent exciting finding has been that maternal-fetal HLA DQ disparity is significantly more frequent in pregnancies associated with remission (17). The HLA system has also been found to be associated with the control of sex hormone levels, particularly testosterone (18).

Pregnancy is associated with a state of immunosuppression indispensable for the survival of the fetal allograft. Many of these immunologic changes have the potential to modify RA. In vitro studies have demonstrated that serum from pregnant women has the ability of reducing or suppressing macrophage and PMN function including chemotaxis and adherence (19), bacterial killing and enzyme release and activity (20) including

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Table I: *Effect of pregnancy in women with rheumatoid arthritis*

Author	Number of Patients	% remission	% relapse at 3 months
Hench, 1938 (1)	22	91	77
Lewis-Faning, 1950 (6)	22	95	81
Torrent, 1951 (7)	15	80	—
Oka, 1953 (8)	93	75	84
Hargreaves, 1958 (9)	11	91	100
Smith, 1960 (10)	12	75	—
Betson, 1964 (11)	24	54	—
Morris, 1969 (12)	17	82	—
Neely, 1977 (13)	20	63	—
Ostensen, 1983 (14)	31	75	62
Ostensen, 1983 (3)	10	90	100
Unger, 1983 (4)	14	71	—
Total	291	77%	81%

cathepsin B, involved in the degradation of collagen (21). However, conflicting results have been published (22) and there is little clinical evidence for changes in other nonspecific inflammatory reactions during pregnancy (23).

Humoral immunity seems to be preserved from major changes during pregnancy: although lower levels of IgG have been reported to occur during gestation (24), humoral responses to different vaccines have been found to be normal (25). A change in the carbohydrate side-chains of IgG, typical of the pregnant state has been suggested as a mechanism by which the formation of potentially aggressive IgG aggregates in RA pregnant women are reduced (26).

Changes in cell-mediated immunity are more readily exemplified by prolongation of skin graft survival (27), reduction in skin tuberculin reaction (28) and increased incidence of specific intracellular infections (29-31). In vitro studies with peripheral lymphocytes from pregnant women have revealed decreased reactivity to viral antigens (32,33) and mitogens like concavalin A and PHA (34). Exactly how and why these changes occur remains unclear. There is a reduction in total lymphocyte count during pregnancy, affecting especially T-cells (35) and in particular the helper-inducer subset (35,36). Fetal-induced suppression of T and B cells from the mother has been demonstrated particularly at the level of the fetoplacental unit (37,38), but a more generalized effect may be caused by the frequent presence of fetal lymphocytes in the maternal circulation (37) and the involvement of factors in serum, like alfa-fetoprotein (38,39).

Several factors produced by the mother or placental tissues have also been proposed to explain the state of immunosuppression. Serum levels of corticosteroids including cortisol increase steadily during pregnancy, at-

taining by the third trimester, levels about double the nonpregnant state (40). The potential significance of these changes is, however, diminished by their poor correlation with disease activity in the individual patient and the gap of several weeks between the return to normal levels and post-partum relapse (41). High levels of sex hormones as well as chorionic gonadotropin, prolactin and human placental lactogen are observed during pregnancy. All have the potential of important immunomodulatory effects (42,43). However, the post-partum relapse is not related temporally with lactation, breast feeding or the return of menstruation (44).

Pregnancy associated alpha-2 glycoprotein (PAG) has received attention due to its broadspectrum immunosuppressive properties (45,46). Raised levels of this protein have been found in synovial fluids of RA patients (47). The serum levels increase considerably during pregnancy in 75 to 90% of all women and two independent groups have found a strong negative relation between PAG levels and RA activity (4, 48). Almost simultaneously, however, another group, using a different assay, failed to find any correlation (49).

A large variety of maternal blocking antibodies has been identified in maternal serum, including anti T-cell, anti B-cell, antiidiotypic and anti Fc receptor antibodies (50-52). They have potential inhibiting effects on cell-mediated immunity, NK cells, humoral immunity and inflammatory responses. The therapeutic efficacy of acid-extracted placental gammaglobulins in RA (53-54) suggests the involvement of these mechanisms in the pregnancy-induced amelioration of the disease. The findings regarding HLA-DQ maternal-fetal disparity, would suggest a mechanism by which genetic and hormonal factors interact to modify the disease (17).

Several of the multiple mechanisms involved in the immunosuppressive state of pregnancy have the potential of interfering with disease activity but the relative importance of these factors remains unclear. It has recently been proposed that pregnancy-related changes in the autonomic nervous system might play a determinant role in the induction of remission, but clear evidence of such changes is still lacking (55). We are not yet in a position to explain why almost 30% of pregnant patients fail to improve despite a normal progression of gestation. When these mechanisms become clearer, we may be able to offer new therapeutic remedies.

#### PREGNANCY EXPERIENCE AND THE RISK OF DEVELOPING RA

Another interesting interaction between pregnancy and RA is the relation between parity and the incidence

Table II: Nulliparity and risk of rheumatoid arthritis

Author (Ref)	Cases	Controls	Type of study	RR for nulliparity (95% CI, where given)
Engel, 1962 (56)	—	—	Population survey	1.3 (Age35-44) 0.5 (age 45-54)
Kay, 1965 (57)	209	209 (popul.)	Case-control	1.97
Lawrence, 1977 (58)	267	1015	Population survey	1.8
Vandenbroucke, 1986(59)	148	186 (OA + Soft tiss)	Case-control	1.79
Hernandez-Avilla, 1988 (60)*	115	121.700	Prospective nurses	No relation reported
Del Junco, 1989 (61)	324	324	Population-based Case-control	3.16
Hazes 1990 (62)	135	378 (OA + Soft tiss)	Case-control (incident)	2.04(1.09-3.70)
Kay, 1990 (63)	88	144	Case-control	No relation reported
Koepsell, 1990 (64)	101	398	Case-control (incident)	2.0
Spector, 1990 (65)	270	292 OA 245 Popul.	Case-control	1.82 (1.09-3.03) 1.83 (1.03-3.06)

\* Prospective study of 121.700 female nurses totaling 883.187 person-year. New cases: 115 definite RA and 102 probable RA.

of the disease. In a population study in West Cornwall in 1958, Hargreaves noted that women with RA appeared to have fewer children than expected (9). Since then, a number of studies have examined this question. A case-control study addressing this question in 1965, found a mean family size among RA patients significantly lower than in controls although this was mainly due to increased nulliparity of RA patients compared with osteoarthritic controls (57). A British population study involving more than 1200 women found a prevalence of RA significantly higher among nulliparous women in comparison to those with 2 or more previous pregnancies, with a relative risk of 1.5 to 1.7 (58). However, as part of the large US National Health Examination Survey of 1960-62, an association of RA with multiparity was seen although the relative risk varied between age groups (56). Discrepancies in the application of diagnostic criteria may have played a role in the contradiction between these two population studies.

More recently, Hazes et al (62) found an adjusted relative risk for RA of 2.0 in nulliparous women compared to parous women. A larger number of previous gestations tended to increase the protective effect, as did a younger age at first pregnancy. Further analysis of the results reported in 1986 by Vandenbroucke (59) also shows an increased risk for RA of 1.8 among nulliparous women. A study by Spector et al (65) involving 270 RA women and two separate control groups also found an association between nulliparity and an increased risk of RA, with a relative risk of 1.8 both in comparison with osteoarthritic patients and general population controls.

Multiple pregnancies, however, did not show additional protective effect. Other studies have also shown a similar increased risk of nulliparity (61), although some failed to find a relationship (60,63).

The relevant studies are given in Table II. Of the case-controls that reported nulliparity rates there appears to be a consistent finding of an increased odds ratio between two and threefold. The only case-control not showing a difference was the smallest, performed with only 88 cases. The only other negative study was the large prospective nurse study. Interestingly, this study also found no protective association with the oral contraceptive pill suggesting that, like the contraceptives, parity may make the resulting RA milder, rather than actually preventing it (66).

Clearly the higher rates of nulliparity in RA women could be due to diminished fertility or increased rate of miscarriages among women with the disease. Kaplan found a significantly increased rate of prior spontaneous abortions among New York RA women predominantly of black and Hispanic origin (67). Most studies, however, have found no difference in the rates of spontaneous abortions or stillbirths between patients and controls. These studies are shown in Table III. Overall, RA does not appear to be associated with an increased risk of poor reproductive outcome, except perhaps, in the context of severe disease with extra-articular involvement or related to therapy (16,73).

The question of subfertility associated with RA is more difficult to address. Reduced fertility is to be expected in the context of a chronic disabling disease and

Table III: *Studies of prior fertility and reproductive outcomes in RA women compared to controls.*

Author (Ref)	Cases	Controls	Fertility (Nr preg/person)	Spont. abortions	Stillbirth	Mean family size
Kay, 1965 (57)*	209	209	↓	NS	—	↓
Kaplan, 1986 (67)	96	113	NS	↑	—	—
Del Junco, 1988 (61)*	324	324	↓	NS	—	—
Siamapolou, 1988 (68)	72	98	NS	NS	NS	—
Silman, 1988 (69)**	40	67	NS	NS	↑	—
McHugh, 1989 (70)	117	100	↓	NS	—	—
Spector, 1990 (71)	195	462	NS	NS	NS	NS
Nelson, 1992 (72)	174	718	—	NS	NS	—

\*Without exclusion of nulliparous women; \*\*Comparison between RA patients and disease-free relatives. Relatives had lower than expected stillbirth rate; NS - No significant difference.

Table IV: *Studies of development of RA in relation to pregnancy*

Author (Ref)	Cases	Controls	RR during pregnancy	RR12 months post-partum
Del Junco, 1988 (61)	324	324	0.31	4.67
Silman, 1992 (63)	88	144	0.3 (0.04-2.0)	5.6 (1.8-17.6) 0-3 months 2.6 (0.9-7.9) 3-12 months
Koepsell, 1990 (64)	101	398	0.2 (0.1-0.7)	—

women with RA have been reported to have a diminished sexual desire and frequency of sexual intercourse (74). One cannot exclude that subfertility could antedate, even for decades, the clinical onset of disease (57) but if this were the case, fertility in parous women would also be reduced, producing smaller family sizes, and this has not been observed (62,70,72).

Another possibility is that nulliparity represents a marker of a different risk factor, like sexual activity or other differences in lifestyle. In fact, if nulliparity is an independent risk factor an increased proportion of single women should be expected among RA women, and this has not been consistently found (58,65). Preliminary results of an uncontrolled study involving 220 nuns failed to show an increased rate of RA above that expected (75). It is naturally difficult to address sexual behaviour and exposure both before and after disease onset and the two alternative hypotheses: namely that subfertility precedes disease or that nulliparity is a true risk factor for RA are difficult to resolve with certainty.

RA has also been found to develop more frequently than expected in the 12 months following delivery and as expected occurs less frequently during pregnancy. This may be a real phenomenon although it is difficult to assess whether the disease actually occurs at this time, or the symptoms are delayed or masked by pregnancy. It is also possible that selection and recall bias are involved, as post partum women are more likely to seek

and attract medical help. Only three studies have so far been performed in this area, although all show a consistent increase in RA in the 12 months post-partum. These are shown in Table IV.

How could a long-term pregnancy-dependent protection occur? Some investigators suggest that the protective effect of pregnancy experience is due to the immunomodulating effects of female hormones (62,65). The immunological effects of sex hormones are well known but a long standing effect offering protection against the onset of disease decades after the event is more difficult to accept. Recent studies suggest that pregnancy can be related to persistent hormonal changes, translated into small differences in sex-hormone binding globulin levels (76). However, the physiological significance of these differences is far from established and their magnitude does not suggest a major role. The lack of a consistent dose-effect relationship in terms of increased protection with multiple pregnancies, suggests a "one-off", vaccination-like, event similar to the one observed with adjuvant induced arthritis (77). It is also possible that pregnancy acts in a similar way to contraception and may modify the subsequent disease process producing a "milder" form of disease rather than protection (78).

In conclusion, the physiological mechanisms involved in pregnancy are undoubtedly interrelated with the mechanisms that control the disease process of RA. If we can understand these natural mechanisms of disease

modification, the development of new synthetic or natural therapies for RA should follow.

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