Prediction of postpartum onset of rheumatoid arthritis

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Abstract

Objective—To investigate the prediction of the postpartum onset of rheumatoid arthritis (RA).

Methods—Two thousand five hundred and forty seven healthy pregnant subjects were examined prospectively and the relation between serum rheumatoid factors (RF) and postpartum onset of RA was observed. Rheumatoid factors were measured in early pregnancy by the antihuman IgG latex agglutination test (Latex test) and antirabbit IgG haemagglutination test (RAHA test).

Results—Latex test and RAHA test were positive in 26 (1.0%) and 64 (2.5%) pregnant subjects, respectively. Four hundred and ten subjects of 2547 pregnant women could be followed up for one year after delivery. None of 401 subjects without RF, or with only one RF on either Latex test or RAHA test, developed RA after delivery. Two (22.2%) of nine subjects with both RFs developed RA at one and three months postpartum, respectively. Transient arthralgia was found within 12 months postpartum in three of nine (33.3%) subjects with both RFs and this prevalence was significantly higher than that in RF negative subjects (8.1%).

Conclusion—Postpartum onset of RA was found in at least 2 of 2547 healthy subjects (0.08%) and onset was predicted by positive test for rheumatoid factors.

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Table 1 Relation of rheumatoid factor and postpartum onset of rheumatoid arthritis

Group	Rheumatoid factor		Screening in early pregnancy Number (%)	Postpartum observation up to one year		
	anti-human IgG antibody (Latex test)	anti-rabbit IgG antibody (RAHA test)		Number examined	Onset of rheumatoid arthritis (%)	Transient arthralgia (%)
1	Negative	Negative	2470 (97.0)	382	0	31 (8.1)
2	Positive	Positive	13 (0.5)	9	2 (22.2)***	3 (33.3)*
3	Positive	Negative	13 (0.5)	6	0	0
4	Negative	Positive	51 (2.0)	13	0	2 (15.4)
Total			2547 (100)	410	2	36

Significantly different at $p < 0.05$ (*) and $p < 0.001$ (***) between group 1 and group 2 by Fisher exact test.

such as Hashimoto's thyroiditis⁵ and Graves' disease,⁶ are also ameliorated during pregnancy and aggravated after delivery.⁷ Moreover, postpartum presentation of thyroiditis has been found in 5-10%^{7,8} and that of Graves' disease in 0.5% of postpartum women in the general population.⁹ Furthermore, postpartum occurrence of thyroiditis and Graves' disease can be predicted by measurement of thyroid microsomal antibody and thyroid stimulation antibody in early pregnancy.¹⁰ Incidence of postpartum onset of RA, however, has not yet been clarified and there is no report on how to predict the onset of disease after delivery.

In this study, therefore, we prospectively investigated the relation between autoantibodies including rheumatoid factors and postpartum onset of RA.

Methods

We studied 2547 healthy pregnant women who attended our maternity clinic. Subjects with previously diagnosed disorders were excluded from this study. The mean (SD) age was 30 (4.4) years old. Eight hundred and ninety nine were primigravidae and 1648 were multiparas. All subjects gave informed consent to participation in this study. One hundred and twenty one subjects could be examined until 12 months postpartum. To confirm the postpartum condition, the questionnaire was sent to 1406 subjects whose mail address was easily available. Unfortunately we could not reach 633 subjects possibly because of a change of home address. The remainder 773 subjects were supposed to have received the questionnaire but only 289 subjects responded (37.4%). Finally we could confirm the postpartum conditions for 410 subjects. The questionnaire asked family history of RA, history of pregnancy, sex of babies, the onset time and lasting period of joint swelling and/or pain, any comments by home doctors, and other information related to medical abnormality, if any.

Venous blood was drawn in early pregnancy from all pregnant subjects and was examined for seven kinds of autoantibody: rheumatoid factor by two measurement procedures, antithyroid microsomal antibody, antithyroglobulin antibody, antinuclear antibody, anti-DNA antibody (anti-double stranded DNA), and anti-mitochondrial antibody, as previously reported.¹¹ Rheumatoid factor (antihuman immunoglobulin G) was measured with a latex agglutination test (Latex test), and the presence of agglutination was considered positive. Rheumatoid factor (antirabbit IgG) was measured with haemagglutination (RAHA test), a

Table 2 Prevalence of antibodies in the groups of normal, transient arthralgia, and rheumatoid arthritis (RA)

Postpartum changes	Number examined	RA	RAHA	TGHA	MCHA	ANA	DNA	AMA	Family history of RA
Normal	372	10 (2.7)	15 (4.0)	11 (3.0)	25 (6.7)	39 (10.5)	2 (0.5)	1 (0.3)	11 (3.0)
Transient arthralgia	36	3 (8.3)	5 (13.9)	1 (2.8)	1 (2.8)	2 (5.6)	0	0	4 (11.1)
RA	2	2 (100.0)	2 (100.0)	0	0	1 (50.0)	0	0	0

Percentages are shown in parentheses. TGHA = antithyroglobulin antibody and MCHA = antithyroid microsomal antibody were measured with commercially available haemagglutination or particle agglutination kits. ANA = antinuclear antibody was measured with the fluorescent antibody technique. DNA = anti-DNA antibody (anti-double stranded DNA) was measured with haemagglutination. AMA = antimitochondrial antibody was measured with the fluorescent antibody technique.

reciprocal titre of 1:40 or more was considered positive.¹² In subjects positive for antibodies, serial blood samples were collected every one or two months. Of the 28 subjects with positive reaction on Latex test or RAHA test, 23 subjects could be measured further for titres of IgM rheumatoid factor (IgM-RF) (normal, less than 16 IU/ml) and IgG rheumatoid factor (IgG-RF) (normal, less than 2.0 index) by immunoturbidimetry and enzyme immunoassay, respectively.

Diagnosis of RA was based on the diagnostic criteria of the American Rheumatism Association (ARA 1987).¹³ After delivery some subjects had joint pain, mainly in the finger joints and either unilaterally or bilaterally, for a few weeks or months only. As these conditions did not reach to the diagnostic criteria, we tentatively called this "postpartum transient arthralgia".

Statistical analysis to compare the incidence of RA between groups that were positive and negative for antibodies was performed using Fisher's exact test. We used the Mann-Whitney U test to compare rheumatoid factor (RAHA test, IgM-RF, IgG-RF) with postpartum change.

Results

Antihuman IgG agglutination antibody (Latex test) and antirabbit IgG haemagglutination antibody (RAHA test) were found in 26 (1.0%) and 64 (2.5%) of 2547 pregnant subjects, respectively. Pregnant subjects were divided

into four groups according to the presence or absence of these antibodies (table 1). Thirteen (0.5%) pregnant subjects were positive on both tests (group 2). None of subjects developed RA during pregnancy. Finally we could confirm postpartum conditions in 410 subjects. None of 382 subjects without antibodies (group 1) developed RA after delivery. However, two (22.2%) of nine subjects examined in group 2 showed onset of RA after delivery. This incidence significantly differed from that in group 1 (table 1). Transient arthralgia was found within 12 months postpartum in 8.1% of subjects examined in group 1, and in 33.3% of subjects examined in group 2 and this was also significantly different between the two groups (table 1), although the difference between RF positive groups overall and RF negative groups did not reach statistical significance. The onset of transient arthralgia was observed at 2.7 (2.7) months postpartum (mean (SD)) and the mean duration was 3.5 (4.1) months. None of subjects in groups 3 or 4 developed postpartum RA. Seven antibodies were examined in the three groups divided by postpartum changes; normal, transient arthralgia, and RA (table 2). However, no useful information were obtained for prediction of RA onset.

The titres of various antibodies in early pregnancy and parity in 13 subjects of group 2 are summarised in table 3. None of the five other antibodies were related to the onset of RA or transient arthralgia. Activities of rheumatoid factors (IgM-RF, IgG-RF, and RAHA

Table 3 Antibody titres in early pregnancy and parity in subjects of group 2

		Antibodies in early pregnancy								
Case no	Postpartum change	Rheumatoid factor			ANA	DNA	MCHA	TGHA	AMA	Parity
		IgM-RF (IU/ml)	IgG-RF (Index)	RAHA test (titre)						
1	Onset of rheumatoid arthritis	78	1.86	160	40	(-)	(-)	(-)	(-)	2
2	Onset of rheumatoid arthritis	488	2.58	2560	(-)	(-)	(-)	(-)	(-)	2
3	Transient arthralgia	41	1.56	320	(-)	(-)	(-)	(-)	(-)	3
4	Transient arthralgia	64	1.36	160	80	(-)	5120	(-)	(-)	2
5	Transient arthralgia	242	2.65	160	40	80	(-)	(-)	(-)	2
6	None	51	1.48	160	(-)	(-)	1600	(-)	(-)	4
7	None	119	1.03	160	(-)	(-)	(-)	(-)	(-)	1
8	None	53	1.26	80	(-)	(-)	(-)	(-)	(-)	2
9	None	24	0.75	40	40	(-)	(-)	(-)	(-)	3
10	Not examined	NT	NT	640	(-)	(-)	(-)	(-)	(-)	5
11	Not examined	4	0.59	640	(-)	(-)	(-)	(-)	(-)	2
12	Not examined	73	1.55	160	20	(-)	(-)	(-)	(-)	3
13	Not examined	36	0.99	160	(-)	(-)	(-)	(-)	(-)	4

ANA = antinuclear antibody was measured with the fluorescent antibody technique. DNA = anti-DNA antibody (anti-double stranded DNA) was measured with haemagglutination. MCHA = antithyroid microsomal antibody and TGHA = antithyroglobulin antibody were measured with commercially available haemagglutination or particle agglutination kits. AMA = antimitochondrial antibody was measured with the fluorescent antibody technique. NT: not tested.

Figure 1 Relation of titres of rheumatoid factors (IgM-RF, IgG-RF, and RAHA test) in early pregnancy and postpartum changes of arthritis within 23 subjects who had rheumatoid factor(s) and could be followed up after delivery. NS= not significant.

test) in early pregnancy were compared with postpartum changes within 23 subjects who had rheumatoid factor(s) and could be followed up after delivery (fig 1). Although there was significant difference in the activities of IgM-RF and IgG-RF between the RA onset and disease free groups, the titres of rheumatoid factors were not useful for differentiating between postpartum RA and non-arthritis subjects. Family history of RA, examined in 410 subjects who could be followed up for one year after delivery, was not useful for prediction of postpartum disease onset (table 2).

Serial changes in the titres of rheumatoid factors are shown in figure 2 (A: case 1 and B: case 2). Case 1 was a 25 year old housewife and delivered a male baby at 41 weeks of gestation without any complication. At one month postpartum, she developed morning stiffness and mild bilateral joint pain and swelling, although erythrocyte sedimentation rate and C reactive protein were not increased initially. Swelling of wrist, metacarpophalangeal, and proximal interphalangeal joints lasted for two months. At three months postpartum, lactation was stopped and non-steroidal anti-inflammatory drug (NSAID) was given until the next pregnancy. After initiation of NSAID, joint swelling disappeared gradually and morning stiffness also disappeared at eight months postpartum. Case 2 was a 33 year old housewife who delivered her second baby at 41 weeks of gestation without any complication. She developed morning stiffness at three months postpartum along with mild bilateral joint pain that was followed by joint swelling. Swelling of proximal interphalangeal, metacarpophalangeal, and wrist joints lasted for two months. This patient also started treatment with NSAID at five months postpartum, but mild joint pain continued intermittently for more than three years. The titre of antirabbit IgG antibody (RAHA test) decreased during pregnancy and increased after delivery in association with the onset of symptoms in case 1 (fig 2A). In case 2, however, RAHA titres decreased after delivery (fig 2B). Titre of antihuman IgG antibody (IgM-RF) increased slightly after delivery in both cases. IgG-RF did not change significantly.

Discussion

It has long been recognised that RA carries an increased risk of disease onset during the postpartum period.¹⁴ In 1953, Oka reported that the onset of RA after delivery occurred in 9.7% (71 of 732) of female patients and concluded that postpartum onset was quite common.⁴ Felbo *et al* found that 28.3% of female patients developed postpartum onset.¹⁵ Del Junco *et al* also reported that the postpartum onset of disease was five times more frequent than that at other periods.¹⁶ Silman *et*

Figure 2 Serial changes in rheumatoid factors during and after pregnancy in two subjects who developed postpartum RA. The shaded area shows the normal range.

al found a numerically greater risk of disease onset during the first three months postpartum in their case-control study using a dummy date for disease onset.² A similar result was reported from another group,¹⁷ however the exact incidence of postpartum onset in the general population and a method for predicting onset are not known.

In this prospective study, we found two cases among 2547 normal pregnant subjects who developed RA after delivery. As we could not follow up all subjects, it is difficult to calculate the real incidence of postpartum onset of RA in general population, but it is clear that at least 0.08% of postpartum women developed RA after delivery.

To our knowledge, there are no data on a method of predicting RA onset. In this study, we found that rheumatoid factor tests were useful for predicting postpartum RA onset. Among subjects without rheumatoid factors, none developed RA, indicating that this screening method can be applied to a large scale population, although the cost effectiveness must be considered. An interesting finding was that both antihuman and antirabbit IgG antibodies were important factors. If we developed more useful specific markers for this disease, we might predict onset more effectively, as in postpartum thyroiditis and Graves' disease.^{9,18}

An interesting finding was the increased frequency of postpartum transient arthralgia in group 2. It is important to detect very early forms of RA. More than half of postpartum thyroiditis and Graves' disease cases involve the transient form and patients recovered to the subclinical condition within one year postpartum.⁹ Therefore, we expected to find transient RA in this study. Two cases developed persistent disease, while others appeared to develop transient RA among patients with both types of anti-IgG antibodies. However, these subjects did not fit the 1987 ARA diagnostic criteria. Even in subjects without antibodies, 8.1% demonstrated transient arthralgia, suggesting that some transient arthralgia is a non-specific condition not related to RA. More precise observation and diagnostic methods are needed to clarify the nature of postpartum transient arthralgia.

Early postpartum aggravation around one to three months may be related to the cytotoxic cellular immunity while later development after five to six months postpartum may be

associated with humoral immunity.¹⁹ In the two cases in this study, serial changes in rheumatoid factors were different and activity of rheumatoid factors was not related to the early postpartum RA onset, suggesting that humoral immunity may not be relevant to the disease progress and cytotoxic cellular reaction is more important for the aggravation or induction of RA.

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