Depression as a potential causal factor in subsequent miscarriage in recurrent spontaneous aborters

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BACKGROUND: Unexplained miscarriage is speculated to be due to a Th1/Th2 cytokine imbalance at the feto–maternal interface and immunological functions are known to be under the influence of various psychological factors. Indeed, the psycho–neuro–immuno–endocrine network has been proposed to contribute to miscarriage. To assess whether psychological disorders might induce spontaneous abortion we carried out a prospective study to determine if any psychological parameter influenced risk in those patients with a history of recurrent miscarriages. METHODS: A prospective study was carried out on 61 patients with a history of two consecutive first-trimester miscarriages. A battery of self-report questionnaires including Symptom Checklist-90 Revised and the NEO Five Factor Index and semi-structured interviews were conducted before a subsequent pregnancy. We investigated whether or not these parameters predicted subsequent miscarriages. RESULTS: Ten (22.2%) of the 45 patients who conceived miscarried again. Baseline depressive symptoms influenced subsequent miscarriage ($P = 0.004$). This statistically significant effect remained when we corrected with Bonfferoni adjustment ($P = 0.036$). CONCLUSIONS: A high depression scale is associated with a high miscarriage rate in those patients suffering recurrent miscarriage.

Key words: depression/neuroticism/personality/recurrent miscarriage

Introduction

Conventional investigation of couples with recurrent miscarriages yields no putative cause in >50% of cases (Hertz-Picciotto and Samuels, 1988). However, unexplained miscarriage is currently speculated to be due to Th1/Th2 cytokine imbalance at the feto–maternal interface (Wegmann et al., 1993) and Th2-type immunity and transforming growth factor b secreted by Th3 cells may play protective roles during pregnancy, hence the nexus between a Th2/Th3 shift and successful pregnancy (Raghupathy, 2001). Activation of coagulation mechanisms, leading to vasculitis affecting the maternal blood supply to the embryo, appears to be a major miscarriage-causing mechanism (a form of ischemic autoamputation). Th1 cytokines trigger this process via up-regulation of a novel prothrombinase while Th1/Th3 cytokines may antagonise the processes involved (Clark et al., 1999).

Immunological functions are known to be under the influence of various psychological factors (Kaplan et al., 1991). Indeed, the psycho–neuro–immuno–endocrine network has been proposed to be involved in miscarriage and thus to be a target for prevention (Clark et al., 1996). Abnormal psychological conditions might thus influence pregnancy outcome via a shift in the balance of the Th1/Th2 cytokines.

It is well known that some patients suffering from recurrent abortion may present with psychological disorders (Berle and Javert, 1954; Neugebauer et al., 1995) and 'tender loving care' has been shown to improve the success rate in patients with unexplained habitual abortion (Stray-Pedersen and Stray-Pedersen, 1984). It is furthermore well established that stress induces abortion in mice (Arck et al., 1995, 2001)

It is therefore only natural to suspect that emotional distress may lead to recurrent spontaneous abortions. Recently, a number of papers concerned with the associations between psychological disorders and reproductive failure have been published (Bergant et al., 1997; Milad et al., 1998; Klonoff-Cohen et al., 2001; Smeenk et al., 2001). Smeenk et al. reported that pre-existing psychological factors are related to treatment outcome in IVF. However, there is no evidence to our knowledge that psychological disorders influence human miscarriage in those patients with recurrent miscarriage.

We have conducted a number of prospective studies concerning this issue (Aoki et al., 1998; Hori et al., 2000) and have previously reported that the women's neuroticism

90 couples eligible for study inclusion

29 couples refused to participate

Self-report questionnaires before interview

61 couples assessed at first preconceptional interview

16 couples excluded
11 infertile
1 refused
4 other reasons

45 couples became pregnant
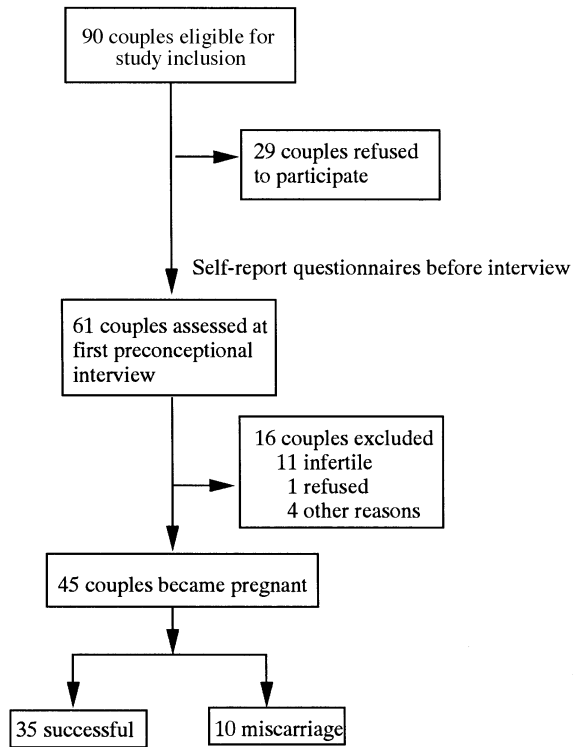
35 successful

10 miscarriage

Figure 1. Trial profile.

personality trait and current depressive symptoms are negatively correlated with preconceptional NK cell activity (Hori *et al.*, 2000), which has been previously reported to predict subsequent miscarriage (Aoki *et al.*, 1995).

Since evidence for this is still limited, the present prospective study was conducted to examine psychosocial factors that may influence subsequent miscarriage rates in those patients with a history of two consecutive first-trimester miscarriages and no live births. The present paper is an exploratory analysis on women's psychological characteristics, including their personality traits and preconceptual emotional distress, that may be associated with the success/failure of subsequent pregnancy.

Materials and methods

Patients

A prospective study was carried out on patients with a history of two consecutive first-trimester miscarriages and with no live birth. All were seen at Nagoya City University Hospital from April 1995 to August 1997.

Tests for identifiable factors for recurrent miscarriages were completed after the first visit. Couples with any uterine anomaly or chromosome abnormality in either partner were excluded from the study. All couples were married.

Of a total of 90 couples eligible for this study, 61 gave written informed consent approved by the Institutional Review Board and received the semi-structured interview. A total of 60 couples completed the questionnaire before interview. There were 45 pregnancies in the 61 patients in the period between July 1995 and June 1999. The trial profile is shown in Figure 1.

The patients were admitted for rest for ~1 month at 4 weeks' gestation to avoid possible external risk factors. Gestational age was calculated from basal body temperature charts. Ultrasonography was performed twice a week during pregnancy.

Analysis of associations between psychosocial variables and subsequent pregnancy outcome was the rationale for the present study.

Methods

Hysterosalpingography, chromosome analysis for both partners, immunological tests for parameters such as natural killer (NK) cell activity and antiphospholipid antibody (aPL), and blood tests for hyperthyroidism, diabetes mellitus, hyperprolactinemia and infections such as chlamydia, were performed prior to conception for all patients.

To detect b2glycoprotein I-dependent anticardiolipin antibody, a modified ELISA system was applied. Lupus anticoagulant was detected by diluted aPTT methods (Ogasawara *et al.*, 1996). Patients with at least one kind of aPL, after testing on separate occasions, were offered treatment with 80 mg/day of aspirin.

Preconceptional semi-structured interviews with tape-recording and self-report questionnaires were administered just before pregnancy at the same time for each couple in separate rooms of the hospital. Self-report questionnaires were completed before interview. Interviews probed the household environment, educational and occupational history.

The subjects were also asked to complete a self-report questionnaire battery including the Symptom Checklist-90 Revised (SCL-90-R) and the NEO Five Factor Index (NEO-FFI).

The mental status of the women was assessed with the SCL-90-R (Derogatis, 1992), one of the most widely used self-report questionnaires for general psychopathology, with good reliability and validity (van Riezen and Segal, 1988). The instrument produces nine subscale scores for Somatization, Obsessive-compulsive, Interpersonal sensitivity, Depression, Anxiety, Hostility, Phobic anxiety, Paranoid ideation and Psychoticism. The Japanese version has been used in an earlier study and its linguistic equivalence with the original English version has been ascertained by means of back translation (Furukawa *et al.*, 1996). In the present sample, the Cronbach's alpha coefficients were 0.84 for Somatization, 0.77 for Obsessive-compulsive, 0.84 for Interpersonal sensitivity, 0.88 for Depression, 0.81 for Anxiety, 0.79 for Hostility, 0.53 for Phobic anxiety, 0.74 for Paranoid ideation, and 0.70 for Psychoticism.

NEO-FFI depicts a person's personality structure along the five orthogonal dimensions of Neuroticism, Extraversion, Openness to experience, Agreeableness and Conscientiousness (Costa and McCrae, 1992). The past two decades have witnessed a rapid convergence of views regarding the structure of personality traits, because these five factors have repeatedly been found to account for a large amount of variance in the data, irrespective of sampling procedures, instruments used and techniques for factor analysis (Digman, 1990). The NEO-FFI is one of the standard measures of the Big Five Factor model. The Japanese version has been tested in a general population (Shimonaka, 1996). In the present sample, the Cronbach's alphas were 0.81 for Neuroticism, 0.73 for Extraversion, 0.55 for Openness, 0.69 for Agreeableness and 0.78 for Conscientiousness.

Statistical analysis

Data were analysed by *t*-tests using SPSS for Windows Version 10.0. Because we were examining two hypotheses, namely whether the women's personality traits predicted subsequent miscarriage and whether their preconceptual psychopathology did so, we corrected for multiple comparisons within each hypothesis by applying the Bonfferoni correction.

Table I. Demographic factors for the miscarriage and delivery groups

Demographic data	Third pregnancy outcome		
	Miscarriage (10)	Delivery (35)	*P*-value
Age of female (years)	30.70 ± 4.17	29.70 ± 2.98	NS
Age of male (years)	33.50 ± 4.06	33.26 ± 3.87	NS
No. of previous miscarriages	2	2	
No. of previous live births	0	0	
Marital status			
Married	10	35	
Single	0	0	
Occupation			
Housewife	7	15	NS
Employed	3	21	
Interval between last miscarriage and data collection (months)	11.7 ± 14.93	7.8 ± 4.93	NS
Interval between data collection and third pregnancy (months)	8.11 ± 4.48	6.28 ± 6.31	NS
Interval between last miscarriage and third pregnancy (months)	19.6 ± 17.14	14.08 ± 8.76	NS

Results

The mean ± SD ages of the women and their husbands were 30.2 ± 3.6 and 32.6 ± 4.1 respectively. The couples had been married, on average, for 3.3 ± 1.8 years. At the time of the data collection, 10.9 ± 13.0 months had passed since their last spontaneous abortion. The interval tended to be longer in the subsequent miscarriage group (not significant, Table I). Demographic variables such as age, education, occupation (housewife or not) did not differ between the miscarriage and delivery groups. A total of 31.8% (seven of 22) of housewives and 12.5% (three of 24) of employed women miscarried (not significant).

Questionnaires scores for Depression, Somatization, Anxiety, Obsessive-compulsive, Interpersonal sensitivity, Hostility, Phobic anxiety, Paranoid ideation, Psychoticism, Neuroticism, Extraversion, Openness to experience, Agreeableness and Conscientiousness did not differ between the housewife and employed groups.

Of the 61 couples, 45 conceived and ten (22.2%) miscarried again. Six of 45 patients were weakly positive for lupus anticoagulant and were treated with 80 mg/day of aspirin from 4 weeks gestation.

Firstly, the influences of baseline psychiatric symptoms on the subsequent pregnancy outcome were examined with the Students *t*-test. The mean ± SD psychological parameters of women who completed questionnaires and conceived are presented in Table II. Since four of the women who miscarried had fetuses with karyotype abnormalities, we compared the personality traits and psychological distress in the remaining 41. The miscarriage rate was positively associated with current depressive symptoms (*P* = 0.004), Neuroticism (0.019), Interpersonal sensitivity (0.01) and Psychoticism (0.034). There were no significant links with Somatization, Anxiety, Obsessive compulsive, Hostility, Phobic anxiety, Paranoid ideation, Extraversion, Openness, Agreeableness or Conscientiousness.

Only Depression emerged as a statistically significant pre-

dictor of subsequent pregnancy outcome after the Bonfferoni correction. The women's personality traits for Neuroticism, Extraversion, Openness, Agreeableness, or Conscientiousness, and the other psychological symptoms such as Somatization, Anxiety, Obsessive compulsive, Interpersonal sensitivity, Hostility, Phobic anxiety or Paranoid ideation did not appear to influence subsequent miscarriage.

There were no differences in preconceptional NK cell activity, serum progesterone and prolactin level between the miscarriage and delivery groups (not shown). Similar results were obtained when the four miscarriage cases caused by an abnormal fetal karyotype were excluded (Table III).

The 14 psychological factors did not correlate significantly with NK cell activity, serum progesterone levels and prolactin levels respectively (not shown).

Discussion

Preconceptional psychological factors also proved to be related to pregnancy outcome in patients with recurrent miscarriage. Recently, studies have been published concerning the associations between psychological disorder and reproductive failure (Bergant *et al.*, 1997; Milad *et al.*, 1998; Klonoff-Cohen *et al.*, 2001; Smeenk *et al.*, 2001). Smeenk *et al.* reported that state anxiety had a stronger correlation with treatment outcome than depression in infertile patients before starting IVF. Klonoff-Cohen *et al.* also described that baseline stress may affect biological endpoints (number of oocytes retrieved and fertilized), pregnancy and live birth delivery.

Miscarriage is a psychological trauma and a stressful life event. In our previous study, the mean (SD, range) value for the self-evaluated intensity of emotional impact after the second miscarriage—when the most severe life event was considered as –100—was reported to be –80.0 (26.8, –100 to 0) (Aoki *et al.*, 1998). Neugebauer *et al.* have noted that women who miscarry, especially those that are childless, are at risk of major depressive disorders in the 6 months after miscarriage (Neugebauer *et al.*, 1995). It is easy to speculate that women with a history of recurrent miscarriage are likely to suffer psychological disorder. There is 'the maternal myth' in Japan whereby old people believe that women should be forced to divorce if they cannot bear heirs for the family within 3 years. Women are ashamed of miscarriage and feel solitary, but little attention has been paid to their psychological care. Chronic stress might cause depression, which, as our findings suggest, might in turn contribute towards another miscarriage.

It is widely recognized that acute and chronic stress has an impact on the immune system. Acute stress may have a stimulating effect, while in the case of chronic stress, particularly in depression, the immune system may be down-regulated. Stress is associated with increased expression of interleukin-1 β (IL-1 β) and tumour necrosis factor-α (TNF-α), and reduced expression of IL-2, interferon-γ (IFN-γ), major histocompatibility complex (MHC) class II molecules and NK activity. Depression is associated with elevated IFN-γ and IL-1 β, downregulated IL-2, and reduced NK activity (Holden *et al.*,

Table II. Psychological parameters and subsequent pregnancy outcome with the four miscarriage cases caused by abnormal fetal karyotype excluded

Each parameter	Third pregnancy outcome			
	Miscarriage (6) Mean ± SD	Delivery (35) Mean ± SD	Unadjusted P-value	P-value after Bonfferoni correction
SCL90R				
Depression	1.039 ± 0.32	0.464 ± 0.50	0.004*	0.036*
Somatization	0.667 ± 0.40	0.393 ± 0.44	NS	NS
Anxiety	0.683 ± 0.48	0.254 ± 0.41	0.082 (NS)	NS
Obsessive-compulsive	0.733 ± 0.26	0.494 ± 0.43	0.09 (NS)	NS
Interpersonal sensitivity	0.796 ± 0.22	0.438 ± 0.51	0.01*	0.090 (NS)
Hostility	0.778 ± 0.59	0.243 ± 0.38	0.079 (NS)	NS
Phobic anxiety	0.262 ± 0.21	0.135 ± 0.22	NS	NS
Paranoid ideation	0.500 ± 0.42	0.205 ± 0.33	NS	NS
Psychoticism	0.500 ± 0.31	0.137 ± 0.20	0.034*	NS
NEO five factor index 60				
Neurotisism	35.8 ± 6.37	27.3 ± 7.99	0.019*	0.095 (NS)
Extraversion	25.2 ± 5.19	27.4 ± 5.21	NS	NS
Openness to experience	27.0 ± 3.52	27.7 ± 4.66	NS	NS
Agreeableness	34.0 ± 7.07	32.9 ± 4.91	NS	NS
Conscientiousness	31.5 ± 6.09	30.3 ± 6.50	NS	NS

*Significant at $P < 0.05$.

Table III. Laboratory data and subsequent pregnancy outcome with the four miscarriage cases caused by abnormal fetal karyotype excluded

Parameters	Third pregnancy outcome		
	Miscarriage (6) Mean ± SD	Delivery (35) Mean ± SD	P-value
NK cell activity	37.0 ± 25.53	48.47 ± 15.85	NS
Progesterone	12.39 ± 3.41	12.37 ± 7.47	NS
Prolactin	10.26 ± 7.28	8.52 ± 6.39	NS

1998). Th1 cytokines such as IFN-γ and IL-1 β are well-known to induce abortion in mice.

Mendlovic *et al.* reported that T-cells of suicidal depressed individuals have Th1 characteristics, while those of non-suicidal depressed patients have Th2 characteristics. Th1 environment is associated with most autoimmune diseases. It is thus speculated that Th1 activation in suicidal depression may reflect a unique form of autoimmune suicide (Mendlovic *et al.*, 1999). Some miscarriage patients who exhibit depressive symptoms might have Th1 characteristics. Recently, Arck *et al.* demonstrated significant elevation in the numbers of CD8+ T cells, TNF-α and tryptase + mast cells in the decidua of women suffering sporadic spontaneous abortion and with a high stress score (Arck *et al.*, 2001). Th1 cytokines may trigger processes that lead to vasculitis affecting the maternal blood supply to the embryo, which is speculated to be a major miscarriage-causing mechanism in those patients with depressive symptoms.

In the present study, preconceptional NK activity, serum progesterone and prolactin levels did not predict subsequent miscarriage. Regarding progesterone, our previous study indicated that a luteal phase defect diagnosed as $P < 10$ ng/ml

does not predict subsequent miscarriage in patients with a history of two consecutive recurrent miscarriages (Ogasawara *et al.*, 1997). Arck *et al.* reported no differences in decidual CD56+ NK cells between low and high stress scores (Arck *et al.*, 2001). The endometrial CD16-CD56bright NK cell subset, which is predominant in normal decidua and endometrium, is reported to be significantly decreased in favour of an important contingent of CD16+CD56+ NK cells in habitual aborters (Lachapelle *et al.*, 1996). A role for decidual or endometrial NK cells in the abortion process is therefore suggested by their altered subsets in habitual aborters. However, peripheral NK activity fluctuates with various factors and it may be difficult to predict subsequent pregnancy simply by blood examination.

In conclusion, a preconceptional depressive state may influence the risk of miscarriage in those patients who have experienced recurrent miscarriage. Recurrent aborters with high depression scale should therefore undergo preconceptional counselling by psychiatrists or receive treatment with antidepressants. There are few known predictors for miscarriage other than antiphospholipid antibodies, chromosome abnormalities, maternal age and number of previous miscarriages (Ogasawara *et al.*, 2000) and the population of recurrent aborters who can be successfully treated with medication is limited. Our findings appear to provide the first evidence of a psychological predictor for recurrent miscarriage. It is simple to measure depression with the SCR90R approach and therefore greater recourse to this tool appears warranted.

Acknowledgement

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