Abnormal IL-2 receptor levels in non-pregnant women with a history of recurrent miscarriage

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BACKGROUND: Immunological abnormalities have been found in pregnant women with a history of recurrent miscarriage. This study compared interleukin-2 receptor (IL-2R) levels in non-pregnant women with a history of recurrent miscarriage with those found in serum from a non-pregnant group with no such history. METHODS: Group 1 comprised 49 non-pregnant women with a history of recurrent miscarriage (at least three consecutive miscarriages). Group 2 comprised 22 non-pregnant women with no history of miscarriage. Serum IL-2R levels were measured in all patients. RESULTS: The results obtained showed that although all women were not pregnant at the time of sampling, IL-2R levels were significantly higher in women in Group 1 compared with those in Group 2 (1589 ± 1289 versus 1082 ± 823 pg/ml; P < 0.05). Follow-up data were available for 21 women from Group 1. The next pregnancy ended successfully for 14 of these women, while seven miscarried again. The IL-2R levels obtained pre-pregnancy were not significantly different between the two groups (1480 ± 910 versus 1356 ± 716 pg/ml). CONCLUSION: This study has shown that non-pregnant women with a history of recurrent miscarriage have raised IL-2R levels. These increased pre-pregnancy IL-2R levels did not necessarily predict miscarriage for the next pregnancy.

Key words: immune function/interleukin-2 receptor/recurrent miscarriage

Introduction
Evidence suggests that bi-directional cytokine interactions between the maternal immune system and the fetoplacental unit are crucial for a successful pregnancy. It has been suggested that immune dysfunction is at least partly responsible for recurrent miscarriage (Clark et al., 1991; Reinhard et al., 1998). There have been reports of immune dysfunction within decidual tissue from women with a history of recurrent miscarriage. Vassiliadou et al. (1999) found there to be increased numbers of leukocytes expressing the early activation markers CD69 and CD25 from spontaneous abortion deciduas compared with those from therapeutic abortions. Increased numbers of activated leukocytes have also been found in the deciduas of women with a history of unexplained pregnancy loss, suggesting that cellular immunity is involved in unexplained pregnancy loss (Quack et al., 2001). Immunological abnormalities have also been found within peripheral blood. Previous studies have found increased interleukin-2 receptor (IL-2R) levels in the serum of pregnant women with a history of recurrent miscarriage (Kilpatrick, 1992; MacLean et al., 2002). Soluble IL-2R has been shown to be a sensitive and quantitative marker of T-cell activation and proliferation, with activation of T cells being associated with increased expression of IL-2R (Matthiesen et al., 1996). It is this activation of the immune system that is thought to be a factor involved in miscarriage.

The aim of this study was to compare IL-2R levels in a group of women with a history of recurrent miscarriage, but who were not pregnant at the time of sampling, with levels found in a group of non-pregnant women with no history of miscarriage to see if there was any residual immune dysfunction.

Materials and methods
Ethical permission was obtained from the local ethical committee, and informed consent was obtained from all women prior to entry into the study.

Venous blood samples were obtained from the two patient groups. Group 1 comprised 49 non-pregnant women of mean age 32 ± 6.9 years with a previous history of recurrent miscarriage. All women had suffered at least three unexplained previous miscarriages, with the group having suffered a mean of 4.2 ± 2.3 previous miscarriages and no live births. All patients had had an antiphospholipid syndrome (APS) screen comprised of anticardiolipin IgG autoantibody and lupus anticoagulant. The lupus anticoagulant screen was comprised of activated partial thromboplastin time (APTT), kaolin clotting time (KCT) and dilute Russell viper venom test (DRVVT). If any of these tests were positive, or one was positive with a positive anticardiolipin antibody (ACL), the lupus screen was said to be positive. Antinuclear antibody with a titre of 1:40 on two occasions was considered positive. The presence of Chlamydia in the blood

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Many previous studies have investigated the response of the maternal immune system to pregnancy and have found that the response differs in women who miscarry (Clark et al., 1991; Reinhard et al., 1998). Previous studies have found that relatively low levels of IL-2R early in pregnancy are associated with obstetric success (Kilpatrick, 1992; MacLean et al., 2002). Increased IL-2R levels have been found at the time of delivery and are associated with the immune activation known to occur at this time (Burns et al., 1999).

We previously have found levels of IL-2R to be increased in first trimester women with a history of recurrent miscarriage, whilst in on-going pregnancies IL-2R levels did not differ significantly from the non-pregnant state (MacLean et al., 2002). The results reported here show that in some non-pregnant women with a history of recurrent miscarriage, IL-2R levels are also elevated, suggesting that they have not returned to normal after miscarriage and there is still activation of the immune system. Although a wide range of IL-2R levels were found in women in Group 1, the levels were not predictive of a successful outcome in the next pregnancy. Whilst few studies have looked at immune function pre-pregnancy, Kilpatrick (1992) also found levels of IL-2R to be elevated in non-pregnant women with a history of recurrent miscarriage, but the results did not reach statistical significance. What distinguishes the present study is that follow-up data were available on some of the women involved.

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References


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Figure 1. The figure gives individual IL-2R levels. The mean values for group 1 (1589 ± 1289 pg/ml) were significantly different from those for group 2 (1082 ± 823 pg/ml) (P < 0.05).

Statistics

Results are given as the mean ± SD, and were analysed for statistical significance using a Mann–Whitney test.

Results

The results are given in Figure 1 and show widely varied results for patients in Group 1. Mean IL-2R levels were significantly higher in non-pregnant women with a history of recurrent miscarriage (Group 1) compared with non-pregnant controls with no history of miscarriage (Group 2) (1589 ± 1289 versus 1082 ± 823 pg/ml P < 0.05).

Of the 49 patients initially recruited, 21 subsequently became pregnant. However, pre-pregnancy IL-2R levels did not differ significantly between the 14 who had a successful pregnancy and the seven who miscarried (1480 ± 910 versus 1356 ± 716 pg/ml).

Discussion

This study found levels of IL-2R to be significantly higher in non-pregnant women with a history of recurrent miscarriage compared with non-pregnant women with no such history.

denoting past exposure was assessed. There were no karyotype abnormalities. At the time of sampling, it had been at least 3 months since any of the women had suffered a miscarriage. Since sampling, 21 subsequently have become pregnant: 14 have had a successful pregnancy and seven have miscarried (four miscarried embryos and three miscarried fetuses).

Group 2 comprised 22 healthy non-pregnant women of mean age 28 ± 8 years with no history of miscarriage, or autoimmune disease. All of the women had already had at least one previous successful pregnancy.

Serum was stored at −70°C until analysed using enzyme-linked immunosorbent asay (ELISA) kits purchased from Laboratory Impex (Impex House, Wimbourne, Dorset, UK).

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