Successful pregnancy outcome following 19 consecutive miscarriages: Case report

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No cause can be found in 50% of patients with recurrent miscarriage. Recent research has shown that high levels of natural killer (NK) cells within the endometrium may be associated with idiopathic recurrent miscarriage. This case report describes a patient in whom an excessive number of uterine NK cells were found. She received preconceptual prednisolone and delivered a live baby. This is a novel observation of untested significance.

Key words: case report/natural killer cells/prednisolone/recurrent miscarriage

Introduction

Recurrent miscarriage (RM) is a distressing condition for which routine investigation fails to find a cause in 50% of cases (Li, 1998). As the fetus is allogeneically different from the mother, an immune aetiology for idiopathic recurrent miscarriage is an attractive concept. Recent publications have highlighted a potential role for natural killer (NK) cells in recurrent miscarriage (Aoki et al., 1995; Clifford et al., 1999; Ntrivalas et al., 2001).

The patient described was found to have the highest number of preimplantation uNK cells within a local study of endometrium from RM patients (n = 21) (Quenby et al., 1999). Following discussion with the patient, prednisolone was prescribed as immunomodulation therapy to attempt improvement in implantation.

Case report

This woman first presented to the miscarriage clinic at Liverpool Women’s Hospital following 14 consecutive miscarriages between 1989 and 1995 that occurred between 8 and 10 weeks of gestation. There was no past medical, surgical, obstetric or gynaecological history of note. The following investigation screen was negative; hormone profile (menstrual LH and FSH), viral screen (toxoplasmosis, cytomegalovirus, hepatitis and herpes simplex virus), autoimmune screen (anti-DNA, mitochondrial and thyroid antibodies), full blood count, random blood sugar, karyotype analysis of both parents, ultrasound scan of the uterus, hysteroscopy, antiphospholipid syndrome screen including IgG and IgM anticardiolipin antibody titres and dilute Russell viper venom time, Leiden factor V gene mutation, prothrombin gene mutation, methylenetetrahydrofolate reductase mutation, antithrombin III deficiency, and activated protein C resistance (Drakeley et al., 1998; Li, 1998). Following a diagnosis of idiopathic recurrent miscarriage, empirical low-dose aspirin was administered from 5 weeks of gestation of each pregnancy combined with folic acid 400 µg/day between 1995 and 1998. Unfortunately she suffered two further early pregnancy losses where the fetal karyotype was subsequently found to be normal.

As part of an ethically approved research study, the patient consented to a mid-luteal phase endometrial biopsy that showed the highest recorded level of uNK cells of those studied (Quenby et al., 1999). Thirty-one percent of this patient’s endometrial cells were uNK cells. The control patients, who had had at least two live births, had 0.2–9.5% uNK cells in their endometrium and the other recurrent miscarriage patients in the study had 0.2–22% uNK cells (Quenby et al., 1999). In light of this information various immunomodulation therapies were discussed, including i.v. immunoglobulin (IVIg) and prednisolone use. The patient decided that a trial of pre-conceptual prednisolone 5 mg/day should be prescribed. Between 1999 and 2001 she suffered three further consecutive losses at 5–6 weeks of gestation, bringing the total number of losses to 19.

An increased dose of preconceptual prednisolone (20 mg/ day) was taken for 6 months prior to conception in May 2002. The prednisolone was stopped at 5 weeks gestation after a home pregnancy test was positive. The pregnancy was monitored with serial ultrasonography and complicated by intrauterine growth restriction and oligohydramnios. A Caesarean section was performed at 32+6 weeks, because of poor growth velocity on serial ultrasonography, with the birth of a female infant weighing 1484 g, in good condition. After observation on the Special Care Baby Unit, baby and mother were discharged home well. At her post-natal visit mother and baby were both well. Bone density measurement of maternal hip and spine showed readings above average for her age.
Discussion
This case report is therefore interesting as it is a case of attempted manipulation of excessive uNK cells in RM with preimplantation glucocorticoids. A previous case report did describe the successful use of pre pregnancy intratuerine therapy in a woman with 10 previous losses; however, it did not include a record of the uNK cells (Ogasawara and Aoki, 2000). uNK cells are the most abundant cells in early pregnancy decidua (Bulmer et al., 1996). High preconceptional peripheral NK activity was found to be predictive of further miscarriages in women with RM (Aoki et al., 1995; Ntrivalas et al., 2001). The endometrium contains a unique subset of uterine-specific NK (uNK) cells. Lachapelle et al. (1996) demonstrated that the endometrium of women with RM contains an increased proportion of CD16+CD56dim NK cells compared with normal fertile women in whom CD16-CD56bright uNK cells predominate. Higher numbers of these uNK cells were found in the preimplantation endometrium of women with RM compared to controls (Clifford et al., 1999; Quenby et al., 1999). Furthermore, women who had higher numbers of uNK cells were more likely to miscarry in subsequent pregnancy (Quenby et al., 1999). However, a more recent study failed to predict pregnancy outcome by immunophenotypic analysis of the endometrium (Michimata et al., 2002). Several authors have suggested an important role for uNK cells in miscarried pregnancies. Higher levels of uNK cells have been also been found in the decidua miscarried from women with RM, compared with controls (Quack et al., 2001). Furthermore, uNK cells from the decidua of recurrent miscarriage patients were more active (Chao et al., 1995) and phenotypically different to those from healthy pregnancies (Yamamoto et al., 1999a; Emmer et al., 2002).

The presence of uNK cells in significant numbers in preimplantation endometrium and the existence of NK cell receptors that can recognize antigens on invading trophoblast (King et al. 2000) mean that uNK cells are considered to have a critical role in implantation. However, the exact role of uNK cells is not yet elucidated. There are two competing hypotheses: either uNK cells are hostile to invading trophoblast or uNK cells may facilitate the implantation of abnormal blastocysts leading to the clinical presentation of RM (Quenby et al., 2002). The latter interpretation is supported by recent data showing CD56+ NK cells are more numerous in the decidua from chromosomally abnormal miscarriages than in chromosomally normal miscarriages (Yamamoto et al., 1999b). Differences were detected in the decidual leucocytes from the miscarried tissue of women with unexplained RM and a normal fetal karyotype compared to women with RM and abnormal fetal karyotype (Quack et al., 2001). As not all this patient’s 19 miscarriages were karyotyped, we do not know how many losses were of karyotypically normal or abnormal pregnancies. The two miscarriages in which tissue was successfully cultured showed a normal karyotype.

uNK cells have recently been found to express the glucocorticoid receptor and the estrogen receptor β1, thereby raising the possibility of pharmacological manipulation of this cell population (Henderson et al., 2003). Several immunomodulation therapies are available. IVIg, third-party donor cell immunization, paternal cell immunization, trophoblast membrane infusion and steroids have all been suggested, with conflicting evidence as to their efficacy. A recent meta-analysis of 19 high-quality trials evaluated IVIg, third-party donor cell immunization, paternal cell immunization and trophoblast membrane infusions, and found no evidence of a beneficial effect (Scott, 2003). However, preimplantation prednisolone for the prevention of RM has not yet been investigated in any trial. Unfortunately we were not able to analyse a second biopsy from this patient’s endometrium whilst taking prednisolone, hence the effect of glucocorticoids on this patient’s uNK cells cannot be verified. Furthermore the patient had three further miscarriages, following the endometrial biopsy and we do not know how miscarriage or aging affects the uNK cell levels. Hence, this case represents a novel observation of untested significance. We do not recommend the measurement and treatment of uNK cells in recurrent miscarriage accept in the context of an ethically approved study or a well designed randomized controlled trial.

References
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Live birth after 19 consecutive miscarriages


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