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REVIEW

Prednisolone for repeated implantation failure associated with high natural killer cell levels

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Women with unexplained repeated IVF failure present a considerable challenge. Some cases are believed to be due to immunological dysfunction preventing effective embryo implantation. As data are still being collected, doctors are faced with the dilemma of treating patients (or not) in the absence of randomised control trial evidence. This review explores a pragmatic approach in using natural killer cell analysis as a means of targeting suitable patients who might attempt treatment with additional immunosuppressive therapy.

Keywords: Implantation, IVF failure, natural killer cells, prednisolone

Introduction

Implantation failure manifests as either unsuccessful IVF or miscarriage. While it is generally accepted that most failures are due to genetic abnormalities of the embryo, it is often difficult or impossible to prove (requiring preimplantation embryo biopsy or miscarriage products of conception for cytogenetic diagnosis). Hence, a pragmatic approach has been to investigate a couple after three or more otherwise unexplained miscarriages, or three or more unsuccessful IVF cycles (Margalioth et al. 2006).

However, approximately half of couples do not have any abnormality detected, and yet continue to have repeated failures. It is the reality of such unexplained cases that has led to the empirical use of immunosuppressive therapy. It has been argued that this is taking advantage of desperate couples. There is however, a strong theoretical case that abnormalities of the immune system could result in repeated implantation failure, and prednisolone has been used in this context for over 20 years.

The case report which follows illustrates two successful pregnancies following the introduction of prednisolone therapy for a woman with previous repeated implantation failure. The rationale and dose of prednisolone was based on the diagnosis of high natural killer (NK) cell levels. A literature review is reassuring of the relative safety of prednisolone in early pregnancy, and we encourage further studies to assess the potential benefit.

Illustrative case report

A couple presented with a 5-year history of infertility due to severe oligoasthenoteratospermia. The woman was 30 years old, with no other significant medical history, a regular 28-day cycle and a body mass index (BMI) of 23. A previous laparoscopy and hysteroscopy were normal. Her partner was aged 33, with no cause for his poor sperm count. They had already experienced three miscarriages following three intracytoplasmic sperm injection (ICSI) cycles and five frozen blastocyst transfer cycles at another clinic. Extensive screening for repeated implantation failure included karyotype, autoantibody and thrombophilia testing. LS was found to have raised anticardiolipin antibodies and was treated with low molecular weight heparin and aspirin in another ICSI cycle. This was unsuccessful, as was a further frozen embryo transfer (the woman's 10th good quality blastocyst in total).

A further hysteroscopy was performed, which confirmed a normal uterine cavity. She also had a midluteal phase endometrial biopsy, which reported a level of uterine NK cells of 28%, and a peripheral blood test, which reported a level of NK cells of 19.1%. Both these levels were considered to be elevated based on previous published work (King et al. 2010; Russell et al. 2011). After discussing the risks and possible benefits, she agreed to take prednisolone 20 mg/day from day 1 of her next ICSI cycle (her 5th) in addition to clexane and aspirin. The woman became pregnant, had a normal pregnancy and delivered a healthy baby boy weighing 3.16 kg. Prednisolone was stopped at 12 weeks' gestation, and clexane and aspirin continued until 34 weeks' gestation. The couple returned 2 years later. Following a similar protocol of prednisolone and clexane, she conceived again with a frozen embryo and had another healthy baby boy weighing 3.5 kg.

Discussion

This is the first report of the use of NK cell testing for targeting prednisolone therapy in a woman with repeated IVF failure. It is of interest because of the long history of unexplained IVF failure in a young woman, because the use of prednisolone led to a successful pregnancy rapidly, and because she had a second successful pregnancy with similar treatment. Did prednisolone make a difference? It certainly appears that it did from the patient's perspective. However, it can be argued that the pregnancies were a result of clexane and aspirin treating her anticardiolipin antibodies, or simply 'regression toward the mean'.

Without randomised trials, it is impossible to determine what brought about the success in this case. Does that make a difference? Is it reasonable to offer such therapy in these circumstances? The answer to these questions revolves around the analysis of potential benefit vs potential risk. In the absence of appropriate randomised trials, a review of the best available evidence is necessary, ongoing outcome monitoring is mandatory and public debate leading to larger trials is recommended.

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Following animal studies from the 1950s, a review of 457 women exposed to glucocorticoids (for SLE, asthma or infertility) in early pregnancy noted two cases of cleft palate where 0.2 should have been expected (Czeizel and Rockenbauer 1997).

A case–control study investigated 322 malformed and 503 normal control infants (Fraser and Sajoo 1995). Although only 26 and 33 women from each group were exposed to systemic glucocorticoids during the 1st trimester, they reported an increased risk of cleft lip with/without cleft palate. This was also demonstrated in another study of 1,184 infants with non-syndromic orofacial clefts (although only five had been exposed to corticosteroids in the 1st trimester) (Rodríguez-Pinilla and Luisa Martínez-Frías 1998). A further study showed that corticosteroids were associated with orofacial clefts but not conotruncal defects, neural tube defects and limb anomalies (Carmichael and Shaw 1999).

A meta-analysis including these trials concluded that while corticosteroids do not present a major teratogenic risk, they convey a 3–4-fold increase in the risk of the child being born with an oral cleft (Park-Wyllie et al. 2000). This represents an increase from 0.1% to 0.3–0.4% where the baseline risk of a malformation in newborns is approximately 3%. Further reassurance was provided by a prospective study, which was unable to find any teratogenic potential of systemic corticosteroids in the 1st trimester (Gur et al. 2004).

Glucocorticoids have also been implicated in pre-term birth, gestational diabetes and hypertension, intrauterine growth restriction, and even postnatal and behavioural effects (Gur et al. 2004; Laskin et al. 1997; Michael and Papageorghiou 2008). However, those studies involved women taking corticosteroids beyond the 1st trimester (and often at doses as high as 80 mg daily). None of those complications have been reported in pregnancies treated with corticosteroids in the 1st trimester only.

A meta-analysis on the use of peri-implantation glucocorticoids for women without autoantibodies undergoing assisted reproductive techniques found no benefit overall (Boomsma et al. 2007). However, there may be benefit when there is evidence of immune dysfunction – such as positive antinuclear antibodies (Taniguchi 2005), anti-DNA antibody or lupus anticoagulant (Ando et al. 1996) and antithyroid antibodies (Revelli et al. 2009).

The case report illustrated here made use of detailed assessment of both blood and uterine NK (uNK) cells, the assays of which have been described elsewhere (King et al. 2010; Russell et al. 2011). Elevated peripheral blood NK cell activity and uNK cell levels have been correlated with reduced IVF implantation rates (King et al. 2010; Tuckerman et al. 2010). Prednisolone may lead to improved reproductive outcomes by suppressing cytokine production and NK cytolysis (Thum et al. 2008). Administration of prednisolone 20 mg daily has been shown to reduce uNK numbers in women with recurrent miscarriage (Quenby et al. 2005) and this approach was reported to lead to a live birth in a woman with a history of 19 recurrent unexplained miscarriages (Quenby et al. 2003). Indeed, it is that case report that provided the basis for this review.

Conclusion

Prednisolone is relatively safe in early pregnancy, although there is an approximate 3-times increased risk of children having an orofacial cleft. It is considered safe enough to treat various medical conditions, including severe hyperemesis gravidarum, asthma and SLE. This case review supports the careful use of prednisolone targeted for women with evidence of immunological dysfunction associated with repeated implantation failure. A randomised controlled trial is required to better assess this benefit and low teratogenic risk.

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