CASE REPORT

Term delivery in a woman with severe congenital neutropenia, treated with growth colony stimulating factor

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The patient was diagnosed in childhood as having severe congenital neutropenia and had recurrent admissions with severe infections. In 1987, prior to getting married, she was sterilized. She continued to require i.v. antibiotics when she contracted a severe infection. On one occasion, she was treated with growth colony stimulating factor (G-CSF). Her increased neutrophil count was sustained following this treatment. In June 1993, she wished to start a family and underwent in-vitro fertilization (IVF) treatment. G-CSF was given prior to oocyte retrieval. She conceived on her first cycle and an ultrasound scan revealed a singleton pregnancy. Throughout the course of the pregnancy, her white cell count was monitored closely and remained at <1.0×10^9/l. The pregnancy progressed uneventfully and at 37 weeks gestation she was admitted for G-CSF injections. At 38 weeks she was delivered of a boy weighing 3350 g, by elective Caesarean section. His white cell count was normal. This is the first case of G-CSF being used before conception and during pregnancy in a patient with congenital neutropenia. It shows that advances in cytokine therapy and close interdisciplinary liaison can lead to a successful outcome and help patients, who would otherwise remain childless, to achieve a family.

Key words: congenital neutropenia/growth colony stimulating factor/pregnancy

Over the next few years she required frequent hospitalization for treatment with intravenous antibiotics. During one of her admissions she was treated with growth colony stimulating factor (G-CSF) and it was noticed that her increased neutrophil count could be sustained. In view of this, as it was now felt that the potential risk of neutropenia could be controlled by this cytokine, she requested advice regarding starting a family in December, 1992. The options of reversal of sterilization and in-vitro fertilization (IVF) were both considered. To perform a reversal procedure would have involved two general anaesthetics (one for a diagnostic laparoscopy and one for the actual reversal procedure). General anaesthesia has a morbidity and mortality with a risk of post-operative wound, chest and urinary tract infection following routine laparotomy. There is also a risk of thromboembolic phenomena. We would also have had to wait up to 12 months to see if the operation was successful, and even then IVF may have been necessary. If the operation had been successful, it would then have left us with a dilemma of future contraception (especially as this patient had had a deep vein thrombosis in the past) and she may well have requested re-sterilization. However, as IVF is less invasive, avoids the need for a general anaesthetic, has fewer complications (especially infective and thromboembolic) and is more successful in the long term without the question of future contraception, it was considered to be the treatment of choice.

A standard IVF protocol was followed, with a long period of down-regulation and the patient was stimulated with three ampoules of metronid (Serono Laboratories UK Ltd, Welwyn Garden City, UK) daily. Human chorionic gonadotrophin (HCG) was given on day 11 of stimulation. The patient was admitted 2 days prior to the egg collection for G-CSF injections. On the day of egg collection 1.2 g of augmentin (Smithkline Beecham Pharmaceuticals, Welwyn Garden City, UK) was given to cover the procedure. Out of 11 eggs, 10 were successfully fertilized and two excellent quality embryos were replaced on June 24, 1993. Five embryos were of good enough quality to be frozen. Luteal support was given in the form of 2000 IU HCG on June 24 and 27. A pregnancy test performed 2 weeks after the embryo transfer was positive.

Her estimated date of delivery was March 17, 1994 and ultrasound scans at 6, 9 and 12 weeks showed a single, viable intrauterine pregnancy. The pregnancy continued to progress normally and was monitored closely by both consultant obstetrician and consultant haematologist. At 16 weeks gestation her haemoglobin was 6.75 mmol/l, platelets 173×10^9/l and her
white cell count was 0.7×10⁹/l, with 41% neutrophils, 47% lymphocytes and 11% monocytes. An midstream specimen of urine (MSU) was sent for microscopy and culture at each clinic visit. An ultrasound performed at 18 weeks gestation confirmed her dates and showed normal fetal anatomy. The placenta was noted to be posterior. The pregnancy progressed uneventfully and the patient attended the antenatal clinic every 4 weeks until 28 weeks, fortnightly until 32 weeks and then weekly until 36 weeks. She continued to be seen by her general practitioner and the haematologists in the intervening period. She remained well and the baby was active. The blood pressure remained normal and the urine clear. Weight gain was good and the baby appeared to be growing on clinical examination and this was confirmed by ultrasound scans at 28, 32, 34 and 36 weeks. Minor colds and sore throats had been treated with oral ampicillin. Her white cell count was checked at each antenatal visit and had remained at <1.0×10⁹/l with ~40% neutrophils up until 37 weeks gestation.

After consultation it was decided to admit the patient at 37 weeks gestation for G-CSF injections. She was started initially on G-CSF 30 μg s.c. daily, which was reduced to twice weekly injections. The patient was to remain in hospital until after delivery. Following G-CSF injections her white cell count increased to 10.4×10⁹/l with 84.2% neutrophils, 8.9% lymphocytes and 6.0% monocytes. Regular MSU and throat swabs were sent and all were negative. The only side-effect noted for treatment in this patient was severe generalized bone pain. This is a well-recognized (but not understood) complication of this treatment and is thought to be related to cytokine production. This was an effect that had been noted previously in this patient and now required morphine for analgesia. At 38+ weeks gestation it was decided to deliver her by elective lower segment Caesarean section (LSCS), as the risks to this particular patient from elective LSCS were fewer than the risks of sepsis from a prolonged labour, with repeated vaginal examinations and the risk of emergency Caesarean section.

A routine LSCS was performed electively on 4th March, 1994. A healthy boy, weighing 3350 g was delivered.

After delivery she continued to receive G-CSF. This maintained her white cell and neutrophil count. The puerperium was uneventful and she was allowed home on day 7. G-CSF was continued for a further 3 weeks until wound healing had occurred and the lochia had settled.

The baby was breastfed and his white cell count was checked on the third day of life. This was normal (11.4×10⁹/l, with 40% neutrophils).

Discussion
Pregnancy has been reported in patients with cyclic neutropenia (Polez et al., 1993) with an amelioration of infectious complications caused by the natural increase in neutrophil count. Initially a potentially lethal condition, severe congenital neutropenia is now compatible with a good quality life which stretches into the reproductive years. G-CSF has been used extensively to combat neutropenia as a result of cytotoxic treatment regimes for malignancy and also in patients with severe congenital neutropenia. We believe that this is the first case of G-CSF being used before conception and during pregnancy in such a patient.

Neutropenia is classically defined as a peripheral neutrophil count <2.0×10⁹/l. The role of the neutrophil in the phagocytic defences of the host is usually fulfilled if the count is >1.0×10⁹/l. Significant neutropenia is a count <1.0×10⁹/l, which results in noticeable increases in infection rates. Severe congenital neutropenia is typically characterized by profound neutropenia, resulting in major clinical infections and occasionally death. Empirical administration of broad-spectrum antibiotics is the cornerstone of treatment. If untreated these infections can be rapidly fatal.

G-CSF is a glycoprotein that regulates the proliferation and differentiation of haematopoietic stem cells and the function of mature blood cells. It increases the proliferation, differentiation and migration of neutrophils. In patients with congenital neutropenia, in the absence of an aplastic marrow, G-CSF has the potential to produce a normal neutrophil count. This is a dose-related phenomenon.

The effects of G-CSF in pregnancy have not been studied in humans. However, in rats it has been shown to cross the placenta and induce a peripheral neutrophilia and increase the neutrophil storage in the marrow and spleen of fetal and newborn rats. However, milk transference was very limited (Novales et al., 1993). One week after delivery, the baby’s white cell count was 11.4×10⁹/l, with 40% being neutrophils. The first blood sample was taken on the third day of life, but any transient neutrophilia would have been reduced by this stage. Normal breastfeeding occurred in the puerperium and the baby’s white cell count remained normal.

In children with severe neutropenia the development of G-CSF for therapeutic use has the potential to change the quality of their life dramatically. Human G-CSF is well tolerated as a long-term treatment for these patients (Welte et al., 1994). The only noticeable side-effect in our patient was that of bone pain, which was alleviated with morphine injections. We have demonstrated that G-CSF can be used safely in pregnancy and with no serious adverse effects on the mother or the baby during the pregnancy or the puerperium.

References

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