gestational-age-matched normotensive pregnant controls. Plasma ADMA was measured by high-pressure liquid chromatography[3] and was significantly lower in pregnant controls than in the non-pregnant women (figure). ADMA concentrations in patients with pregnancy-induced hypertension did not differ from those in healthy pregnant women, but in the patients with pre-eclampsia the values were significantly higher.

These preliminary data support the idea that there are changes in the endogenous inhibitors of NO in pregnancy and pre-eclampsia, which may be of pathophysiological significant importance.

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Intrauterine bone-marrow transplantation at 12 weeks' gestation

SIR—In animals, intra-uterine bone marrow transplantation (BMT) in the formation of haemopoietic chimeras is feasible without the development of graft-versus-host disease (GVHD).[1] Attempts in women have been unsuccessful, presumably because BMTs were done after 16 weeks' gestation[2,3] when the fetal immune system can reject grafts.[4] Fetal blood has phenotypically mature T lymphocytes in significant numbers only after 14 weeks,[5] suggesting that induction of tolerance to self-antigens occurs before this gestation.

A 42-year-old rhesus (Rh) D-negative mother with a homozygous D-positive husband had thirteen previous pregnancies resulting in two normal deliveries, five spontaneous abortions, and six prenatal deaths due to severe red-blood-cell isoimmunisation. At 12 weeks in her 14th pregnancy, intrauterine BMT was done to establish a stable haemopoietic chimera with Rh-negative cells in the fetus to reduce the severity of the disease or to delay fetal anaemia until intrauterine blood transfusion would be safer. Mononuclear cells were isolated from maternal bone-marrow and T cells were depleted twice.[6] The suspension ($2{\cdot}3 \times 10^7$ cells) was concentrated to 200 μL. Flow cytometry demonstrated 5% CD34 haemopoietic progenitors and under 1% CD3 T-cells. The processed marrow was injected into the fetal peritoneal cavity under ultrasound guidance via a 20-gauge spinal needle. At 20 weeks' gestation, fetal anaemia (haemoglobin 3·8 g/dL) was diagnosed by cordocentesis and corrected by transfusing freshly packed, irradiated maternal blood. Intravascular fetal blood transfusions were given another five times over 14 weeks, and a healthy boy was delivered by elective caesarean section at 34 weeks' gestation. The infant, now 11 months, is developing normally and has no features of GVHD. 1000 stimulated lymphocytes from the fetus and the neonate had a normal male karyotype. DNA fingerprinting on these samples showed no evidence of haemopoietic chimerism. The infant and mother were HLA-haploidentical.

Estimation of cytotoxic T-lymphocyte precursor (CTLP) frequencies in blood from the infant at 6 and 9 months of age demonstrated absence of reactivity (< 1 in 1000 000) against maternal antigens (expected frequency for haploidentical samples, 1 in 10 000 to 1 in 100 000),[7] and normal reactivity versus an unrelated third party. In another infant managed by intrauterine blood transfusion only, there was a normal response (1 in 80 000) to maternal antigen at 6 months. Therefore the lack of reactivity in the transplanted infant was not the consequence of repeated intrauterine blood transfusions.

These findings suggest that exposure to maternal antigens in early fetal life may have led to long-term tolerance, which is comparable to studies in mice by Billingham et al.[8] Peripheral blood chimerism may have been established in less than 1% of circulating cells, which is the level of sensitivity of DNA fingerprinting. Chimerism may be detecable as the child ages, as in studies in animal and human fetuses, where fetal donors have been used.[1,9]

When pre-immune animal fetuses are made tolerant to immunologically incompatible donor cells, postnatal transplantation of donor tissues can be done without rejection or GVHD.[8] Our findings suggest the same for the human fetus and that intrauterine BMT could find an application in the treatment of congenital disorders, such as sickle cell anaemia, β-thalassaemia, chronic granulomatous disease, and Gaucher's disease. The major barrier to postnatal transplantation is rejection of the T-lymphocyte-depleted bone marrow, because in 70–80% of cases an HLA-identical sibling donor is not available. Since many hereditary disorders can now be diagnosed by chorionic villus sampling during the first trimester, intrauterine BMT would be possible by 12–13 weeks' gestation. Subsequently, definitive postnatal BMT can be done before the onset of disease-related complications and with reduced requirements for immunosuppression, as an appropriate donor is available and graft rejection is unlikely.

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