MASSIVE FOETAL HAEMORRHAGE INTO MATERNAL CIRCULATION AS A COMPLICATION OF CHORIOCARCINOMA

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In nearly all previous reports of foetal haemorrhage into the maternal circulation the placenta and uterus have appeared normal (Chown, 1954, 1955; Colebatch *et al.*, 1956; Borum *et al.*, 1957; Gunson, 1957; Shiller, 1957; Zuelzer, 1957; Goodall *et al.*, 1958; McGovern *et al.*, 1958; Weiner *et al.*, 1958; Krivit *et al.*, 1959; Nevanlinna, 1959; Finn *et al.*, 1961a). In two cases old or recent placental haemorrhages were observed (Chown, 1955; Pearson and Diamond, 1959), and in another case the placenta was thought to have been damaged by a Drew Smythe catheter (Apley *et al.*, 1961).

The present report is thought to be the first in which massive foeto-maternal "transfusion" occurred during a pregnancy complicated by a choriocarcinoma.

Case Report

The mother was a primigravida of 22 years and in good health. She was of blood group A, rhesus (D) negative. The pregnancy was normal until the 35th week, when the patient complained of vomiting, frequency, pain on micturition, and pain in the loins. A urinary infection was diagnosed clinically, although she was afebrile and examination of the urine revealed no abnormality. She was treated with nitrofurantoin 100 mg. eight-hourly, her symptoms subsiding after four days. At no time were abnormal antibodies demonstrated in her blood. Premature labour began with a "show" at 36 weeks on April 27, 1961, and regular contractions started next day. Spontaneous delivery of a pale infant, male, weighing 6 lb. 3 oz. (2,800 g.) occurred on April 29, the membranes having ruptured 12 hours earlier. The loss of blood was average at all stages of labour. Respiration became established after three minutes.

The infant's liver and spleen were not palpable. He was group O, rhesus (D) negative. The total bilirubin in the cord blood was 2.3 mg./100 ml. (indirect 0.7 mg./100 ml.). There was evidence of rapid blood regeneration, the nucleated red cell count being 210/100 white cells. The haemoglobin (Hb) at 22½ hours was 6.8 g./100 ml. (44%). The red cells showed anisocytosis and polychromasia. Haemolytic disease of the newborn due to rhesus incompatibility was excluded by a negative anti-human-globulin (Coombs) test. There were no signs of shock, and the infant took his feeds well. His Hb levels on May 1, 2, and 4 were 9.3 g./100 ml. (60%), 8.6 g./100 ml. (55%), and 7.6 g./100 ml. (49%) respectively. On May 5 a blood transfusion of 53 ml. of packed cells was given through the umbilical vein, and on the following day the Hb had risen to 15.6 g./100 ml. (100%). Subsequently progress was normal.

Foetal haemorrhage into the maternal circulation was proved by demonstrating that on the fifth day post partum

3.35% of red cells in the maternal circulation were foetal, using the Kleihauer (Kleihauer *et al.*, 1957) technique (Zipursky *et al.*, 1959; Finn *et al.*, 1961b), and by the finding of an elevated foetal Hb (FHB) of 8% in the mother (normal 1.4%). The FHB of the infant was 66%.

The puerperium was uneventful except for persistence of a brown vaginal discharge. At post-natal examination in the sixth week involution appeared complete, abdominal and pelvic examinations being normal.

Three months after delivery a dilatation and curettage was performed at another hospital because of irregular vaginal bleeding. Histologically the curettings showed a fair amount of syncytium and membrane, but no evidence of malignant degeneration was seen. However, a month later a total hysterectomy was performed as an emergency because of intractable uterine haemorrhage. The uterus was found to contain an advanced choriocarcinoma. Pulmonary metastases were evident on chest x-ray.

Estimation of Size of Haemorrhage and Survival of Foetal Cells

Assuming the average Hb of a full-term infant to be 19.85 g./100 ml. (Smith, 1959), and the blood volume of our infant to be 348.9 ml. (Mollison *et al.*, 1950; Sisson *et al.*, 1959), the loss of blood from the infant calculated from the Hb at birth would have been about 229 ml. Assuming that the placenta contained 125 ml. of blood (Smith, 1959) and that the Hb of the placental blood was the same as that of the infant, the loss from the placenta would have been 82 ml. and the total loss from the combined foetal and placental circulation 311 ml.

The Chart shows the rate of fall of foetal cells and FHB in the maternal circulation. It will be seen that the proportion of foetal to adult cells in the mother's blood fell from 3.35% on the fifth day to 0.5% on the 76th day after delivery, while the FHB fell from 8% on the fifth day to 1.6% on the 93rd day. This suggests that foetal cells survived about 80 days post partum. The rate of disappearance of foetal cells from the maternal circulation after foeto-maternal transfusion has been variously estimated previously, using either the rate of fall of FHB or quantitative differential agglutination, as 80 days (Gunson, 1957), 100 days (Pearson and Diamond, 1959), and about 100 days (estimated from the Figure in the article by Nevanlinna, 1959). Using ⁵¹Cr, Hollingsworth (1955) estimated the survival of foetal cells in the adult circulation as about two-thirds

Rate of fall of foetal cells and foetal haemoglobin in the maternal circulation after delivery.

that of adult cells; but this is probably an underestimate, since ^{51}Cr is eluted approximately three times as fast from foetal as from adult cells (Suderman *et al.*, 1957). With differential agglutination, however (Seelemann, 1954; Mollison, 1956), the foetal red-cell life in the adult circulation has been found to be similar to that of adult cells. Assuming, therefore, this survival to be about 120 days, the foeto-maternal transfusion in the present case would have occurred about 40 days before birth, since there is no reason to suppose that the foetal cells were haemolysed at an excessive rate. This estimate, however, can only be approximate, since the mother continued to bleed from her uterus throughout the period when cell counts were made and since maternal haemopoiesis was probably accelerated because of the haemorrhagic anaemia. If foeto-maternal transfusion occurred several weeks before birth, foetal haemopoiesis was probably also accelerated and the haemorrhage was almost certainly spread out over several days, since a sudden blood loss of 200–300 ml. would not have been compatible with survival. The absence of clinical signs of oligaemic shock at birth supports the contention that the greater part of the haemorrhage occurred at least some days before birth.

Assuming a constant rate of fall, it can be estimated that at the time of birth approximately 3.6% of cells in the maternal circulation were foetal. If the mother's blood volume at term was 6 l. (Dieckmann and Wegner, 1934) the foetal cells represent 205 ml. of blood.

Contrary to former belief, small foetal haemorrhages into the maternal circulation are probably quite frequent. Using the Kleihauer technique, foetal cells have been demonstrated in the maternal circulation in 37% (Kleihauer and Betke, 1960), 11.7% (Finn *et al.*, 1961b), and 18% (Taylor and Kullman, 1961) of pregnancies. These figures are probably too low, since when foetal cells are incompatible with the mother's blood they will be rapidly eliminated and such cases will remain undetected (Finn *et al.*, 1961b). O'Connor *et al.* (1957) have demonstrated a relation between anaemia in the newborn and an elevated FHB in the mother.

The precise mechanism by which foetal cells cross the placental barrier is not known, but they are commonly found in the maternal intervillous spaces of the normal placenta (Kline, 1948). Since small foeto-maternal transfusions occur frequently during normal pregnancies, it can be readily understood how a large foetal haemorrhage into the maternal circulation may occur when a malignant growth of trophoblastic tissue arising from the foetus invades the uterine muscle and maternal vascular spaces. Choriocarcinoma is characterized by such invasive properties and by areas of haemorrhage and necrosis (Novak and Seah, 1954).

An elevation of FHB in four women whose pregnancies were complicated by hydatidiform moles was reported by Bromberg *et al.* (1957). The authors considered, however, that there had been an increased production of FHB by the mothers and that transplacental haemorrhage could not have occurred since no embryo was present.

There have been several reviews of choriocarcinoma (Teacher, 1903; Pollosson and Violet, 1913; Szathmary, 1930; Park and Lees, 1950; Novak and Seah, 1954) and metastases have been reported in the foetus (Daamon *et al.*, 1961), but foetal haemorrhage into the maternal circulation has not been observed previously as a complication.

Summary

A case is reported of massive foetal haemorrhage into the maternal circulation complicating choriocarcinoma.

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A film of the Hull poliomyelitis vaccination campaign is now available from the Pfizer Film Library to medical officers of health. The film shows in documentary form the way in which the Public Health Department at Kingston-upon-Hull set about the task of vaccinating the whole of the city's population. It ends with a discussion of many points of interest concerning the organization of a vaccination campaign using oral vaccine. The film (16 mm. black-and-white) lasts about 20 minutes and is available on free loan from Medical Film Library, Pfizer Limited, Sandwich, Kent.