Attention is directed to the frequent presence of a loud souffle heard over the small area of abdominal wall overlying the hypertrophied vessels supplying the placenta.

While most cases should be dealt with by immediate laparotomy, it may be justifiable on some occasions and with adequate safeguards to allow the pregnancy to continue until the foetus is certainly viable. When the foetus has just died it may be safer to defer operation until the placenta has become avascular.

It is suggested that, whenever possible, the placenta should be removed together with the structures to which it is attached. The special case of the placenta situated within the broad ligament is described. Severe retro-placental bleeding seems inevitable in such circumstances.

A preliminary report of histological studies of the implantation of the extrauterine placenta is included. The problem of how the placenta maintains its precarious attachment until late pregnancy is raised but not solved.

Our thanks are due to our colleagues past and present, notably Professor J. H. M. Pinkerton and Dr. G. T. M. Cummins, who have shared with us the tribulations and rewards of these cases. We are especially indebted to Dr. W. B. Robertson for his invaluable help and advice on the histology.

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"In the years during which I was surgeon to the Albert Dock Hospital (1919 to 1956), I saw many changes in the Health Faculty of my patients. An observer, if he could see and compare the out-patient department of fifty years ago with that of to-day would, I think, be struck first by the revolution in personal cleanliness. In my young days the patient had to be scrubbed before being admitted to bed in the general ward. Their bodies were not just soiled with the dust and sweat of the day's work, but were ingrained with the grime of weeks of neglect. Women, if anything, were worse than men with their greasy straggly rat-tails of hair covered with equally greasy cloth caps. No woman was admitted until her head had been deloused. All patients were verminous." (*The Health of the Dock Worker*, Sir Hugh Griffiths. National Dock Labour Board, Education Booklet No. 2.)

D

CLINICAL ANALYSIS OF 100 CASES OF SEVERE MEGALOBlastic ANAEMIA OF PREGNANCY

BY

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The purpose of this paper is to report on the medical and obstetrical aspects of 100 cases of severe megaloblastic anaemia of pregnancy which have been diagnosed in a six-year period (1953 to 1958 inclusive) at the Rotunda Hospital, Dublin. The findings are compared with those of several similar studies made recently in other centres. The importance of this condition as a cause of maternal and foetal complications is discussed.

Incidence and Degree of Anaemia

It is now realized that megaloblastic anaemia is a comparatively common complication of pregnancy. This series of 100 cases represents an incidence of 1 in 240 confinements (Table I). This figure is slightly lower

TABLE I.—Incidence of Megaloblastic Anaemia at Rotunda Hospital

Year	No.	Year	No.
1953	15	1957	22
1954	13	1958	21
1955	12		
1956	17	Total	100

Incidence approximately 1 in 240 pregnancies. 23 cases occurred in primigravidae.

than the true one because some cases which were delivered on the hospital district were not included owing to incomplete documentation. Higher incidences of this complication have been reported by other workers: Forshaw (1958) found an incidence of 1 in 67 hospital confinements, and Giles and Shuttleworth (1958) found a frequency of megaloblastic anaemia as high as 2.8% of hospital confinements. It seems that the marrow may become megaloblastic in pregnancy with a relatively high haemoglobin (Forshaw *et al.*, 1957), and therefore such patients may in fact be physically well and not in need of treatment. It is emphasized that all cases here reported were clinically anaemic or ill, and that each represented examples of the disease of moderate or severe degree. Each case was a practical problem requiring immediate treatment. Table II shows the degree of anaemia in these cases at the time of diagnosis.

TABLE II.—Degree of Anaemia When Diagnosed

Hb (g.)	No.	Hb (g.)	No.
2.0-2.9	1	6.0-6.9	18
3.0-3.9	5	7.0-7.9	28
4.0-4.9	10	8.0-8.9	15
5.0-5.9	22	9.0-9.9	1

Seasonal Incidence.—In 1957 Thompson, reporting a series of 100 cases from Newcastle taken from the records of over twenty years, found an increased incidence of the disorder during the winter and spring months. He believed that this suggested that dietary deficiency was at least a contributory cause of this disorder. Forshaw (1957) found a similar seasonal incidence amongst his cases, but this was not found by

Giles and Shuttleworth (1958) nor by Mollin *et al.* (1959). In our series a convincing seasonal pattern was not shown.

Recognition and Diagnostic Criteria

Approximately 30% of these cases presented as patients with progressive anaemia of pregnancy which had failed to respond to oral or parenteral iron. In many other cases anaemia was not the presenting problem, and more prominent features were such symptoms as vomiting, diarrhoea, and pyrexia (Table III). Oedema and albuminuria at some stage were

TABLE III.—Symptoms Other than Those of Anaemia (100 Cases)

Oedema	51	Pyrexia	71
Albuminuria	44	Urinary infection ..	11
Hypertension	23	Diarrhoea	10
Vomiting	17		

particularly common. This led to some of these cases being mistaken initially for toxæmia of pregnancy (see below). Vomiting, pyrexia, urinary infection, and diarrhoea were present in a smaller proportion of cases, particularly in the puerperium, and often led to delay in diagnosis.

Final diagnosis was established in all cases by the finding of megaloblasts in the bone marrow, or in the peripheral blood by examination of the buffy coat. In all these cases 20 mg. of folic acid daily caused a reticulocyte response and a rise in haemoglobin level.

TABLE IV.—Associated Conditions

Carcinoma stomach ..	1	Urinary infection ..	11
Hodgkin's	1	Epilepsy	3
Lymphadenopathy ..	1		

Associated Conditions (Table IV)

Megaloblastic anaemia may occasionally arise in pregnancy as a complication of some other disease. Carcinoma of the stomach presented in this way in one patient, and another patient with Hodgkin's disease developed megaloblastic anaemia. Urinary infection has already been mentioned, and the incidence in megaloblastic anaemia is undoubtedly higher than normal. Three out of 100 cases of megaloblastic anaemia were under treatment for epilepsy. This incidence is very much higher than the average incidence of epilepsy in the overall attendance at the hospital over the period under study, which was about 1 in 400. It has been shown in recent years that certain anticonvulsants can cause the development of megaloblastic anaemia (Badenoch, 1954; Berlyne *et al.*, 1955; Hawkins and Meynell, 1958). It seems likely that the administration of these drugs was a factor in the development of megaloblastic anaemia in these cases. This aspect is fully discussed in a separate publication (Gatenby, 1960).

Time of Diagnosis

In earlier papers on this subject diagnosis was made more often during the puerperium (Davidson *et al.*, 1942; Miller and Studdert, 1942). More recently, as the anaemia is being watched for more closely, nearly half these cases are being recognized antenatally. In this series 41 of 96 were diagnosed before delivery (Table V). Giles and Shuttleworth (1958) by intensive investigation managed to find 62 antenatal cases as against 28 in the puerperium. Chanarin *et al.* (1959) have summarized

TABLE V.—Time of Diagnosis

	Pregnancy (41 Cases)											Puerperium (48 Cases)						
Weeks	30	31	32	33	34	35	36	37	38	39		1	2	3	4	5	6	7
Number	1	0	2	1	2	1	8	4	10	12		24	13	5	3	1	1	1

the findings in relation to time of diagnosis from 20 reports in literature. Their tabulation shows clearly that most of the cases recognized before delivery are diagnosed between 31 and 40 weeks' gestation. All our antenatal cases were found during this period, and most of these were during the last four weeks of pregnancy. The puerperal cases are usually recognized within the first fortnight (Table V) after delivery.

Obstetrical Aspects

Toxaemia.—The association of megaloblastic anaemia of pregnancy with toxæmia has been noted on many occasions (Davidson *et al.*, 1948; Scott and Govan, 1949; Giles and Shuttleworth, 1958; Tacchi, 1958). Difficulty may arise in differentiating the two conditions owing to the frequency of oedema and albuminuria in patients with megaloblastic anaemia. In this series oedema was noted in 51 cases and albuminuria in 44. Hypertension (B.P. of 140/90 or greater on one or more occasions) was noted in 23 patients. It is felt that whenever hypertension is present the cause must be regarded primarily as one of toxæmia, but when oedema and/or albuminuria occurs without hypertension these features may be due to, or directly associated with, the anaemia itself, and the case cannot be regarded as one of toxæmia. Thus in the present study hypertension alone occurred in 23% of cases, hypertension with oedema or albuminuria in 22%, and hypertension, oedema, and albuminuria in 14%. The hospital incidence of toxæmia over the same period was approximately 6%, thus, whichever criterion of toxæmia is accepted, it would appear that it is much more frequent in association with megaloblastic anaemia.

Parity.—There were 23 primigravidae in this group of 100 cases. In the remainder full-time parity varied from 2 to 16. The average figure for the whole group was 3.8.

Twins and Hydramnios.—An increased incidence of multiple pregnancy has been mentioned by several authors (Thompson, 1957; Giles and Shuttleworth, 1958; Tacchi, 1958; Chanarin *et al.*, 1959). This is borne out in the present series with an incidence of 8% (twins, 7; triplets, 1). An association with hydramnios has not been previously recorded. Hydramnios was noted in nine cases whereas the general hospital incidence is in the region of 1.2%. This high incidence cannot be explained by the frequency of multiple pregnancy as only two of these cases were multiple pregnancies (twins, 1; triplets, 1), and thus it was found in seven cases of single pregnancies. One of these was a case of hydrops foetalis, but there was no foetal abnormality in any of the remaining six.

Premature Labour.—Premature labour is said to be common in this group (Stevenson, 1938; Callender, 1944). Tacchi (1958) reported 18 out of 52 who were delivered before the 38th week. In the present series, 22 out of 80 known cases were delivered before the 38th week, an incidence of 27%. On the other hand, 23 infants from 17 pregnancies were premature by weight, that is, less than 5½ lb. (2.5 kg.). As these figures were taken from a total of 88 known cases the premature incidence was 19.3%. Excluding multiple pregnancies, the premature incidence in single pregnancies was 12.5%. The incidence of prematurity (by weight) in the hospital is approximately 8%, and therefore there is an increased incidence of premature labour and prematurity even when multiple pregnancy is excluded.

Haemorrhage.—Badenoch *et al.* (1955) reported two cases of post-partum haemorrhage out of nine cases under review and drew attention to this high incidence. In the present series there were two cases of P.P.H.—one traumatic following normal delivery and the other secondary. This incidence corresponds with the general incidence of P.P.H. in the hospital, which is approximately 2.2%. Considering the supposedly high incidence of toxæmia, accidental haemorrhage was not unduly common, and was seen on two occasions. There was one case of placenta prævia.

Duration of Labour.—In 8% of cases the duration of labour exceeded 24 hours, but in only one case did it exceed 48 hours. This is of little significance, as the hospital incidence of prolonged labour (greater than 48 hours) is approximately 1.7%. However, the general impression was that labour is usually short and the preponderance (increased incidence) of multiparity is probably a sufficient explanation.

Method of Delivery.—The only finding of any significance so far as method of delivery is concerned was a relatively lowered incidence of forceps delivery (10% against a general incidence of 13–16%). This again is probably explained by the increased multiparity.

Induction of Labour.—Induction of labour is generally better avoided in these cases. Occasionally, for some associated reason, it becomes necessary, and in this series 8% of cases were induced (five surgical inductions and three medical inductions). This corresponds with the general incidence, which for surgical induction is approximately 6–7%.

Stillbirths and Neonatal Deaths.—In the series there were three stillbirths, none of which could be ascribed to the anaemia, and the incidence corresponds with the hospital stillbirth rate of 2.9%. As would be expected, considering the high incidence of prematurity, the neonatal death rate was increased. There were six neonatal deaths—five due to prematurity and one to anencephaly. The hospital neonatal death rate is approximately 1.5%, and the high incidence of 6% is entirely explained by the frequency of premature labour, prematurity, and multiple pregnancy.

Pyrexia and Morbidity.—The association of pyrexia has been frequently noted (Dockeray, 1938; Ungley, 1938; Miller and Studdart, 1942; Callender, 1944). Pyrexia was found in 71% of cases and puerperal morbidity in 30%.

Maternal Mortality.—There were two deaths in the 100 cases, not from anaemia, but, from underlying malignant disease. One was a case of Hodgkin's disease and the other carcinoma of the stomach. Both cases presented with megaloblastic anaemia.

Recurrence of Megaloblastic Anaemia.—This was not common. Megaloblastic anaemia occurred in a second pregnancy in four cases in the six-year period.

Discussion

Megaloblastic anaemia promptly responds to folic acid, and Chanarin *et al.* (1959) have shown that there is clearly a folic acid deficiency of the tissues in this disease. Lack of sufficient folic acid in the diet to meet the demands of pregnancy could certainly cause anaemia, and this would explain the high incidence in multiple pregnancy. However, no clear relationship between inadequate diet and the incidence of this anaemia has yet been demonstrated in these islands. Impaired

absorption of folic acid or interference with its metabolism may be important in many cases. Certainly this anaemia may occur in women, who apparently have had adequate nourishment before and during their pregnancies.

Over the last few years evidence has been gathered from many different centres in the British Isles that megaloblastic anaemia occurs as a complication in pregnancy much more frequently than was formerly thought. In our experience 1 in 240 pregnant women will have serious anaemia of this type, and milder degrees of the same condition must occur quite often. Apart from causing a period of serious ill-health in the mother, there is an increase in neonatal deaths due to the high rate of prematurity in this group. There is also an associated increase in the incidence of hydramnios and multiple pregnancy, which in turn may be partly responsible for the higher incidence of toxæmia.

The prevention of megaloblastic anaemia by the routine administration of folic acid in pregnancy would seem an obvious solution to this problem. Some have accepted this principle (Lowenstein *et al.*, 1955; Francis and Scott, 1959). The main disadvantage in the prophylactic use of folic acid therapy is that megaloblastic anaemia not caused purely by the demands of pregnancy will be masked and lead to delay in recognizing the underlying cause, which may be serious. Admittedly this is a small group, but malignant disease occurring in pregnancy may first manifest itself by megaloblastic anaemia (as in two of our cases). Again, there is always the possibility of an Addisonian anaemia being masked, and it is well known that folic acid may precipitate serious neurological changes; but this anaemia is very rare in pregnancy, and we have seen only one case since 1953. On the whole the argument in favour of routine antenatal administration of folic acid is very strong, and probably this procedure will be adopted more widely in the future. It is suggested, at any rate, that in all cases of multiple pregnancy supplementary folic acid should be given.

Summary

The incidence, clinical features, and obstetrical aspects of 100 cases of severe megaloblastic anaemia in pregnancy and the puerperium occurring over a six-year period (1953 to 1958 inclusive) at the Rotunda Hospital, Dublin, are recorded. The incidence has been 1 in 240 confinements, and is associated with an increase in the neonatal death rate (6%), largely due to prematurity.

The advisability of using folic acid as a routine prophylactic in pregnancy is discussed.

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MEGALOBlastic ERYTHROPOIESIS IN PREGNANCY

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During recent years a great deal of attention has been paid to the problem of anaemia in pregnancy. In the antenatal clinic of Sunderland Maternity Hospital, which caters for about 1,800 cases a year, 25% of mothers have at the 32nd week of pregnancy haemoglobin levels below 70%, which Whitby and Britton (1957) regard as the lower limit of normality. Undoubtedly most cases of anaemia in late pregnancy are due to iron deficiency, but there is a growing volume of opinion that many cases are anaemias of megaloblastic type.

As recently as 1951 Thompson and Ungley described 45 cases of megaloblastic anaemia of pregnancy collected over a period of 17 years, while Clark (1952) reported 18 cases in a 7½-year period, an incidence of one case in 1,708 hospital deliveries. During the last five years Lowenstein *et al.* (1955), Scott (1957), Cowan (1957), Forshaw *et al.* (1957), and Forshaw (1958) have reported a much higher incidence of this condition. Giles and Shuttleworth (1958) found one case in 39.5 hospital deliveries, and consider this to be an underestimate of the real incidence.

This increase in the described frequency of megaloblastic anaemia of pregnancy is probably due to increased haematological supervision of expectant mothers at antenatal clinics. Formerly a clinical state of severe illness in pregnancy was described, whereas more recent studies are based on haemoglobin levels, irrespective of symptoms and clinical condition of the patients.

Chanarin *et al.* (1959) produce convincing evidence that megaloblastic anaemia of pregnancy is due to a deficiency brought about by poor absorption of folic acid by the mother or by insufficient dietary supply to meet the needs of mother and foetus. In any deficiency disease, for every case of severe deficiency there must be many cases in which the lack is moderate or even very slight. Goodall (1957) describes cases of moderate

anaemia of pregnancy without megaloblastic erythropoiesis but which respond only to folic acid. On the other hand, we have found cases with megaloblastic marrows without anaemia, and because of this we have attempted to assess the frequency of this condition by regular haematological studies on all patients attending antenatal clinics at Sunderland Maternity Hospital over the period of 12 months from September, 1958, to September, 1959.

Method

To reduce the incidence of iron deficiency all patients were given routine oral iron (usually "fergon" tablets, one thrice daily) at first attendance at the antenatal clinic when a haemoglobin estimation was performed. At about the 30th week of pregnancy a further haemoglobin estimation was done, and patients with a level of 70% (10 g./100 ml.) or less had P.C.V. and M.C.H.C. estimations and a stained blood film was examined. Patients showing iron deficiency were given 1 g. intramuscular iron ("imferon") in four divided doses and were re-examined in four weeks (haemoglobin, P.C.V., M.C.H.C., and blood film). On admission to hospital at term or for other obstetrical reasons a haemoglobin and blood film from all mothers was examined.

At any stage particular attention was paid to the following features in the blood films.

1. A normochromic normocytic film with haemoglobin below 70% even after intramuscular iron therapy.
2. Hypersegmented neutrophils.
3. Howell-Jolly bodies.
4. Large erythrocytes (macrocytes), even though they be few.
5. Numerous very large fully haemoglobinized erythrocytes, usually about 12 μ in diameter, were sometimes found after intramuscular iron therapy. This "exaggerated response" to iron is strikingly different from the normal response to iron. It is almost certainly the same feature described by Scott (1954) after intravenous iron therapy in some cases of antenatal anaemia.

If one or more of these features were seen in any blood film a marrow biopsy was carried out.

At least four marrow smears were stained by the May-Grünwald-Giemsa method or by Leishman's stain. Marrow fragments aspirated were sectioned, using the method of Cappell *et al.* (1947), and stained with haemalum and eosin and for iron (Hutchison, 1953).

Results

Marrow Findings.—During the 12 months there were 1,996 hospital deliveries, and 95 marrow biopsies were performed for one or more of the reasons mentioned. 73 cases showing megaloblastic erythropoiesis (40 frankly so, and 33 showing transitional or intermediate change). Two further cases without marrow biopsies are included in the series; both had severe anaemia with megaloblasts in the peripheral blood. The incidence of megaloblastic erythropoiesis is therefore 1 case in 26.6 deliveries. Of the 73 megaloblastic marrows, 56 were associated with a marked cellular hyperplasia and virtually complete absence of fat spaces; the remaining 17 showed a normal histological picture. Iron could be demonstrated in 16 cases only (10 frankly megaloblastic and 6 transitional); the amount was always very small.