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SHORT REPORT

Pregnancy and severe aplastic anaemia: causal relation or coincidence?

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Summary. The relationship between aplastic anaemia (AA) and pregnancy remains uncertain. To assess whether an association between pregnancy and severe aplastic anaemia (SAA) exists, we compared the frequency of pregnancy in 35 young women with newly diagnosed SAA with the expected frequency in the general population. The observed pregnancy rate in the SAA group was 3–6%. This percentage approximates the expected pregnancy rate of 4·4% in the general population and is not compatible with a strong association between pregnancy and SAA.

Keywords: aplastic anaemia, pregnancy.

Aplastic anaemia (AA) is a rare disease characterized by pancytopenia and a hypocellular bone marrow (Young & Alter, 1994). It was first defined as a clinical entity by Ehrlich (1888), in a pregnant woman. Since that time 61 cases of AA in pregnancy have been documented (Rovinsky, 1959; Knispel *et al*, 1976; Suda *et al*, 1978; Aitchison *et al*, 1989; van Besien *et al*, 1991; Pajor *et al*, 1992). The relationship between pregnancy and AA has remained a matter of speculation. Knispel *et al* (1976) doubted the causal relation between pregnancy and AA. However, pregnancy is still mentioned in a recent review article (Young & Maciejewski, 1997) as one of the possible causes of acquired aplastic anaemia. In this study we attempt to assess whether there is an association between pregnancy and AA and compare our results with previous reviews. To avoid questionable cases and any dilution of effect, we selected only women with severe aplastic anaemia (SAA).

PATIENTS AND METHODS

Between August 1972 and November 1996, 124 patients (69 men and 55 women) were referred to the University Hospital Leiden with a diagnosis of SAA. Only women in their reproductive period (age 15–44 years) at the time of diagnosis were included in the study. SAA was defined as pancytopenia with at least two of the following abnormalities: an absolute neutrophil count of $< 0{\cdot}5 \times 10^9$/l, a platelet count of $< 20 \times 10^9$/l, and anaemia with (haematocrit corrected) reticulocytes < 1%, in association with either a bone marrow cellularity of < 25% or a bone marrow cellularity < 50%, but with < 30% haemopoietic cells.

From the medical records we reviewed whether patients were pregnant or in the puerperium (6 weeks postpartum) at time of diagnosis. The percentage of pregnancies in this SAA group was compared with the percentage of pregnancies in the general female population of reproductive age using data from the annual reports from the Centraal Bureau voor de Statistiek (CBS, 1993). The expected number of pregnant women was estimated from the number of 56·5 newborn in the Netherlands per 1000 women aged 15–44 years in 1980. This number was supplemented with the number of 6·6 stillborn per 1000 newborn in 1980. The proportion of women in pregnancy was estimated as 0·044 women aged 15–44 years in 1980 ($56{\cdot}9 \times 280/365\,000$). The same proportion was found when this calculation was made for 1990.

RESULTS

Of the 55 women with SAA, 35 were of reproductive age (age 15–44 years) at the time of diagnosis. The mean age was 27 years. None of them had a history of exposure to toxins, viral infection or hepatitis. One woman was at 26 weeks gestation when the diagnosis of SAA was made. After delivery of a healthy child at 35 weeks, treatment was initiated, followed by a complete remission. Although this woman became pregnant another four times, she never had a relapse of her SAA. A second woman was 2 months postpartum after an uncomplicated pregnancy and delivery of her second child (no direct postpartum haematology values available), when haemorrhagic diathesis developed. The diagnosis SAA was

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made 2 months later. A third woman was 4 months postpartum after the birth of her second child when the diagnosis of SAA was made. The pregnancy and delivery had been uncomplicated and the haemoglobin level directly postpartum was 12·9 g/dl. Because the diagnosis of SAA was made postpartum, both the latter cases were considered at first not to be pregnancy related. Thus, of the 35 women in their reproductive age only one (3% [CI 0·07–14·9%]) was pregnant at the time of diagnosis when very strict criteria were used. If one takes into account that the SAA in the second woman might have started during pregnancy, the maximal prevalence is 2/35 (6% [CI 0·7–19·1%]). In the third woman the knowledge of a normal haemoglobin level directly postpartum militates against the existence of SAA at that time. The confidence intervals largely overlap with the expected pregnancy rate of 4·4% in the general female population of this age group.

During the follow-up period (median 9 years, range 9 months to 24 years) six women had in total 11 pregnancies. None of these pregnancies led to a relapse of SAA.

DISCUSSION

We found no association between pregnancy and the development of SAA or a relapse of this disease. Many case reports (Rovinsky, 1959; Knispel *et al*, 1976; Suda *et al*, 1978; Aitchison *et al*, 1989; van Besien *et al*, 1991; Pajor *et al*, 1992) on AA in pregnancy have been published, but not all concerned severe AA. Nevertheless, we limited our study only to SAA because the diagnostic criteria for SAA are more strict and uniform.

We found only one epidemiological survey in which pregnancy was studied as a possible aetiologic factor in AA (Mary *et al*, 1997). In a 3-year prospective multicentric study concerning incidence, patient follow-up, and suspected aetiology in aplastic anaemia, Mary *et al* (1997) reported two pregnancy-associated cases in 32 women aged 15–44 years (6%). This percentage was within the range of the percentages found, both in the patient group and the general population.

Since pregnancy is age related we wanted to make sure that we compared groups of the same age. The mean age of the SAA group at diagnosis was 27 years. This was comparable to the mean age of a mother at time of birth of a child in the general female population: in The Netherlands age at childbirth ranged from 27·5 years in 1980 to 29·2 years in 1990 (CBS, 1993).

It is unclear why, for so many years, pregnancy has persistently been mentioned as an aetiologic factor in AA. Possibly, since the first reported case of AA by Ehrlich (1888) was associated with pregnancy, clinicians focused on pregnancy and assumed a causal relation. This view was supported by descriptions of spontaneous haematological improvements following (induced) abortion or delivery, and relapses during subsequent pregnancies (Aitchison *et al*, 1989). In addition, pre-existing aplastic anaemia sometimes worsened in pregnancy (Fleming, 1973).

An alternative explanation for these observations is that patients with AA cannot respond to the stress of pregnancy with a normal marrow response, which will result in a worsening of pre-existing but undiagnosed pancytopenia. In addition, it is likely that the damaged bone marrow of patients with AA in remission can also not respond normally to the stress of pregnancy which might result in a decrease in circulating blood cells (Aitchison *et al*, 1989). More evidence against an association between pregnancy and AA includes that AA associated with pregnancy shows no predeliction for a specific period: the disease develops either early or late in the gestational period, as well as in a first or in later pregnancies (Rovinsky, 1959; Knispel *et al*, 1976; Aitchison *et al*, 1989; van Besien *et al*, 1991; Pajor *et al*, 1992). Moreover, in only one third of cases the aplasia resolved spontaneously after abortion or delivery (Fleming, 1973; Suda *et al*, 1978; Aitchison *et al*, 1989). Finally, the prevalence of AA is equally distributed among men and women (Young & Alter, 1994).

Although the percentage of pregnant women does not deviate from the expected, neither in our study nor in the studies found in the literature, a small contribution of pregnancy to the development of SAA cannot be excluded. Nevertheless, we maintain that there is no conclusive evidence to implicate pregnancy as an aetiologic agent in the pathogenesis of aplastic anaemia.

REFERENCES

Aitchison, R.G.M., Marsh, J.C.W., Hows, J.M., Russell, N.H. & Gordon-Smith, E.C. (1989) Pregnancy associated aplastic anaemia: a report of five cases and review of current management. *British Journal of Haematology*, **73**, 541–545.

CBS (1993) Geboorte, sterfte, migratie, huwelijkssluiting en huwelijksontbinding. *Statistisch Jaarboek 1993* (ed. by Centraal Bureau voor de Statistiek), p. 36. SDU uitgeverij, 's-Gravenhage.

Ehrlich, P. (1888) Ueber einen Fall von Anämie mit Bemerkungen über regenerative Veränderungen des Knochenmarks. *Charité-Annalen*, **13**, 300–309.

Fleming, A.F. (1973) Hypoplastic anemia in pregnancy. *Clinics in Hematology*, **2**, 477–496.

Knispel, J.W., Lynch, V.A. & Viele, B.D. (1976) Aplastic anemia in pregnancy: a case report, review of the literature, and a re-evaluation of management. *Obstetrical and Gynecological Survey*, **31**, 523–528.

Mary, J.Y., Baumelou, E. & Guiguet, M. (1997) Epidemiology of aplastic anemia in France: a prospective multicenter study. *Blood*, **75**, 1646–1653.

Pajor, A., Kelemen, E., Szakacs, Z. & Lehoczky, D. (1992) Pregnancy in idiopathic aplastic anemia (report of 10 patients). *European Journal of Obstetrics, Gynecology and Reproductive Biology*, **45**, 19–25.

Rovinsky, J. (1959) Primary refractory anemia complicating pregnancy and delivery. *Obstetrical and Gynecological Survey*, **14**, 149–170.

Suda, T., Omine, M., Tsuchiya, J. & Maekawa, T. (1978) Prognostic aspects of aplastic anemia in pregnancy: experience on six cases and review of the literature. *Blut*, **36**, 285–298.

van Besien, K., Tricot, G., Golichowski, A., Padilla, L. & Hoffman, R. (1991) Pregnancy-associated aplastic anaemia: report of three cases. *European Journal of Haematology*, **47**, 253–256.

Young, N.S. & Alter, B.P. (1994) *Aplastic Anemia, Acquired and Inherited*, p. 12. Saunders, Philadephia.

Young, N.S. & Maciejewski, J. (1997) The pathophysiology of acquired aplastic anemia. *New England Journal of Medicine*, **336**, 1365–1372.