Acquired anemia as a cause of female infertility

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ABSTRACT
The association between anemia and female subfertility has been largely linked to hereditary anemias such as beta-thalassemia major and sickle cell anemia. Data on acquired anemias as a cause of infertility has been scanty. This report describes two female patients with pernicious anemia (PA) and a third patient with iron deficiency anemia who suffered from primary infertility. Successful conception followed the correction of their anemia with the appropriate therapy.

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Case reports

Patient no. 1 The patient was a 26-year old woman who had been married for three years but had never been pregnant despite regular periods and frequent intercourse. Both husband and wife had been repeatedly investigated for infertility but the investigations had always given normal results except for mild macrocytic anemia. The patient attended the hospital complaining of shortness of breath on exertion, fatigue, palpitation and dizziness of three weeks’ duration. The physical examination was unremarkable except for severe pallor. Complete blood count (CBC) showed WBC 5.7 x 10^9/L, RBC 1.44 x 10^12/L, Hb 60 g/L, Hct 16.8%, MCV 116.7 fl, platelets count 148 x 10^9/L and reticulocyte percentage of 1.3%. The peripheral smear showed red blood cell (RBC) macrocytosis and hypersegmentation of the neutrophils. The bone marrow was megaloblastic. Serum vitamin B12 level was 46 ng/ml (normal 180-712). Serum and RBC folate levels were normal. The anti-intrinsic factor antibody (AIFA) and the anti-parietal cell antibody (APCA) were detectable in the patient’s serum. Fasting gastric pH was 7.0. Gastric biopsy showed chronic atrophic gastritis. Thus, the diagnosis of pernicious anemia (PA) was established. The patient was started on parenteral vitamin B12 supplementation. She became pregnant six weeks after initiation of vitamin B12 therapy when her CBC showed: WBC 7.2 x 10^9/L, RBC 4.02 x 10^12/L, Hb 109 g/L, Hct 32.4%, MCV 80.5 fl and platelets 275 x 10^9/L. The patient gave birth to a healthy baby boy at 38 weeks gestation.

Patient no. 2 A 23-year old woman who had been married for 4 years but had never become pregnant despite regular periods, frequent intercourse and lack of contraception. She presented to the hospital with a two week history of shortness of breath and dizziness. Physical examination was unremarkable except for pallor and a tinge of jaundice. CBC showed: WBC 5.1 x 10^9/L, RBC 1.19 x 10^12/L, Hb 48 g/L, MCV 114 fl, MCH 29.2 pg, MCHC 364 g/L, RDW 15.3%, platelets 297 x 10^9/L. The peripheral smear showed macrocytosis and hypersegmented neutrophils. The bone marrow was megaloblastic. Serum vitamin B12 level was 33 ng/ml (normal 180-712); serum and RBC folate levels were normal. The AIFA and APCA were detectable in the serum. Gastroscopy showed a fasting gastric pH of 7.0 and the gastric biopsy showed chronic atrophic gastritis. Thus, the diagnosis of PA was established. The patient was started on parenteral vitamin B12 therapy with remarkable improvement in her hemogram. The patient became pregnant after four months of therapy when her CBC was entirely normal.

Patient no. 3 This patient was a 25-year old married woman with no children who was being seen for severe chronic anemia. Her initial presentation to the hospital was because of a five-year history of primary infertility associated with

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regular but heavy menstrual periods. She underwent an extensive hormonal work-up for infertility but no abnormality could be identified. Investigations of the husband were also normal. Repeated courses of clomiphene were given but pregnancy did not take place. On presentation to the hematology service, she was pale and had koilonychia of the finger nails. The CBC showed Hct 20.5%, Hb 58 g/l, MCV 54.5 fl, MCH 15.5 pg, MCHC 268 g/l, RDW 23.2. The WBC and platelets counts were normal. Serum iron was 3 μmol/l (normal 14-32), total iron binding capacity (TIBC) was 77 μmol/l (normal 45-72) and serum ferritin was 3.1 μg/l (normal 8.3-115). Hemoglobin electrophoresis was normal. Thus, the diagnosis of severe iron deficiency anemia secondary to menorrhagia was established. The patient was started on ferrous gluconate (180 mg elemental iron per day) with remarkable improvement in her hemoglobin level over the following few weeks without any noticeable decrease in her heavy menses. The patient became pregnant for the first time after 3 months of iron therapy when her Hb was 126 g/l.

Discussion Two of the patients described in this report had pernicious anemia (PA) which was not thought of as a possible cause of their infertility. In fact PA is rarely included in the differential diagnoses of female infertility. This is not only because of lack of awareness of the association between PA and infertility but also because PA is rare in women in their child-bearing ages. The exact mechanism by which vitamin B12 deficiency leads to infertility is not well understood. Factors other than anemia itself must play a role in producing infertility since the latter could be encountered in the absence of severe anemia. In addition, patients may have a successful pregnancy after the initiation of vitamin B12 therapy and before the complete resolution of the associated anemia. The absence of anemia in some infertile vitamin B12 deficient patients may indicate that quantities of vitamin B12 in excess of those required for proper hematological function are needed for the establishment of pregnancy. Several abnormalities have been described in patients with vitamin B12 deficiency. These include amenorrhea, anovulatory cycles and developmental and chromosomal abnormalities in the ovum. Abnormalities in the endometrium and placenta have also been suggested.

Although autoimmunity plays a role in the etiology of vitamin B12 deficiency in PA, it seems that the vitamin B12 deficiency itself rather than autoimmunity is the major factor in the development of infertility. This assumption is based on the observation that vitamin B12 therapy resumes fertility without curing the underlying PA. In addition, folate deficiency which can lead to a megaloblastic anemia indistinguishable from that associated with PA, except for the lack of autoimmune manifestations, can also lead to a state of female infertility. Since the administration of folic acid may correct the hematological abnormalities but may precipitate serious neuropathy in patients with vitamin B12 deficiency, the safety of the prophylactic administration of folic acid to all pregnant women has been questioned. This concern seems, however, to be hypothetical since patients with vitamin B12 deficiency have a low likelihood of getting pregnant.

The third patient described in this report had severe iron deficiency anemia associated with primary infertility that resolved following the correction of iron deficiency anemia. Data on iron deficiency as a cause of infertility is scanty. Animal data suggests some correlation between the iron content of the body fluids and fertility in ruminants, since iron depletion adversely affects their reproduction. Although data on the effect of iron deficiency on human fertility is lacking, Rushton and associates reported an interesting observation while treating iron deficient women for increased scalp hair shedding. Three women with a 5 to 9 year history of infertility became pregnant on iron therapy. In addition, four other patients who did not become pregnant in the preceding 30 months, despite regular menses and unprotected intercourse, became pregnant on iron therapy as well. The authors hypothesized that iron deficiency was the major factor behind the infertility of these women.

As both vitamin B12 and iron deficiency may account for some cases of female infertility, we would recommend that physicians should consider them when evaluating anemia in an infertile woman. Vitamin B12 level should probably be also checked in any woman, with unexplained infertility, even in the absence of significant anemia, since subclinical deficiency of this vitamin could be the cause of infertility. The absence of frank macrocytosis in an anemic infertile woman should not be taken against the possibility of vitamin B12 deficiency since macrocytosis could be masked by coexisting iron deficiency or concurrent thalassemia minor.

References

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