Pernicious Anemia, Vitiligo, and Infertility

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Abstract: Though rarely encountered in women of childbearing age, untreated pernicious anemia has been found to be a cause of infertility. Once treated, conception often occurs within months. The case presented here is a woman who had a restoration of fertility after initiation of vitamin B₁₂ treatment for vitiligo-associated pernicious anemia. Previous reports have shown the occurrence of pregnancy in treated pernicious anemia, but none has indicated the presence of vitiligo in the same patient. Pernicious anemia is a rare but treatable cause of infertility in women. (J Am Board Fam Pract 1990; 3:217-20.)

Addisonian pernicious anemia occurs rarely in women of childbearing age and almost never during pregnancy. There are a few poorly substantiated reports of its diagnosis during pregnancy, and a few more describing subclinical or latent forms in pregnancy or within 6 months after delivery. On the other hand, there are at least 20 reported cases of infertility in women, presumably caused by pernicious anemia, and in most cases, fertility has been restored by treatment with vitamin B₁₂.

Pernicious anemia occurs in 4 to 8 percent of patients having vitiligo. Perhaps this is not surprising because both conditions are familial and autoimmune in their pathophysiology.

The case presented here is a woman with vitiligo who developed pernicious anemia and whose fertility was restored promptly after treatment with vitamin B₁₂. This is an uncommon occurrence but merits the attention of family physicians because it represents a treatable form of infertility in women.

Case Report

A white woman, 27 years old and married, complained of progressive weakness, pallor, upper abdominal pain, and nausea for at least 2 weeks in October 1986. The most important items of medical history were obstetrical and gynecological.

Her first pregnancy ended at term in January 1980 with Cesarean section because of failure to progress in labor and occiput posterior fetal presentation. The infant weighed 2.91 kg (6.56 pounds). Her blood count was normal (hemoglobin, 12.5 g/dL [125 g/L]; hematocrit, 35.0 percent [0.350]; mean corpuscular volume [MCV], 88 μm³ [88 fl]; mean corpuscular hemoglobin [MCH], 31.3 pg). Following this pregnancy, she was infertile even though she menstruated regularly and used no contraceptives.

In December 1981, she was found to have an ovarian cyst. Her weight then was 38.2 kg (84 pounds), and her blood count was normal (hemoglobin, 14.5 g/dL [145 g/L]; hematocrit, 41.3 percent [0.413]; MCV, 94 μm³ [94 fl]; MCH, 33.8 pg).

Three and one-half years later, April 1985, a pelvic laparotomy showed bilateral ovarian cysts. The surgeon performed right salpingo-oophorectomy, left ovarian cystectomy, and incidental appendectomy. The right ovary contained several follicular and luteal cysts, up to 6 cm diameter; and the left ovary had a benign, simple, serous cystadenoma plus follicular cysts. Her blood count then showed macrocytosis (hemoglobin, 16.3 g/dL [163 g/L]; hematocrit, 48.9 percent [0.489]; MCV, 110 μm³ [110 fl]; MCH, 37.1 pg).

After surgery, she became first oligomenorrheic, then hypermenorrheic, but she resumed a regular cycle after 2 months of oral contraceptives in mid-1986.

At the October 1986 visit, she reported taking no medicines. She smoked one-half pack of cigarettes daily but drank no alcohol. Generally, she avoided drinking milk but ate cheese and other animal proteins. There was no history of diarrhea or hematochezia.

Her mother had diabetes mellitus and at least two paternal relatives had vitiligo.

On examination, she weighed 38 kg (83.75 pounds) and appeared sallow. She had rapid
heart rate, 116 beats/min, and her blood pressure was 94/60 mmHg. There was symmetrical, patchy vitiligo on her distal upper and lower extremities and trunk.

Laboratory findings included the following: hemoglobin, 7.3 g/dL (73 g/L); hematocrit, 20.5 percent (0.205); MCV, 108 μm³ (108 fL); MCH, 38.4 pg; platelets, 100,000/mm³ (100,000,000/L); white cell count, 4100/mm³ (4,100,000/L); and normal differential count. The Westergren erythrocyte sedimentation rate was 33 mm/h.

Other tests showed total serum bilirubin, 3.1 mg/dL (53.0 μmol/L); serum folate, 5.9 ng/mL (13.6 nmol/L); anti-parietal cell antibody cell by immunofluorescence, 1:80; anti-intrinsic factor antibody titer, none; and serum vitamin B₁₂, less than 100 pg/mL (74 pmol/L). A Schilling test was not done.

A diagnosis of pernicious anemia was made on the basis of her clinical appearance, the low level of vitamin B₁₂, the anti-parietal cell antibody titer, and the known association of vitiligo and pernicious anemia.

She was treated with intramuscular injections of vitamin B₁₂, 1000 μg, first twice weekly for 3 weeks, then monthly. After 5 weeks, her blood count and serum bilirubin returned to normal (hemoglobin, 14.4 g/dL [144 g/L]; hematocrit, 43.3 percent [0.433]; MCV, 95 μm³ [95 fL]; MCH 31.7 pg; platelets, 226,000/mm³ [226,000,000/L]; white cell count, 4700/mm³ [4,700,000/L]; and bilirubin, 0.14 mg/dL [2.39 μmol/L]).

Her last menstrual period occurred 2 weeks after beginning vitamin B₁₂, and a urine pregnancy test was positive in January 1987. The pregnancy was terminated by dilatation and curettage in February 1987 because of blighted ovum.

She became pregnant again later in 1987 and subsequently was delivered of her baby by repeat Cesarean section at 37 weeks’ gestation because of the spontaneous onset of preterm labor.

Discussion
Pernicious anemia, caused by a deficiency of vitamin B₁₂, is rare in persons aged less than 40 years; the average age is 60 years. Cases occur almost equally in men and women. Nutritional deficiency of vitamin B₁₂ as a cause of anemia or other problems in the pregnant or nonpregnant state is rare because depletion of the vitamin stores may take 3 years.

Autoimmune factors may be important in the pathogenesis of pernicious anemia, but they are not well understood. Anti-parietal cell antibodies occur in 90 percent of cases but also may be present in up to 15 percent of the general population. Anti-intrinsic factor antibodies, a more specific finding, are present in only 60 percent of cases.¹⁸

Typical findings in pernicious anemia include atrophic gastric mucosa with deficient intrinsic factor secretion. Lack of intrinsic factor inhibits absorption of vitamin B₁₂, leading to megaloblastic anemia, glossitis, and gastrointestinal symptoms. Eventually, a demyelinating process affecting the spinal cord and peripheral nerves may become irreversible, causing hypoesthesia, ataxia, and dementia. Vitamin B₁₂, generally administered parenterally, corrects hematologic and neurologic abnormalities when given before irreversible demyelination has occurred. Folic acid reverses the anemia but does not correct neurologic abnormalities, and by masking the anemia of B₁₂ deficiency, contributes to the development of subacute combined degeneration of the spinal cord.

Diagnosis of pernicious anemia is made by appropriate clinical and laboratory findings noted above. A confirmation of the diagnosis can be provided by the Schilling test, which entails saturation of B₁₂ stores, then comparing urinary excretion of radioactively labeled B₁₂ given orally without and with intrinsic factor.

Pernicious anemia has been reported in at least 20 cases of infertility in women.⁵,⁶,¹⁰-¹⁴ Postulated mechanisms include anovulation despite normal menses; developmental or chromosomal abnormalities of the ovum, preventing fertilization or implantation; and abnormalities of the endometrium or placenta, preventing successful implantation and growth of the embryo.⁵

Infertility lasted from 18 months to 19 years and often was preceded by one or more spontaneous abortions. Some of the women had successful pregnancies before the period of infertility. The majority had rapid restoration of fertility after vitamin B₁₂ therapy was initiated, with conception often occurring within 4 months and usually within 1 year. There have been several additional reports of cases where pernicious anemia was diagnosed before pregnancy, but the status of treat-
ment, the period of infertility, if any, and the subsequent time before infertility was restored were not always clear.\textsuperscript{7,19-21} The existing literature does not allow a clear assessment of the risk of spontaneous abortion or other pregnancy complications in women with pernicious anemia before or after treatment.

Previous literature reviews and surveys have found no convincing cases of pernicious anemia first diagnosed during pregnancy,\textsuperscript{3,22} supporting the strong association between untreated pernicious anemia and infertility. There are a few poorly substantiated claims of its first diagnosis during pregnancy,\textsuperscript{1-4} and there are at least seven cases of subclinical or latent pernicious anemia in pregnancy or diagnoses within 6 months postpartum.\textsuperscript{5,9}

Several authors have expressed reservations about routine daily dietary supplementation of folate in pregnancy because of the possibility of masking pernicious anemia and precipitating subacute combined degeneration of the spinal cord.\textsuperscript{2,5,6,10} However, no such cases have been reported,\textsuperscript{9,23} and the unlikely chance that a woman with untreated clinical or subclinical pernicious anemia would conceive and carry to term nearly excludes the possibility of this potential complication in pregnancy. Also the advantages of folate supplementation in preventing megaloblastic anemia in pregnancy far outweigh the theoretical and unlikely risk of masking a true pernicious anemia.\textsuperscript{24,25}

The extremely high rate of infertility in untreated pernicious anemia also nearly eliminates the concern about a mother with pernicious anemia inducing $B_{12}$ deficiency in her neonate. However, transplacentally acquired anti-intrinsic factor antibody leading to $B_{12}$ deficiency anemia in a 3-month-old infant of a mother with partially treated pernicious anemia\textsuperscript{26} and $B_{12}$ deficiency anemia in a 4-month-old secondary to $B_{12}$ deficient breast milk from a mother with subclinical pernicious anemia\textsuperscript{8} have been reported.

Vitiligo is the progressive acquired loss of skin pigmentation because of the absence of melanocytes. It is familial with an autosomal dominant transmission in 30 percent of cases and affects the sexes equally. One percent of the general population is affected, with 50 percent of cases starting before age 20. Though thought to be an autoimmune process, the exact etiology is undetermined. In the presence of vitiligo, there is an increased occurrence of thyroid disease, including hyperthyroidism, hypothyroidism, thyroiditis, and nontoxic goiter, as well as alopecia areata, Addison disease, diabetes mellitus, melanoma, and, as in this case, pernicious anemia.\textsuperscript{27,28} Though several authors have reported the occurrence of pregnancy in treated pernicious anemia, none has indicated the presence of vitiligo in the same patient.

**Conclusions**

Pernicious anemia is a rare but treatable cause of infertility in women. The diagnosis of pernicious anemia should be entertained in the presence of a high mean corpuscular volume, which precedes the fall in hemoglobin and hematocrit. The presence or history of other auto-immune diseases involving the endocrine system or skin should also raise the suspicion of clinical or subclinical pernicious anemia in the infertile woman.

A history of pregnancy loss may precede a prolonged interval of infertility in untreated pernicious anemia, but fertility is rapidly restored after repletion of vitamin $B_{12}$ stores. The frequency of pregnancy loss after restoration of fertility is unknown.

**References**