

# Atypical Postpartum Psychosis Possibly Associated With Metronidazole Therapy

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In the more than 100 years since postpartum psychosis was first described, the semantic argument continues as to whether it is a distinct entity whose etiology, presentation, and prognosis differ from other psychoses, or, as in the American literature, it is an atypical psychosis or simply an illness in the affective or schizophrenic spectrum that happens to occur in the puerperium.<sup>1</sup> Brandon<sup>2</sup> and others believe that the risk of illness requiring psychiatric hospitalization is greater in the first year postpartum than at any other time in a woman's life. That this is especially true for high-risk women (with prior history of affective disorder or psychosis) was demonstrated in a prospective study by McNeil.<sup>3</sup>

The following are some features described as typical of postpartum psychosis: (1) it often occurs after an asymptomatic period of two to three days, (2) 54 percent of affected women are primiparas, (3) once a woman has had a postpartum psychosis, her chances of another episode after a subsequent pregnancy range from 13 to 20 percent,<sup>4,5</sup> (4) there is no difference in susceptibility in different cultures or socioeconomic groups, (5) there does not seem to be an increased incidence in postpartum psychosis in women with such stressors as twin deliveries, stillbirths, neonatal deaths, premature delivery, or being a single mother,<sup>1</sup> and (6) approximately 40 percent of new mothers with a history of bipolar affective disorder will develop postpartum psychosis, and new mothers with first-degree relatives who have bipolar disorder have a 20 percent chance of developing postpartum psychosis.<sup>1</sup> An excellent review of this and other psychiatric illness associated with childbearing has been done by Casiano and Hawkins.<sup>6</sup>

Metronidazole is usually administered orally in doses below 1.0 g/d for *Trichomonas*, *Gardnerella vaginalis*, and *Giardia* infections. Higher oral doses were approved for the treatment of *Entamoeba histolytica*, and intravenous metronidazole (typically in doses of approximately 2.0 g/d) has been approved for the treatment of certain anaerobic infections.<sup>7</sup> Metronidazole and some of its metabolites cross the blood-brain barrier, and there have been reports of convulsions and encephalopathy,<sup>8</sup> peripheral neuropathy,<sup>9</sup> disorientation and confusion,<sup>10</sup> agitated depression,<sup>11</sup> central nervous system toxicity,<sup>12,13</sup> and confusion, agitation, and hallucinations<sup>14,15</sup> associated with metronidazole use. Many of these reports involved elderly or seriously ill patients<sup>8,9,12-14</sup>; however, some of the affective symptoms possibly associated with metronidazole have occurred in young, healthy individuals.<sup>10,11</sup> The case reported here involves a woman in generally good health.

## CASE REPORT

The patient was a 44-year-old Laotian woman, married for 21 years, who had no prior history of affective symptoms, psychosis, alcohol use, or substance abuse. There was no history of psychiatric illness, substance abuse, or suicide in the family. She escaped Laos in 1976 with her family, lived with her extended family intact in the United States for six years, and felt positive about her family's future in the United States. She was considered a very stable, cheerful, reliable, active member of her relocated Laotian community prior to her illness.

The patient presented for her first obstetric visit for this planned pregnancy at 16 weeks' gestation. She is a gravida 9, para 8, Ab 1, spontaneous. Her first child died two to three hours after a premature delivery; her fourth pregnancy was a spontaneous abortion at 3 months' gestation; her fifth child died at the age of 6 years of accidental drowning in a refugee camp, and her seventh child died in the camp at the age of 1 month with a rash and fever. All of her deliveries were at home except the last one. In December 1986, she was noted to have *Entamoeba coli*

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cysts in her stool but was asymptomatic. Because of her age, parity, time since last delivery, and the risk factor of chronic hepatitis B antigen carrier state (asymptomatic, with normal liver function tests), she was followed in the high-risk obstetric clinic throughout her prenatal care.

On May 8, 1987, the patient was admitted in active labor at 6:50 AM. At 6:59 AM, she had a normal, spontaneous vaginal delivery with no anesthesia, episiotomy, or complications. The male infant weighed 6 lb 5 oz with an Apgar score of 8 at one and 9 at five minutes. Bonding between mother and infant in the delivery room and at subsequent feeding times was excellent. At noon that same day her obstetrician started treatment with metronidazole, 750 mg orally, three times a day, apparently because of the *Entamoeba coli* cysts in her stool. She was discharged at noon on the next day and was noted to be doing very well by the staff. The infant remained in the nursery because of prematurity (37 weeks' gestation) and for "sepsis workup." He did quite well and was ready for discharge by May 14, 1987. The patient stated that she did not consider her baby seriously ill, did not worry that he might die, did visit him every day in the nursery, and was eager to have him home.

The patient's family reported that from her first night at home, she did not sleep well, she ate poorly, and complained of abdominal and chest pain and nausea, and by May 10, she began to "act weird and talk nonsense." She came to the emergency room at 12:30 AM on May 14 complaining that the skin lotion she used was making her extremities disappear. The physician felt that she was hyperventilating; he advised a visit to the baby in the nursery, and the nurses described her behavior as very appropriate with her baby, who was ready for discharge later that day.

The patient came to the emergency room again at 1:00 AM on May 15, complaining that her legs were missing and that "people" were trying to kill her. The family reported that she was not eating or sleeping and the psychiatrist was called. She was admitted to a residential psychiatric treatment center on the same day. Later that day, her nausea, vomiting, and abdominal pain increased, and she was taken to the emergency room, where she was advised that the cause of her distress was the metronidazole, which should be stopped. The medication was discontinued that evening. The family stated that the patient was very much improved after stopping metronidazole, so much so that they felt no further treatment was needed on May 16 and 17.

In the evening of May 18, however, the patient had auditory and visual hallucinations, including commands telling her to commit suicide. She refused food and drink, stating it was poison, and claimed she was still pregnant. She did not sleep and physically resisted aid from her family. She laughed inappropriately and stated she was a queen and would give money to everyone. She was admitted to the psychiatric unit on May 19; she ran about spitting, expressing her disgust to a "man" she saw chasing her,

threatening to rape her. She fought with staff, stating they were trying to kill her, and seclusion and restraints were required. The unit had 23 percent Southeast Asian patients, a full-time, experienced, medical interpreter staff, and family and cultural healers were accepted on the unit as much as possible. She was treated with haloperidol, initially, 35 mg/d, which was gradually decreased to 5 mg/d at the time of discharge. Her psychotic symptoms abated approximately 70 percent in the first week, and after one month of hospitalization, the patient was free of hallucinations and delusions and was in good control and good contact with reality. Her husband described her affect and behavior as "normal" at the time of discharge.

Laboratory studies during her hospitalization included complete blood count, complete chemistry panel, liver function tests, complete thyroid panel, serologic screening for syphilis, folic acid level and antinuclear antibody determinations, and urinalysis—all of which were within normal limits. The urine drug screening test on admission was negative. Hepatitis B surface antigen was positive, and antibody was negative (unchanged from December 1983). Results of an encephalogram were normal. A computed tomographic scan of the head showed a very small radiolucent area in the anterior left temporal lobe, suggesting a remote small stroke or remote head injury with a small area of encephalomalacia. By history, the latter is more likely.

## DISCUSSION

While postpartum psychosis can occur following any pregnancy,<sup>16</sup> the fact that more than one half of these cases occur in primagravidas<sup>1</sup> would suggest that earlier pregnancies are at highest risk. A history of prior psychotic illness in the woman or her family also increases the risk of postpartum psychosis and other psychoses, and the onset of so-called functional psychoses in general is much more common in the second, third, and fourth decades of life. The case described here contains signs and symptoms commonly seen in postpartum psychosis.<sup>6</sup> This patient, however, with no personal or family history of psychiatric illness or substance abuse, presenting in her fifth decade of life, after her ninth normal vaginal delivery with her first psychotic episode, would seem atypical for either a postpartum psychosis or other functional psychosis.

Metronidazole therapy has been associated with multiple neurologic, central nervous system, and psychiatric adverse reactions.<sup>7-15</sup> Schentag et al<sup>14</sup> described the case of a man with psychotic symptoms following 2 g/d of intravenous metronidazole, and these symptoms resolved when 500 mg/d was used. They concluded that metronidazole can be associated with a dose-dependent and serum-concentration-related mental confusional state that is reversible upon discontinuing the drug. It has been

shown that metronidazole is almost completely absorbed following oral administration, and serum levels are similar in equal oral and intravenous doses.<sup>7,17</sup> This patient took metronidazole, 750 mg three times a day, for seven and one-half days. She developed gastrointestinal symptoms after only two doses and developed psychotic symptoms at 48 hours, a pattern similar to that in the case reported by Schentag et al.<sup>14</sup> In addition to projected pharmacokinetics, the onset of gastrointestinal and psychotic symptoms suggest that the serum metronidazole levels of this patient were very likely similar to those in the case reported by Schentag et al.<sup>7,14,17</sup> If metronidazole alone was responsible for this patient's psychosis, her recovery would have been expected upon discontinuing the drug.<sup>14</sup> She did show prompt improvement when the drug was stopped, but psychotic symptoms continued, requiring hospitalization.

Metronidazole has been widely used in obstetric and gynecologic practice, including antibiotic prophylaxis immediately prior to cesarean section delivery and other gynecologic surgery.<sup>7,17-22</sup> Concern has been raised regarding the prolonged half-life of metronidazole in newborn infants<sup>17,18</sup> and the risk of time exposure to metronidazole in relation to mutagenicity, carcinogenicity, and teratogenicity.<sup>17</sup> Because of these issues, as well as concerns about the presence of metronidazole in breast milk, Robbie and Sweet<sup>17</sup> have called for caution in the use of metronidazole, especially in obstetric practice.

## CONCLUSIONS

In more than 25 years of use, metronidazole has proven to be an effective and useful tool in the antibiotic arsenal. Metronidazole did not necessarily cause the patient's psychosis as described in this report. Her psychosis was unusual in many respects, however, and among possible precipitating factors, there was a temporal association between the use of a drug reported to cause similar symptoms when used in similar doses and the onset of this patient's psychosis. The duration of the illness (three to four weeks) is likely too long to be explained by metronidazole exposure alone. The most probable multifactorial hypothesis is that the patient, because of her postpartum status, was in a state of biologic vulnerability and that the use of high doses of metronidazole in some way facilitated the expression of her atypical psychosis.

In their review of metronidazole use in obstetrics, Robbie and Sweet<sup>17</sup> conclude, "A call for caution in the use of metronidazole in women is voiced. . . ." That review is cited in the *Williams Obstetrics* section on the treatment of puerperal infections,<sup>23</sup> and the caution is echoed. Clearly further studies on the therapeutic action, drug interaction, and side-effect profile of metronidazole (including psychiatric symptoms) are indicated. Until further clarified, high-dose metronidazole therapy in the puerperium should

be carefully evaluated for potential risks vs benefits, including the possibility that such treatment might contribute to the expression of serious postpartum psychiatric illness.

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