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Mirtazapine (Remergil) for treatment resistant hyperemesis gravidarum: rescue of a twin pregnancy

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Abstract *Case report:* We present the case of a 25-year-old woman with treatment resistant hyperemesis gravidarum in the 15th week with a 13 kg loss of body weight. When the patient asked for termination of the pregnancy because of the unbearable symptoms, treatment with intravenous mirtazapine (Remergil) was started. *Results:* Nausea and vomiting disappeared within hours, pregnancy termination was no longer desired. The patient was discharged two weeks later in good health and at 36 weeks gestation a cesarean section was performed. Post partum evaluation as well as 6-month post-partum revealed no dysmorphism or laboratory abnormalities in the children.

Keywords Mirtazapine · Antidepressant · Hyperemesis gravidarum · Termination of pregnancy

Introduction

It is estimated that 50 to 80% of pregnant women experience nausea and vomiting beginning by the 4th week and commonly ending by the 12th week after conception. Symptoms may persist throughout pregnancy in up to 20% of pregnant women. Of this large group 1 to

3% experience a more severe form of nausea and vomiting termed hyperemesis gravidarum, described as intractable vomiting associated with weight loss of more than 5% of prepregnancy weight, dehydration, and electrolyte imbalance, which may lead to hospitalization. In this condition, anxiety can be exacerbated and 55% of pregnant women with hyperemesis gravidarum feel depressed [10]. Case reports have associated hyperemesis gravidarum in its extreme forms to a higher desire for elective termination of pregnancy [8]. Current management of this disease is based primarily on clinically observed responses to diverse management modalities and has not significantly changed for several decades. Everyone who provides prenatal care is acutely aware that in some cases we do not have any effective medications to treat hyperemesis gravidarum.

We report a case of a successful treatment with mirtazapine (Remergil, Organon, Oberschleißheim, Germany) of a woman, who asked for termination of the pregnancy, because of treatment resistant hyperemesis gravidarum.

Case report

A 25-year-old woman was referred to the Women's University Hospital in Bonn in a state of despair and asked for termination of pregnancy in her 15th week. She had been emergently admitted the night before with severe nausea, vomiting and stomach cramps. Because of her psychopathology, including secondary depression, suicidal thoughts (she felt unable to tolerate the situation any longer) and resulting peculiar behavior, she had spent the night on the acute psychiatric ward. In the morning following admission she was in the same state, asking for pregnancy termination, unable to bear any more nausea and vomiting.

She and her husband had recently been treated for infertility in the Department of Reproductive Medicine and conceived after two cycles of IVF/ICSI; an intact twin pregnancy developed. The patient was completely healthy prior to pregnancy without any psychopathological symptoms. In the 3rd week of pregnancy, the persisting nausea and vomiting manifested, soon accompanied by stomach cramps. Several hospitalizations in the regional Gynecological hospital and treatment trials with conventional antiemetics and other medications (e.g., dimenhydrinate [Vomex, Yamanouchi, Heidelberg, Germany]; metoclopramide [Paspertin, Solvay, Han-

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nover, Germany]; trifluorpromazine [Psyquil, Sanofi-Synthelabo, Berlin, Germany]; Pyridoxine [Vitamine B₆-Inject, Jenapharma, Jena, Germany]) during the subsequent 10 weeks had only minimal and short-term effects and resulted in additional psychological stress. After losing a total 13 kg of body weight, the patient was referred to our clinic and asked for termination of the pregnancy. Upon presenting with hyperemesis gravidarum, no somatic cause was found, and neither the first nor following psychosomatic interviews led to a psychosomatic hypothesis regarding the cause of the symptomatology.

The patient agreed to treatment with mirtazapine (Remergil), an antidepressive drug previously mentioned in case reports as potentially useful for cases of hyperemesis gravidarum [3, 13]. Upon treatment with 6 mg/day of intravenous mirtazapine, the nausea, vomiting and stomach cramps resolved within hours. The next morning she was able to eat and, at day 3, the use of mirtazapine was changed to an oral dose of 30 mg/day. Termination of the pregnancy was no longer desired and the patient was discharged 2 weeks later in good health. Over the course of the next 4 weeks her dosage was slowly tapered and finally discontinued. At 27 weeks' gestation the patient presented with a gastrointestinal infection complicated by recurrence of nausea and vomiting and responded again to a cycle of mirtazapine. Three weeks before delivery, the medication was discontinued without reappearance of symptoms. At 36 weeks gestation, a cesarean section was performed. Healthy male twins were delivered (Twin I: birth weight 1,940 g, APGAR 9/10/10; Twin II: 1,940 g, APGAR 9/10/10); there were no dysmorphism or laboratory abnormalities and the neonatal course was uneventful. A follow-up pediatric examination at 6 months was completely normal as well as the mother's somatic and mental state.

Discussion

Hyperemesis gravidarum can lead to weight loss, dehydration, electrolyte disturbances and occasionally organ damage if improperly treated or left untreated [4, 5, 7, 12]. Case reports have associated hyperemesis gravidarum in its extreme forms with a desire for termination of pregnancy [9]. Mazzotta et al. have recently explored motivation for termination of pregnancy among women with hyperemesis gravidarum. In their study 413 of 3,201 women with hyperemesis gravidarum had considered termination of pregnancy because of hyperemesis gravidarum and 108 reported termination because of this disease [8].

Multifactorial etiology with the interaction of biological, psychological and sociocultural factors has been implicated [2, 4, 5]. Although treatment options are wide and include antiemetics, vitamin B₆, corticosteroids, antihistamines (H₁ blockers), anticholinergics, dopamine antagonists and HT₃ antagonists, usually supported by infusions with electrolytes and liquid nutrient medium [1, 5, 7, 12], effective treatment is lacking in some cases.

Mirtazapine (Remergil) is a Noradrenergic and Specific Serotonergic Antidepressant (NaSSA). Because the 5-HT₂- and 5-HT₃-receptors are blocked, unwanted serotonergic symptoms like agitation or sickness do not occur, while the activation of the 5-HT_{1a}-receptors results in an antidepressive and anxiolytic effect [11]. Blocking the 5-HT₃-receptors (similar to some antiemetics, e.g., Ondansetron) results in the antiemetic effect. Because of reports of successful treatment of chemotherapy-induced

nausea and vomiting with mirtazapine and the treatment of hyperemesis gravidarum in seven pregnant patients, reported by Saks et al. [13], we decided to use this medication. We initially prescribed it intravenously because the patient was not able to swallow an oral medication.

In cases of hyperemesis gravidarum with secondary psychic symptoms (like depression, anxiety, agitation, sleep disturbances) the antidepressant mirtazapine may have an additional benefit because this substance positively influences symptoms mentioned, with a rapid onset. For cases like ours, mirtazapine might be a good choice compared to other new substances for which also only limited experiences with pregnant patients exist (i.e., Ondansetron). When a patient asks for termination of pregnancy as final solution after conventional therapy failed, the benefit of the use of mirtazapine may outweigh the risk. It is noted that animal studies of mirtazapine in pregnancy using 17 and 20 times the maximum recommended human dose have demonstrated no intrauterine fetal loss after the first trimester, no teratogenicity, and no developmental differences compared to controls [13].

Conclusion

Although the data regarding teratogenicity and fetotoxicity are limited in human [6], the use of the antidepressant mirtazapine should be considered as alternative treatment strategy in severe cases of treatment resistant hyperemesis gravidarum, especially with secondary psychopathology. Such treatment should only be undertaken when the benefits outweigh the risks—as was the situation in the reported case.

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