CASE REPORT

Patients with a history of hyperemesis gravidarum have similar symptoms during egg stimulation and develop ovarian hyperstimulation syndrome: case series

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Objective: To investigate the symptoms and outcomes of ovarian stimulation in patients with a history of hyperemesis gravidarum.
Design: Retrospective case series.
Setting: Research laboratory of a university hospital.
Patient(s): Participants in an ongoing study on hyperemesis gravidarum that reported ovarian stimulation for gestational surrogacy.
Intervention(s): Review of medical records.
Main Outcome Measure(s): Pregnancy history, symptoms, estradiol level and mature oocyte number in cases, and nausea and vomiting level reported in surrogate.
Result(s): Three cases in their early thirties with a history of hyperemesis gravidarum presented with severe nausea and vomiting during ovarian stimulation and ovarian hyperstimulation syndrome. Gestational carriers reported normal nausea and vomiting of pregnancy.
Conclusion(s): This series provides lessons for in vitro fertilization for cases with a history of hyperemesis gravidarum and their gestational carriers as well as insight into the cause of hyperemesis gravidarum and its potential role in fertility. A link between hyperemesis gravidarum and an evolutionary advantage of increased fertility suggests a novel theory to explain the selection for nausea and vomiting in pregnancy. (Fertil Steril® 2009;■:■–■. ©2009 by American Society for Reproductive Medicine.)

Key Words: Hyperemesis gravidarum, ovarian hyperstimulation syndrome, surrogacy, fertility

Hyperemesis gravidarum (HG)—severe nausea and vomiting during pregnancy—is the most common cause of hospitalization during the first half of pregnancy, and it is second only to preterm labor for pregnancy overall (1). HG can be associated with serious maternal and fetal morbidity, such as Wernicke's encephalopathy (2), fetal growth restriction, and even maternal and fetal death (3).

Despite the prevalence of nausea and vomiting during pregnancy and its burden on patients, families, the health care system, and society, nausea and vomiting during pregnancy and HG have received relatively little attention. There has been a tendency to underestimate the effects of HG on the mother and fetus, which contributes to the low rates of specific therapy recommended by physicians, even in severe cases (4). Because of the lack of safe and effective treatment, some women with extreme HG have turned to other methods to grow their family, including adoption and gestational surrogacy.

Cases including a history of HG concurrent with ovarian stimulation for gestational surrogacy have not been reported previously. The purpose of this study is to describe symptoms and outcomes of ovarian stimulation in three patients with a history of HG.

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MATERIALS AND METHODS

The University of Southern California–Los Angeles is currently conducting a study of the genetics and epidemiology of HG, and more than 650 participants have been recruited, primarily through advertising on the Hyperemesis Education and Research Foundation Web site at www.HelpHer.org. The inclusion criteria for the study are a diagnosis of HG and documented treatment with IV fluids and/or total parenteral nutrition. Participants are asked to [1] submit their medical records, [2] provide a saliva sample, and [3] complete an online survey regarding family history, treatment, and outcomes.

Three patients were identified after reporting subsequent ovarian stimulation for gestational surrogacy, and their medical records are described herein. This study was approved by the Institutional Review Board of the University of Southern California, ID HS-06-00056.

RESULTS

Case 1

A 33-year old woman (gravida 2), with a history of HG and ptyalism treated with total parenteral nutrition, presented for ovum donation for IVF using a gestational surrogate. The patient underwent programmed ovarian stimulation and was treated first with a GnRH agonist (leuprolide) administered subcutaneously to inhibit gonadotropin secretion, followed by a combination of GnRH-analog (GnRH-a) and FSH administered intramuscularly to stimulate the development of ovarian follicles. FSH levels were reduced from 3 to 1.5 ampules on day 9 because of oocyte hyperstimulation. Five days before oocyte retrieval, the patient reported severe nausea, vomiting, and ptyalism similar to HG symptoms, and she was unable to eat or drink. The patient was given ondansetron and IV hydration for 3 days before oocyte retrieval. The E_2 level was 4,936 pg/mL 2 days before oocyte retrieval. Thirty-seven oocytes were retrieved approximately 34 hours after intramuscular treatment with chorionic gonadotropin, including 30 mature oocytes, two immature oocytes, and five atretic oocytes. Symptoms of nausea and vomiting resolved immediately following oocyte retrieval. Ptyalism, bloating, and fatigue persisted for 3 days after oocyte retrieval. The surrogate carried two female infants to term with normal levels of nausea and vomiting.

Case 2

A 32-year old woman (gravida 2), with a history of HG and ptyalism requiring total parenteral nutrition, presented for ovum donation for IVF using a gestational surrogate. The patient was treated with leuprolide, FSH, and GnRH-a. The FSH dose was reduced from 225 to 150 IU on day 5 because of oocyte hyperstimulation. The E_2 level was 3,689 pg/mL 2 days before oocyte retrieval. The patient complained of severe nausea, vomiting, and ptyalism resembling HG symptoms beginning 2 days before oocyte retrieval and lasting approximately 1 week afterward. The patient described discomfort due to bloating and fatigue lasting the week following retrieval. Twenty-two mature oocytes were retrieved approximately 34 hours after intramuscular treatment with chorionic gonadotropin and were prepared for ovum donation. The surrogate became pregnant with a female and reported normal nausea and vomiting during pregnancy.

Case 3

A 31-year old woman (gravida 1), with a history of severe HG treated with a peripherally inserted central catheter, presented for ovum donation for IVF using a gestational surrogate. The patient was treated with leuprolide, Fertinex (FSH; EMD Serono Laboratories Inc., Rockland, MA), and Repronex (FSH and LH; EMD Serono Laboratories Inc.), and medication was stopped after day 9 until oocyte retrieval because of oocyte hyperstimulation. The E_2 level was 3,392 pg/mL 2 days before oocyte retrieval. The patient complained of severe nausea and vomiting that persisted throughout the week before oocyte retrieval. The nausea resolved after retrieval, but the patient complained of discomfort from extreme bloating. Twenty-eight mature oocytes were retrieved approximately 34 hours after intramuscular treatment with chorionic gonadotropin and were prepared for donation. The surrogate became pregnant with a female and reported normal nausea during her pregnancy.

DISCUSSION

There are several interesting points to be made with this case series. First, all three patients had symptoms similar to HG while not pregnant and before treatment with chorionic gonadotropin, suggesting that for these patients, the pregnancy state, and more notably, chorionic gonadotropin is not the likely cause of their severe nausea and vomiting during pregnancy. In more than 25 reports regarding the relationship between serum concentrations of nonthyroid hormones and nausea and vomiting during pregnancy, only chorionic gonadotropin and E_2 have been significantly associated with nausea and vomiting during pregnancy in multiple studies. This series provides evidence that chorionic gonadotropin is not directly causal and is consistent with the estrogen hypothesis, because all three patients produced a large number of mature follicles and therefore a high level of estrogen.

Second, all three patients reported that their surrogates had normal nausea during pregnancy. Thus, surrogates are not likely at an increased risk of severe nausea and vomiting while carrying a fetus with a maternal history of HG. All three surrogates carried female fetuses—one was a twin pregnancy of two females. This finding is of particular interest because an increased incidence of HG has been reported with multiple gestations and for mothers of female offspring (5, 6), but the surrogates all reported normal levels of nausea and vomiting. This finding suggests that a paternal–fetal component in these cases is not a likely cause of HG. In the past, evidence for a paternal–fetal contribution has been controversial. Although one study noted that HG recurrence decreases with a change in partner, suggesting that paternal genes expressed in the fetus may play a role, this conclusion was recently refuted by a separate study (7, 8). In addition, a consanguinity study also found no increased risk of HG, suggesting that recessive fetal genes might not be involved in risk for HG (9). This case series is consistent with these findings: whereas other factors may contribute to the severity of symptoms, a maternal genetic component, possibly ovarian rather than fetal or placental in origin, is most likely causal.

More evidence for this conclusion lies in the fact that all three cases produced extremely high numbers of mature follicles (well above the expected range of 2 to 16 for women aged <40 years) via ovarian stimulation, suggesting a possible ovarian component to HG. Interestingly, the high number of mature follicles also suggests a new theory to explain why HG has not been removed by natural selection, despite its obvious reproductive disadvantage. Until the introduction of IV fluid treatment in the 1950s, HG was a common cause of maternal and fetal death, making its existence during pregnancy an evolutionary enigma. Perhaps extreme nausea during pregnancy is coupled with an increase in healthy follicles or ovarian reserve, resulting in an overall fertility advantage that surpasses the hereditary disadvantage historically caused by maternal and fetal death, extreme weight loss, malnutrition, prolonged dehydration, Wernicke's encephalopathy, and fetal growth restriction (2, 3, 9, 10). Several lines of evidence support a genetic predisposition to nausea and vomiting during pregnancy (11–14). It is therefore possible that in finding the genes predisposing to HG, one may simultaneously identify genes that contribute to increased fertility and more successful ovarian stimulation.

Finally, practitioners and caretakers of patients undergoing follicle stimulation for HG should be wary of ovarian hyperstimulation syndrome in patients with a history of HG. A family history of HG

should also be taken into consideration, as HG has been shown to cluster in families (12). Overall, this case series provides lessons in IVF for women with a history of HG and their surrogates, as well as insight into the cause of HG and its potential role in fertility. Genes predisposing to HG and their potential link to increased fertility merit further investigation.

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