Published in final edited form as:

Fertil Steril. 2010 January 1; 93(1): 267.e9–267.e11. doi:10.1016/j.fertnstert.2009.09.022.

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

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Abstract

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.

Patients—Participants in an ongoing study on hyperemesis gravidarum that reported ovarian stimulation for gestational surrogacy.

Interventions—Review of medical records.

Main Outcome Measures—Pregnancy history, symptoms, estradiol level and mature oocyte number in cases, and nausea and vomiting level reported in surrogate.

Results—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.

Conclusions—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.

Keywords

Hyperemesis Gravidarum; Ovarian Hyperstimulation Syndrome; Surrogacy; Fertility

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Introduction

Hyperemesis Gravidarum (HG), severe nausea and vomiting of pregnancy, is the most common cause of hospitalization in the first half of pregnancy and is second only to preterm labor for pregnancy overall (1). It 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 of pregnancy and its burden on patients, families, the health care system and society, nausea and vomiting of pregnancy and consequently HG have received relatively little attention. There has been a tendency to underestimate the impact of HG on the mother and fetus, which contributes to the low rates of specific therapy recommended by physicians, even in severe cases (4). Due to the lack of safe and effective treatment, some women with extreme HG have turned to other methods to increase their family size including adoption and gestational surrogacy.

Cases with a history of HG undergoing ovarian stimulation for gestational surrogacy have never been reported previously. **The purpose of this study is to describe symptoms and outcomes of ovarian stimulation in three cases with a history of HG.**

Methods

The University of Southern California, Los Angeles is conducting a study of the genetics and epidemiology of HG. Currently this study has over 650 participants recruited primarily through advertisement on the Hyperemesis Education and Research Foundation website at www.HelpHer.org. The inclusion criteria for HG is a diagnosis of HG and documented treatment with intra venous fluids and/or total parenteral nutrition. Participants are asked to 1) send in their medical records, 2) provide a saliva sample, and 3) complete an online survey regarding family history, treatment, and outcomes. Three cases were identified from the ongoing study that reported on 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 female gravidity two, with a history of HG and pytalism requiring total parenteral nutrition presented for ovum donation for in vitro fertilization using a gestational surrogate. Case 1 underwent programmed ovarian stimulation. The woman was treated first with a gonadotropin-releasing hormone agonist (leuprolide), administered subcutaneously, to inhibit gonadotropin secretion, followed by a combination of gonadotropin-releasing hormone-analog (GnRH-a) and follicle-stimulating hormone (FSH), administered intramuscularly, to stimulate the development of ovarian follicles. FSH levels were reduced from 3 to 1.5 ampules on day 9 due to oocyte hyperstimulation. Five days prior to retrieval the case reported severe nausea, vomiting, and pytalism similar to HG symptoms and was unable to eat or drink. The case was treated with Ondansetron and intravenous hydration for three days prior to egg retrieval. Estradiol level was 4936 pg/ml two days prior to retrieval. Thirty-seven oocytes were retrieved approximately 34 hours after intramuscular treatment with chorionic gonadotropin, including 30 mature oocytes, 2 immature, and 5 atretic oocytes. Symptoms of nausea and vomiting resolved immediately following oocyte retrieval. Pytalism, bloating, and fatigue persisted for

3 days post retrieval. The surrogate carried two female infants to term with normal levels of nausea and vomiting.

Case 2

A 32-year old female gravidity two, with a history of HG and pytalism requiring total parenteral nutrition presented for ovum donation for in vitro fertilization using a gestational surrogate. Case 2 was treated with leuprolide, FSH, and GnRH-a. FSH was reduced from 225 to 150 IU on day 5 due to oocyte hyperstimulation. Estradiol level was 3689 pg/ml two days prior to retrieval. Patient complained of severe nausea and vomiting and pytalism similar to HG symptoms beginning 2 days prior to oocyte retrieval and lasting approximately a week after retrieval. 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 prepared for ovum donation. The gestational carrier became pregnant with a female and reported normal nausea and vomiting in pregnancy.

Case 3

31-year old female gravidity one, with a history of severe HG treated with a peripherally inserted central catheter presented for ovum donation for in vitro fertilization using a gestational surrogate. Case 3 was treated with leuprolide, Fertinex (FSH) and Repronex (FSH and LH) and coasted after day 9 until oocyte retrieval due to oocyte hyperstimulation. Estradiol level was 3392 pg/ml two days prior to retrieval. Patient complained of severe nausea and vomiting that persisted throughout the week prior to retrieval. The nausea resolved after retrieval, but the patient complained of discomfort due to extreme bloating. Twenty-eight mature oocytes were retrieved approximately 34 hours after intramuscular treatment with chorionic gonadotropin and prepared for donation. The gestational carrier became pregnant with a female and reported normal nausea during her pregnancy.

Discussion

There are several interesting points to be made from this case series. Firstly, all three cases had symptoms similar to HG while not pregnant and prior to 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 non-thyroid hormones and nausea and vomiting of pregnancy, only chorionic gonadotropin and estradiol have been significantly associated with nausea and vomiting of 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.

Another interesting lesson is that all three cases reported their gestational carriers had normal nausea in 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 female fetuses. This is of particular interest because an increased incidence of HG has been reported with multiple gestations and for mothers of female offspring (5,6), yet the gestational carriers all reported normal levels of nausea and vomiting. This suggests a paternal and fetal component in these cases is not a likely cause of HG. In the past, evidence for a paternal and fetal contribution has been controversial. While one study noted that HG recurrence decreases with a change in partner, suggesting paternal genes expressed in the fetus may play a role, this conclusion was recently refuted by a separate study (7,8). Additionally, a consanguinity study also found no increased risk of HG,

suggesting recessive fetal genes may not be involved in HG risk (9). This case series is consistent with these findings-while other factors may contribute to the severity of symptoms, a maternal genetic component, possibly expressing in ovarian rather than fetal or placental origin is most likely causal.

More evidence for this lies in the fact that all three cases produced extremely high numbers of mature follicles (way above the expected range of 2 to 16 for women under forty) 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 selected out in nature despite its obvious reproductive disadvantage. Until the introduction of intra venous fluid treatment in the 1950s, HG was a common cause of maternal and fetal death making its existence in pregnancy an evolutionary enigma. Perhaps extreme nausea of 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 and more recently, by extreme weight loss, dehydration and malnutrition in pregnancy, Wernicke's encephalopathy and fetal growth restriction (2,3,9,10). Several lines of evidence support a genetic predisposition to nausea and vomiting in pregnancy (11,12,13,14). 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 cases undergoing follicle stimulation for HG should be wary of ovarian hyperstimulation syndrome in cases that present 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 in vitro fertilization for women with a history of HG and their gestational carriers as well as insight into the cause of HG and its potential role in fertility. Gene(s) predisposing to HG and their potential link to increased fertility merits further investigation.

Acknowledgments

This research was supported (in part) by the Intramural Research Program of the National Institute of Child Health and Human Development, NIH, DHHS.

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