OBSTETRICS

Hyperemesis gravidarum and long-term health of the offspring

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Nausea and vomiting of pregnancy is a very common occurrence, but the reported incidence of hyperemesis gravidarum (a more severe form of vomiting in pregnancy) is much lower, estimated to vary from 0.3-3.6%. Studies have shown that nausea and vomiting of pregnancy is associated with improved fetal outcomes, such as lower rates of miscarriage. However, there are limited data on outcomes associated with hyperemesis gravidarum, which have focused on pregnancy and neonatal outcomes. Recently, studies showed adverse health outcomes, such as a reduction in insulin sensitivity in childhood and increased incidence of psychological disorders in adulthood. The effects of hyperemesis gravidarum in the offspring need to be further examined throughout childhood, adolescence, and into adulthood, so that long-term disease risks can be evaluated.

Key words: childhood, consequences, health, hyperemesis gravidarum, nausea and vomiting of pregnancy

Nausea and vomiting of pregnancy is a very common event, occurring in 35-91% of pregnancies.[1] In contrast, the reported incidence of hyperemesis gravidarum (a more severe form of vomiting in pregnancy) is much lower, estimated to vary from 0.3-3.6%.[1] There is considerable variation among nations, with the incidence of hyperemesis gravidarum ranging from 0.3% in Sweden[2] to 1.2% in the United States[3] and 3.6% in Japan.[4]

There are a number of definitions used to describe hyperemesis gravidarum. However, the Fairweather[5] criteria provides the clearest definition, stating that hyperemesis gravidarum is characterized by severe vomiting in pregnancy that requires antenatal hospital admission <20 weeks' gestation.[6] Others have created more detailed definitions, such as the presence of intractable vomiting during pregnancy associated with dehydration, electrolyte, and/or metabolic disturbances, as well as a weight loss ≥5%.[7,8] Hyperemesis gravidarum and its potential adverse effects have been more dramatically described as "a debilitating and potentially life-threatening pregnancy disease marked by rapid weight loss, malnutrition, and dehydration due to unrelenting nausea and/or vomiting with potential adverse consequences for the mom-to-be and the newborn(s)," by the Hyperemesis Education and Research Foundation.[9]

Diagnosis of hyperemesis gravidarum is primarily clinical rather than biochemical.[10] Its onset occurs very early in pregnancy (4-8 weeks' gestation), and usually lasts up to beginning of the second trimester of pregnancy.[11] However, some mothers may experience symptoms of hyperemesis gravidarum in mid and late gestation.[11-13] In its most severe form, hyperemesis gravidarum may lead to starvation and dehydration, possibly with severe ketonuria, hemoconcentration, and electrolyte and/or liver enzyme abnormalities.[14,15]

Etiology of hyperemesis gravidarum

There is suggestion of a possible genetic component to nausea and vomiting of pregnancy, as indicated by its similar incidence in subsequent pregnancies in the same mother.[16,17] However, another study revealed no association between nausea and vomiting in earlier and later pregnancies.[18] In the case of severe hyperemesis gravidarum, Fejzo et al[19] observed that its incidence is greater among relatives of affected individuals. Others have suggested that environmental factors may influence the occurrence of hyperemesis gravidarum, with a lesser influence from the fetal genotype.[20]

Nonetheless, the cause(s) of hyperemesis gravidarum remain unclear. Numerous factors (either in isolation or in combination) have been suggested, such as *Helicobacter pylori* infection, increased levels of human chorionic gonadotropin (hCG), thyroid hormones, or serotonin.[21-27] Some studies have indicated a very high incidence of *H pylori* infection in women with hyperemesis gravidarum (approximately 90%).[25,28] Two recent metaanalyses have both found an elevated (although variable) incidence of *H pylori* infection in association with hyperemesis gravidarum.[26,27] Although these associations have not determined whether *H pylori* is a cause or consequence of hyperemesis gravidarum, antibiotic treatment has been shown to relieve symptoms of nausea and vomiting in women with hyperemesis gravidarum and *H pylori*,[29,30] suggesting a causative role.

Activation of the thyroid axis has been proposed to occur through elevated hCG levels and/or enhanced thyroid-stimulating hormone receptor sensitivity.[31-33] Elevated hCG concentrations have been shown in hyperemesis

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gravidarum,[34] but findings are inconsistent and Wilson et al[35] observed no association between hyperemesis and hCG or thyroid hormones. Increased serotonin levels have also been hypothesized to play a role in the onset of hyperemesis gravidarum, but these mothers were shown to have normal serotonin concentrations.[36] Thus, in reality there is no conclusive evidence implicating altered hormone levels in the etiology of hyperemesis gravidarum.

Maternal consequences of hyperemesis gravidarum

In the past, hyperemesis gravidarum was associated with greater maternal mortality,[37] which has been considerably reduced with improvements in medical care. In the United Kingdom, recorded maternal mortality due to hyperemesis gravidarum was dramatically reduced from an alarming 159 per million pregnancies in 1931 through 1940 to 3 per million in 1951 through 1960 with the introduction of intravenous fluid replacement.[38] The famous English novelist Charlotte Brontë (author of *Jane Eyre*) is widely regarded as having perished due to hyperemesis gravidarum, but her death has been more recently attributed to tuberculosis with secondary Addison disease.[39] Only 2 maternal deaths due to hyperemesis gravidarum were recorded in 1991 through 1993 in the United Kingdom,[38] and such deaths are now very rare. Nonetheless, hyperemesis gravidarum is a known risk factor for venous thromboembolism, pulmonary embolism,[40] and preeclampsia,[41] and it is therefore occasionally implicated in maternal death.[40]

Despite the major reduction in maternal mortality, extensive maternal morbidity still results.[10,42] Many mothers with hyperemesis gravidarum experience major nutritional and/or electrolyte disturbance, requiring enteral (via a nasogastric tube) or total intravenous nutrition,[43] impairing maternal weight gain.[44] In a survey of 819 mothers with hyperemesis gravidarum, 26% had extreme weight loss defined as a loss >15% of prepregnancy weight.[12] Further, associated with the weight loss, some mothers experienced liver dysfunction, gall bladder dysfunction, or retinal hemorrhage.[12] In rare instances, violent vomiting and severe electrolyte disturbances may cause more serious complications, including Wernicke encephalopathy.[45]

Clearly, hyperemesis gravidarum may have devastating personal and economic consequences to the mother and the family.[46] Not surprisingly, therefore, hyperemesis gravidarum can lead to considerable psychosocial effects on the mother. These include behavioral and cognitive dysfunction, and emotional distress that may lead to posttraumatic stress disorder.[47-49]

Fetal and perinatal outcomes

Although hyperemesis gravidarum causes considerable physiological and psychological stress to the mother, less severe nausea and vomiting during pregnancy does not appear to be harmful to the offspring. In fact, it has been suggested that nausea and vomiting of pregnancy protects the mother and her fetus from harmful substances in food,[50,51] conferring an evolutionary advantage to maximize fitness and survival. It has also been hypothesized that nausea and vomiting of pregnancy results from altered secretion of certain hormones to favor placental development.[18,52,53]

Studies have shown that nausea and vomiting of pregnancy is associated with improved fetal outcomes,[53] such as lower rates of miscarriage.[51,54] There is also evidence of lower rates of congenital defects[55] and preterm birth,[56] but these findings have not been consistently observed.[51]

In regards to severe nausea and vomiting of pregnancy (ie, hyperemesis gravidarum), there are reports of adverse fetal and perinatal outcomes. Hyperemesis gravidarum invariably leads to a reduction in maternal weight gain throughout pregnancy,[44] which may result in suboptimal fetal outcomes.[6,57] As a result, hyperemesis gravidarum has been shown to be associated with increased rates of small-for-gestational-age infants and preterm birth.[6,58,59] Other studies also showed reductions in gestational age and birthweight, as well as an increase in postnatal hospital stay.[44,60]

However, there are limited and inconsistent data examining more serious fetal and perinatal outcomes associated with hyperemesis gravidarum. Data from the 1950s suggested that mothers experiencing hyperemesis gravidarum were less likely to spontaneously abort.[61,62] Two metaanalyses found no consistent link with perinatal mortality.[54,59] Conversely, a large study on >520,000 births showed an increased rate of fetal and neonatal deaths in association with hyperemesis gravidarum.[58] Although the metaanalysis of Veenendaal et al[59] observed no effects on congenital anomalies, Czeizel et al[63] observed a protective effect of hyperemesis gravidarum for nonsyndromic oral clefts. More recently, a large population study in Sweden showed an association between hyperemesis gravidarum and placental dysfunction disorders, including risk of preterm preeclampsia, placental abruption, and small-for-gestational-age birth.[41]

Long-term outcomes in the offspring

Children born to mothers who experienced nausea and vomiting of pregnancy were shown to have higher nonverbal intelligence scores, and the increasing severity of symptoms was associated with improved outcomes.[53] In the case of hyperemesis gravidarum, intellectual development assessed in early and late infancy did not reveal any abnormalities in the offspring.[64] However, in utero exposure to hyperemesis gravidarum has been associated with an increased risk of depression, bipolar disorder, and anxiety in adulthood.[65] Hyperemesis gravidarum has also been suggested to lead to an increased risk of testicular cancer in the adult offspring.[66]

A study in sheep evaluated the effects of maternal nutritional restriction in early to mid gestation (simulating the weight loss associated with hyperemesis gravidarum), observing metabolic and anatomical alterations on skeletal muscle in the offspring.[67] As muscle is the primary tissue regulating peripheral insulin sensitivity,[68] the authors postulated that the observed changes in skeletal mass

may predispose the offspring to later insulin resistance and type 2 diabetes mellitus.[67]

Surprisingly, until recently there were no studies on long-term metabolic and cardiovascular outcomes. However, Ayyavoo et al[13] examined the offspring born to mothers with severe hyperemesis gravidarum, among whom severe symptoms of hyperemesis persisted >16 weeks' gestation in 32 of the 36 pregnancies. Compared to the offspring of control pregnancies, prepubertal children born to mothers with severe hyperemesis gravidarum had insulin sensitivity that was 20% lower.[13] These children also had higher fasting insulin and lower insulin-like growth factor binding protein 1 concentrations than control subjects.[13]

Notably, the observed reduction in insulin sensitivity as a result of hyperemesis gravidarum is of similar magnitude to the change in insulin sensitivity achieved by aerobic exercise training in overweight and obese girls.[69] A reduction in insulin sensitivity of similar magnitude has also been observed in 13-year-old children who were overweight (in comparison to children of normal weight).[70] Although there have been no studies examining the long-term consequences of reduced insulin sensitivity in children, insulin resistance in adulthood is associated with an increased risk of type 2 diabetes mellitus, hypertension, coronary heart disease, stroke, and cancer many years later.[71,72]

Hyperinsulinemia and low insulin-like growth factor binding protein 1 are also associated with increased likelihood of developing cardiovascular disease.[73] In addition, baseline cortisol concentrations were 22% higher in the severe hyperemesis gravidarum offspring.[13] It is conceivable that suboptimal nutrition or stress early in pregnancy due to hyperemesis gravidarum might have led to reprogramming of the hypothalamic–pituitary–adrenal axis in the offspring. Increasing circulating cortisol levels have been previously observed in those born of low birthweight (thought to be nutritionally compromised), not only at birth but also in adulthood.[74]

The study of Ayyavoo et al[13] has provided the first evidence of long-term adverse metabolic outcomes in the offspring of mothers with severe hyperemesis gravidarum. Interestingly, that cohort showed similarities to survivors of the Dutch famine exposed to an undernutrition in early gestation. Both groups were born of normal birthweight and displayed adverse effects on glucose homeostasis.[13,75] Other studies have shown that adults exposed to the Dutch famine in early gestation had higher rates of obesity,[76-78] a more atherogenic lipid profile,[78] greater incidence of coronary heart disease,[79] disturbed blood coagulation profiles, as well as increased rates of breast cancer in women.[80] As a result, there may be similar long-term health implications in children born to mothers with hyperemesis gravidarum.

Further, possible placental changes in association with hyperemesis gravidarum have not been previously assessed, and should be the focus of future investigations. In addition, recent animal evidence has indicated that serotonin blockade could affect pancreatic β-cell development.[81] As serotonin antagonists are regularly used in the management of hyperemesis gravidarum, it is important to assess the possible effects of such medications on the offspring in the long-term. Importantly, while many mothers experiencing hyperemesis gravidarum take metoclopramide (partial 5-hydroxytryptamine receptor agonist), a few also take an additional antiemetic that is a serotonin antagonist (5-hydroxytryptamine receptor antagonist). Therefore, the possible effects of administering both drugs together on long-term offspring outcomes are also of interest.

Conclusion

Although hyperemesis gravidarum usually lasts to 14-16 weeks' gestation,[11] for many women symptoms may persist throughout pregnancy.[12,13] Thus, in a number of pregnancies, the associated physiological stress to both mother and fetus is not simply a short-term event. Not surprisingly, mothers who experienced severe hyperemesis gravidarum go through a traumatic experience, and invariably display a great interest in understanding what that means for their children.

As it was recently shown, hyperemesis gravidarum may lead to adverse health outcomes in the offspring.[13] The findings of reduced insulin sensitivity in particular, suggest that the long-term effects of hyperemesis gravidarum in the offspring need to be properly examined. These cohorts need to be closely evaluated not only throughout childhood and adolescence, but particularly in adulthood, so that long-term disease risks can be adequately evaluated. ■

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