Treatment Options for Hyperemesis Gravidarum

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Abstract

Hyperemesis gravidarum (HG) is a severe and prolonged form of nausea and/or vomiting during pregnancy. HG affects 0.3-2% of pregnancies and is defined by dehydration, ketonuria, and more than 5% body weight loss. Initial pharmacologic treatment for HG includes a combination of doxylamine and pyridoxine. Additional interventions include ondansetron or dopamine antagonists such as metoclopramide or promethazine. The options are limited for women who are not adequately treated with these medications. We suggest that mirtazapine is a useful drug in this context and its efficacy has been described in case studies. Mirtazapine acts on noradrenergic, serotonergic, histaminergic, and muscarinic receptors to produce antidepressant, anxiolytic, antiemetic, sedative, and appetite-stimulating effects. Mirtazapine is not associated with an independent increased risk of birth defects. Further investigation of mirtazapine as a treatment for HG holds promise to expand treatment options for women suffering from HG.

Keywords

Hyperemesis gravidarum; mirtazapine; gastrointestinal disorders in pregnancy; nausea and vomiting in pregnancy; hyperemesis

Introduction

During pregnancy, up to 80% of women experience nausea and/or vomiting (N/V) (Gazmararian et al., 2002) (Gadsby et al., 1993). For the majority of women, N/V resolves by the 16th week of pregnancy (Eliakim et al., 2000) (Gadsby et al., 1993). A severe and prolonged form of N/V, hyperemesis gravidarum (HG), affects 0.3-2% of pregnancies (Hod et al., 1994). The criteria that define HG include dehydration, ketonuria, and more than 5% weight loss (Nelson-Piercy, 1998) (McCarthy et al., 2014). HG is the most common indication for hospital admission in the first 20 weeks of pregnancy (Klebanoff et al., 1985) (Eliakim et al., 2000). Although it usually occurs between weeks 4 and 9 of pregnancy and resolves by mid-gestation (Eliakim et al., 2000), between 15 and 20% of women continue to experience symptoms until the third trimester and 5% through delivery (Goodwin, 2008) (Fell et al., 2006).

Women with HG often present with increased blood urea nitrogen and hematocrit and, in 15-25% of cases, hyponatremia, hypokalemia, and hypochloremia (Goodwin, 1998). Electrolyte abnormalities are corrected with intravenous replacement fluids, however in severe cases, sustained weight loss requires enteral or total parenteral nutrition (Ayyavoo et al., 2014; Levine and Esser, 1988). Between 15 and 50% of patients with HG have elevated serum aminotransferases and total bilirubin (Morali and Braverman, 1990) (Wallstedt et al., 1990).

HG is a clinical diagnosis; however, tools such as the Pregnancy Unique Quantification of Emesis (PUQE) score or Rhodes index have been used to assess the severity of symptoms in research studies (Koren et al., 2002; Rhodes and McDaniel, 1999). HG is a diagnosis of exclusion, and alternative diagnoses should be considered when the N/V begins after 9 weeks gestation, or if bilious emesis, fever, abdominal pain, headache, focal neurological findings, leukocytosis, or hypertension are present. Comorbid conditions, most commonly reflux, should also be evaluated and treated (Gideon et al., 2009). Women presenting with HG are evaluated with serial measures of maternal weight, orthostatic blood pressures, heart rate, electrolytes,

urine ketones, and an obstetric ultrasound if not previously obtained (2015). The differential diagnosis for HG is provided in Table 1.

Table 1. Differential Diagnosis for Nausea and Vomiting in Pregnancy

Gastrointestinal Disorders
Gastroenteritis Cholecystitis Gastroesophageal reflux disease Pancreatitis Appendicitis Peptic ulcer disease Hepatitis Gastroparesis Bowel obstruction
Endocrine and Metabolic Disorders
Hyperthyroidism Hyperparathyroidism Hypercalcemia Diabetic ketoacidosis
Genitourinary and Renal Disorders
Nephrolithiasis Pyelonephritis Uremia
Neurological Disorders
Migraines Pseudotumor cerebri Tumors of the central nervous system Vestibular disease
Psychiatric Disorders
Substance use disorders—alcohol intoxication and withdrawal, opioid withdrawal, sedative/hypnotic/anxiolytic withdrawal, stimulant intoxication Cannabinoid hyperemesis syndrome Eating disorders—anorexia nervosa, bulimia Antidepressant discontinuation syndrome (due to abrupt discontinuation of medication with confirmation of pregnancy)
Other
Medications—antiarrhythmic, antihypertensives, narcotics, anticonvulsants, antibiotics, iron supplementation Cyclic vomiting syndrome
Compiled from: (Goodwin, 1998; Herrell, 2014; Quigley et al., 2001; Wegrzyniak et al., 2012)

Women of African-American, Indian, or Pakistani descent have higher rates of HG compared to European women (Klebanoff et al., 1985) (Price et al., 1996). Primiparous women, adolescents, women with increased BMI, multiple gestations, gestational trophoblastic disease, and women with HG during a previous pregnancy also have increased risk for HG (Klebanoff et al., 1985) (Depue et al., 1987; Eliakim et al., 2000). The risk of recurrent HG is 15-20% (Dodds et al., 2006; Trogstad et al., 2005). Women with a sister or mother who had HG also are also at increased risk, which suggests that genetic factors play a role (Zhang et al., 2011) (Fejzo et al., 2008). Female fetuses are more commonly born to women with HG (Veenendaal et al., 2011). Additionally smoking appears to be a protective factor (Fell et al., 2006; Källén et al., 2003; Vikanes et al., 2010), although the mechanism has not been elucidated. Taking a multivitamin in early pregnancy or prior to conception was associated with decreased N/V (Czeizel et al., 1992; Emelianova et al., 1999; Källén et al., 2003).

Pathogenesis

Hormonal factors have been evaluated as etiologic contributors to HG. Several investigators have reported an increased level of free β-hCG in women with HG compared to matched controls (Goodwin et al., 1994). Additionally, hCG peaks in the first trimester when N/V is typically the most severe. HG is also more common in conditions characterized by high hCG levels such as multiple gestations and gestational trophoblastic diseases (Goodwin et al., 1992; Kimura et al., 1993).

There is homology between the beta-subunit of hCG and TSH which causes hCG to have thyroid-stimulating activity (Ballabio et al., 1991). Initial studies found an increased free thyroxine in 40% and 73% of women with HG (Boullion et al., 1982) (Bober et al., 1986); however, these finding were not confirmed in another investigation (Wilson et al., 1992).

Patients with hyperthyroidism rarely experience N/V, which suggests that thyrotoxicosis is an unlikely etiology of HG.

Additionally, total estradiol and sex hormone binding globulin were 26% and 37% higher, respectively, in women with HG (Depue et al., 1987). As progesterone increases throughout gestation, it is associated with decreased esophageal and gastric motility as well as lower esophageal sphincter pressure. However, progesterone concentrations are most pronounced in the third trimester, not early in pregnancy when HG is most common (Lagiou et al., 2003; Van Thiel et al., 1977).

Several systematic reviews and meta-analyses have shown a significant correlation between *H.pylori* infection and N/V of pregnancy (Golberg et al., 2007; Li et al., 2015; Niemeijer et al., 2014; Sandven et al., 2009). Treatment of *H.pylori* has been shown to improve N/V in infected women (El Younis et al., 1998; Jacoby and Porter, 1999); however, the overall sensitivity and specificity for screening for *H. pylori* in women presenting with HG were only 73% and 55% respectively (Niemeijer et al., 2014).

Historically, HG was thought to be a response to stress or ambivalence about pregnancy (Buckwalter and Simpson, 2002); however, no differences in psychological or personality characteristics between women with and without HG have been demonstrated (Orazio et al., 2011; Sheehan, 2007; Simpson et al., 2001). An analysis of insurance data of 11,016 women who gave birth found that a pre-pregnancy psychiatric diagnosis doubled the risk of developing HG and pre-pregnancy psychiatric and somatic conditions quadrupled the risk, which suggest that these disorders, or a common etiologic factor, may play a role in the development of HG in some women (Seng et al., 2007). Women with HG have been found to have significantly higher levels of plasma serotonin compared to women with N/V of pregnancy and pregnant controls (Cengiz et al., 2015).

Maternal, Fetal and Child Outcomes associated with HG

Maternal Outcomes

Women with HG are at risk for complications from excessive vomiting including hematemesis and from dehydration including dizziness and syncope (Mullin et al., 2012). More severe complications include Wernicke's encephalopathy, central pontine myelinolysis, and peripheral neuropathy due to vitamin B6 or B12 deficiency (Gardian et al., 1999) (Peeters et al., 1993) (Goodwin, 1998).

Women with HG are at increased risk for developing secondary depression and anxiety (McCarthy et al., 2011) (Hizli et al., 2012) (Annagür et al., 2014) (Tan et al., 2010b) which typically resolve with remission of N/V by the third trimester of pregnancy (Tan et al., 2014). In a survey of women's experiences with HG, 15.2% women with had voluntarily terminated at least one pregnancy (Poursharif et a., 2008).

Fetal Outcomes

Decreased rates of early pregnancy loss in women with HG (2000; Bashiri et al., 1995; Hinkle et al., 2016; Weigel and Weigel, 1989) have been reported. One speculation is that N/V eliminates harmful substances from food or alters hormones that facilitate placental development, thereby improving embryologic health (Huxley, 2000; Nulman et al., 2009; Sherman and Flaxman, 2002).

A Norwegian cohort study of 2,270,363 births found a decreased risk of very preterm birth (<32 weeks gestation; odds ratio 0.79, 95%CI, 0.67-0.93) born to women with HG (Vandraas et al., 2013). HG was associated with slight reductions in (21.4 g) and gestational length (0.5 days)

compared with unexposed infants (Vandraas et al., 2013). HG has been associated with increased rates of low birth weight and small for gestational age infants (Bailit, 2005) (Dodds et al., 2006) (McCarthy et al., 2011; Veenendaal et al., 2011) whereas other studies have not confirmed these findings (Vikanes et al., 2013) (Depue et al., 1987) (Tsang et al., 1996). Further, some studies found that stratification by severity of HG (defined by losing greater than 5% of body weight) demonstrated that women with severe HG were more likely to have babies with smaller birth weight and in the $<10^{th}$ percentile at birth compared to women who maintained 95% of their body weight (Gross et al., 1989), although other authors have not replicated this finding (Hallak et al., 1996).

No association was found between HG and decreased Apgar scores, or perinatal mortality (Veenendaal et al., 2011). Boneva et al (1999) observed lower rates of cardiac malformations in women with severe N/V (Boneva et al., 1999) however an association between HG and other anomalies has not been found (Veenendaal et al., 2011).

Child Outcomes

Few data have been published on long term outcomes for children born to mothers with HG. One study showed 20% lower insulin sensitivity in prepubertal children of mothers with severe HG compared to children with mothers without HG (Ayyavoo et al., 2013). A retrospective case control study of adults showed an increase in psychological and behavioral disorders in a composite mental health outcome measure, but individual analyses did not show increases in depression, anxiety, or bipolar disorders (Mullin et al., 2011).

Treatment

Most women who experience N/V are counseled on the self-limited course of symptoms and on avoiding foods, odors, or activities that exacerbate symptoms (Davis, 2004; Matthews et al., 2014). Eating small meals frequently (Bischoff and Renzer, 2006) and snacks of carbohydrate-rich foods, such as soda crackers, may reduce nausea (Jednak et al., 1999).

Indications for hospital admission include significant weight loss, electrolyte abnormalities, and severe or persistent vomiting after rehydration. Inpatient treatment includes intravenous hydration with appropriate electrolyte replacement. Symptoms typically improve within one to two days of rehydration (Summers, 2012).

Alternative Therapies

Non-pharmaceutical approaches to treating N/V include herbs, such as ginger and chamomile, acupuncture, and massage (Davis, 2004; Murphy, 1998; Niebyl and Goodwin, 2002). Capsules of ginger decreased episodes of N/V within one week compared to placebo tablets (Keating and Chez, 2002; Nasrin et al., 2011; Ozgoli et al., 2009). A systematic review and meta-analysis found that ginger reduced nausea, but not vomiting when compared to placebo (Viljoen et al., 2014).

Treatment with acupuncture was associated with decreased severity of N/V compared to placebo in one study (Aghadam and Mahfoozi, 2010). However, three other studies have not confirmed improvement associated with acupuncture compared to placebo (Belluomini et al., 1994; Can Gürkan and Arslan, 2008; Norheim et al., 2001).

Compared to placebo, pyridoxine or vitamin B6 supplementation reduced nausea but not vomiting (Sahakian et al., 1991; Vutyavanich et al., 1995). Vitamin B6 supplementation resulted in similar reductions in nausea and vomiting compared to ginger and acupuncture (Chittumma et al., 2007; Ensiyeh and Sakineh, 2009; Jamigorn and Phupong, 2007; Smith et al., 2004; Sripramote and Lekhyananda, 2003). The mechanism of therapeutic effect is unclear and no correlation between vitamin B6 level and severity of nausea was observed (Schuster et al.,

1985). Vitamin B6 has minimal side effects and is not associated with fetal malformations (2015; Shrim et al., 2006).

Psychotherapeutic Interventions

There are few studies examining psychotherapy treatment for HG, including no randomized trials (2015). However, there are several case studies reporting the efficacy of hypnotherapy (Fuchs et al., 1980; McCormack, 2010; Simon and Schwartz, 1999). Psychological support from family and the medical team has been shown to reduce symptoms of HG (Faramarzi et al., 2015; Liu et al., 2014; Tamay and Kuscu, 2011).

Pharmacologic Therapies

Antihistamines (H1 antagonists), including doxylamine used in combination with pyridoxine, meclizine, dimenhydrinate, and diphenhydramine, are effective in reducing N/V. None of these agents has been associated with fetal malformations (Magee et al., 2002; Seto et al., 1997).

The combination of doxylamine and pyridoxine (Diclegis®) is the only FDA-indicated agent for the treatment of N/V in pregnancy. This formulation, previously sold under the name Bendectin®, was voluntarily withdrawn from the market in 1983 due to alleged teratogenic effects, although multiple studies demonstrated both its efficacy (Geiger et al., 1959; Koren et al., 2010; Magee et al., 2002; Maltepe and Koren, 2013b; Wheatley, 1977) and safety (Brent, 1995; Einarson et al., 1988; Kutcher et al., 2003; McKeigue et al., 1994; Neutel and Johansen, 1995). After Bendectin® was withdrawn from the US market, a three-fold increase in hospitalizations of women with HG was observed (Neutel and Johansen, 1995). Diclegis® received FDA approval in 2013 with a Pregnancy Category A safety classification (Slaughter et al., 2014). Diclegis® is considered first-line pharmacotherapy for N/V in pregnancy by the American Professors in Gynecology and Obstetrics and the American College of Obstetricians

and Gynecologists (2015). However, 97.7% of prescriptions for N/V during pregnancy in the USA are for medications other than Diclegis® , the only drug with an FDA indication for treatment (Koren, 2014).

No adverse effects on cognitive development in children ages 3 to 7 with mothers who had HG both with and without treatment with pyridoxine/doxylamine were observed (Nulman et al., 2009), although another larger study of eight year old children of mothers with HG, regardless of treatment received, showed significantly increased rates of neurodevelopmental delay (Fejzo et al., 2015).

Ondansetron, a serotonin antagonist acting at the 5-HT3 receptor, is the most commonly prescribed medication for the treatment of N/V during pregnancy and its use is rapidly increasing (Koren, 2014). In 2008, the rate of prescriptions per month was 50,000 and in 2013, 110,000 per month. Ondansetron is effective in reducing N/V during pregnancy, and a double-blind randomized controlled study of 36 women found that ondansetron was significantly more effective than combined pyridoxine and doxylamine treatment in reducing nausea and vomiting (Oliveira et al., 2014). Side effects include headache, fatigue, constipation, QT prolongation, and, rarely, serotonin syndrome (Freedman et al., 2013).

The safety of ondansetron during pregnancy was assessed in a Danish study of 1970 exposed infants, which did not show an increased risk of fetal malformations or adverse pregnancy outcomes (Pasternak et al., 2013). However other studies have found that ondansetron was associated with birth defects. A Swedish cohort with 1349 exposed infants found a significantly increased risk of cardiac septal defects (Danielsson et al., 2014) and a US cohort found an increased risk of cleft palate (Anderka et al., 2012). Additionally, a second Danish study using

the same registry but including more infants over more years found a two-fold increase in cardiac malformations (Andersen et al., 2013).

Dopamine antagonists, such as metoclopramide and promethazine, and droperidol, have been used to treat HG (Fadi et al., 2003). Metoclopramide was found to be more effective at reducing N/V than other dopamine antagonists. For example, intravenous metoclopramide with diphenhydramine was more effective at reducing vomiting compared to droperidol with diphenhydramine (Lacasse et al., 2009). Also, metoclopramide with pyridoxine was also more effective than other dopamine antagonists, prochlorperazine and promethazine (Fadi et al., 2003). When metoclopramide was compared to ondansetron, they were comparable in reducing nausea, although ondansetron had a greater effect on reducing vomiting (Kashifard et al., 2013). Both medications resulted in similar improvement in N/V, although metoclopramide was associated with sedation, dry mouth, and dystonias (Abas et al., 2014; Pasricha et al., 2006). Cohort studies have shown that metoclopramide does not increase the risk of fetal malformations (Matok et al., 2009; Pasternak et al., 2014).

Promethazine is primarily an anti-histaminergic medication, and it also acts as a weak dopamine antagonist. It is effective in relieving N/V in pregnancy but has significant maternal side effects including sedation, dystonia, and decreased seizure threshold (Braude and Crandall, 2008; Fitzgerald, 1955; Magee et al., 2002; Seto et al., 1997; Tan et al., 2010a). Droperidol was studied in combination with diphenhydramine and was found to reduce days in the hospital for HG (Nageotte et al., 1996). It has not been associated with fetal malformations, though it is associated with QTc prolongation in some women (Jackson et al., 2007).

Treatments for Refractory HG

Many women do not experience resolution of their symptoms with existing treatments. Studies demonstrating the efficacy of ondansetron, for example, show that most women continue to have at least one episode of vomiting per day even after initiating therapy (Abas et al., 2014). The impairment associated with HG is demonstrated by women who pursue elective abortion due to the severity of their symptoms in otherwise desired pregnancies (Maltepe and Koren, 2013a; Mazzota et al., 1997). One third of women surveyed with HG chose not to become pregnant again because of their experience with HG (Fejzo et al., 2011). In patients refractory to these treatments, several other options have been studied.

Glucocorticoids did not reduce rates of re-hospitalization when compared to placebo (Yost et al., 2003). Furthermore, they have been associated with a possible increased risk of oral cleft when used in the early first trimester (Carmichael and Shaw, 1999; Park-Wyllie et al., 2000; Pradat et al., 2003; Shepard et al., 2002). Other therapeutic options for refractory cases include transdermal clonidine to reduce symptoms in women who cannot tolerate oral therapies. A randomized placebo-controlled clonidine trial with thirteen patients showed significant decreases in symptoms and reduced need for enteral or parenteral nutrition (Maina et al., 2014). A study of seventy patients hospitalized with HG showed reduced re-hospitalizations with diazepam and intravenous fluid compared to intravenous fluid alone (Tasci et al., 2009). Additionally, several case reports have suggested the efficacy of gabapentin (Guttuso et al., 2010; Spiegel and Webb, 2012).

Women who do not respond to any of these interventions and continue to lose weight should be supported with enteral or parenteral nutrition in addition to any medication that provides improvement in symptoms (Stokke et al., 2015). Enteral nutrition provides more relief from N/V compared to parenteral nutrition (Hsu et al., 1996). Some women decline pharmacologic

treatments due to concern about the risk of congenital defects associated with medications taken during early pregnancy.

Mirtazapine

We have included the antidepressant drug mirtazapine in this review to suggest consideration of its use for women who have not responded to other therapies. This drug is not included in recommendations for the treatment of N/V or HG from obstetrical publications (ACOG, 2015). However, mirtazapine is used to treat patients undergoing cancer treatment with rapid onset of efficacy for nausea (day 1) and sleep (within the first five days) (Cardona, 2006; Dupuis and Nathan, 2010; Kim et al., 2008). Its pharmacologic profile of actions is similar to other drugs used to treat HG.

Pharmacology

Mirtazapine acts on noradrenergic, serotonergic, histaminergic, and muscarinic receptors. It is an indirect agonist of the 5-HT_{1A} receptor, an antagonist at the 5-HT_2 receptors, and an inverse agonist at the 5-HT_{2C} receptor to produce the antidepressant effect (Blier and Abbott, 2001). Antagonism of the 5-HT_2 receptor also contributes to the anxiolytic, sedative, and appetite stimulating effects (Fawcett and Barkin, 1998). It is an inverse agonist on the H_1 receptor which contributes to the sedative effect. The antiemetic properties come from antagonism of the 5-HT_3 receptor, which is the same receptor that ondansetron affects (Anttila and Leinonen, 2001). Mirtazapine exerts its antiemetic effect regardless of whether the patient has a psychiatric disorder, though a patient with depression or anxiety may benefit from both of these actions.

Mirtazapine's side effects were rated as average compared to other antidepressants and commonly include sedation, weight gain, dry mouth, and constipation (Cipriani et al.). Similar to other antidepressants, patients should undergo screening for bipolar disorder using an instrument such as the Mood Disorder Questionnaire (Hirschfeld et al., 2000) before starting

mirtazapine and educated about the rare possibility of anxiety, agitation and suicidal ideation at the beginning of treatment.

Mirtazpine is metabolized in the liver and its elimination half-life is between 20 and 40 hours. Mirtazapine is a weak inhibitor of CYP-isoenzymes and is unlikely to cause many clinically relevant drug interactions (Anttila and Leinonen, 2001). Mirtazapine has been associated with serotonin syndrome in multiple case reports, typically when multiple serotonergic drugs are combined (Ansermot et al., 2014). Ondansetron and metoclopramide have also been associated with serotonin syndrome when used as monotherapy and when combined with other serotonergic agents. Though no case reports of serotonin syndrome have been found with the combination of mirtazapine and metoclopramide or ondansetron, it remains a theoretical risk. Signs of serotonin syndrome are diarrhea, diaphoresis, fever, hyperreflexia, confusion, ataxia, myoclonus, tremor, and rhabdomyolysis (Ables and Nagubilli, 2010).

Winterfeld and colleagues (Winterfeld et al., 2015) conducted a prospective cohort study comparing birth defects in infants of women treated antenatally with mirtazapine to two comparison groups, each with 357 subjects. The comparison groups were: 1) mothers treated with selective serotonin reuptake inhibitor antidepressants, and 2) and a general population of women without antidepressant treatment or exposure to known teratogenic agents. No statistically significant difference in the rate of major birth defects after first-trimester exposure between mirtazapine, SSRI-exposed, and non-exposed pregnancies was found. A marginally higher rate of birth defects was, observed in the mirtazapine and SSRI groups compared with the low rate of birth defects in the general control subjects, which is consistent with other studies that evaluated the risk factors related to the underlying depressive disorder (Huybrechts et al, 2014). Rates of preterm birth did not significantly differ across groups.

We present case series of mirtazapine for HG to summarize the published clinical data. A total of fifteen reports of successful treatment of HG with mirtazapine have been published. Six women requested termination of their pregnancy due to the severity of their HG symptoms. Seven patients presented with symptoms of depression and five reported a history of depression. These patients had previously failed other treatments for HG, including patients who did not respond to the following drugs: metoclopramide (n=8); ondansetron (n=5); promethazine (n=4); dimenhydrinate (n=2); and pyridoxine (n=1). Patients began treatment with mirtazapine between gestational weeks 6 and 25. Eight of the patients were treated with 15 mg/day of mirtazapine, four with 30 mg/day and two with 45 mg/day. In eight patients for whom the time to resolution was reported, all responded within one week and five responded in three days. Mirtazapine was continued for between 6 days and 22 weeks. Delivery of healthy babies was reported in twelve of the patients and pregnancy outcomes were not reported in the other three cases (Dorn et al., 2002; Guclu et al., 2005; Rohde et al., 2003; Saks, 2001; Schwarzer et al., 2008; Uguz, 2014).

Future Directions

In a recent Cochrane review (Boelig, et al., 2016) concluded that little evidence existed to support the superiority of one intervention over another in the treatment of HG, and the authors recommended research comparing the side-effect profiles, safety, economic costs and benefits of treatments to inform selection. Comparative evaluation of current treatments and expansion of therapies for severe or refractory HG, which has been associated with requests for termination of desired pregnancies, is imperative. Mirtazapine has highly promising but efficacy and side effect data are limited to multiple case studies. Mirtazapine may expand the options for treating HG, especially in women who are also experiencing psychiatric symptoms, such as depression and anxiety. Such studies should determine characteristics of women who would benefit most from each treatment option to personalize care.

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