Secular Trends in the Treatment of Hyperemesis Gravidarum

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ABSTRACT

The purpose of this study was to describe the treatment of women with hyperemesis gravidarum (HG). Women with HG pregnancies of at least 27 weeks duration occurring between 1985 and 2004 described their treatment on an HG website from 2003 to 2005. The usage and effectiveness of > 20 treatment options were reported by 765 women for 1193 pregnancies. The women who used intravenous (IV) hydration, serotonin inhibitors, and parenteral nutrition (PN) reported the highest rates of effectiveness, with 84%, 83%, and 79% reporting that these respective treatments may have contributed to decreased nausea/vomiting. The use of conventional treatments increased from 20 to 30% to > 60% between 1985 and 1989 and 2000 and 2004; serotonin inhibitor use increased to 55% after its introduction in the 1990s. Over the past 20 years, multiple treatments have been used for women with HG, with a trend toward treatment with reportedly more effective modalities, such as IV hydration and serotonin inhibitors.

KEYWORDS: Hyperemesis gravidarum, nausea, vomiting, pregnancy

Nausea and vomiting of pregnancy (NVP) affects up to 80% of pregnancies, [1,2] often interfering with performance of daily activities, disrupting family life, and causing time loss from work.[3,4] Hyperemesis gravidarum (HG) is the most severe form of NVP and occurs in 0.3 to 2.0% of pregnancies.[5] It can lead to weight loss below prepregnancy body weight, dehydration, and, in some cases, electrolyte or liver function abnormalities.[6,7] Serious maternal morbidity such as Wernicke's encephalopathy is still reported,[8] and fetal growth restriction[9] and even fetal death are seen.[10] Despite the substantial burden of this disease, little progress has been made toward understanding its etiology.

The lack of a unifying pathophysiological mechanism underlies the observed variation in strategies for HG management. Typical management of HG symptoms consists of empirical dietary modification and psychological support.[11] Ingestion of ginger or ginger teas[12] and the use of acupressure or accustimulation[13]

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have been the main alternative approaches to treat symptoms of HG. In refractory cases, a variety of antiemetic medications are used,[11,14] yet the information regarding safety and efficacy of these medications for HG management remains sparse.[15]

Following the devastating thalidomide experience and its removal from European and Canadian markets in the early 1960s, there was a general overestimation of the teratogenic risk of medications during pregnancy.[16] This concern on the part of the public and physicians as well was reflected in the litigation related to Bendectin (Merrell Dow Pharmaceuticals Inc., Reading, NY), which culminated in its removal from the U.S. market in 1983. Prior to that time, Bendectin (a combination of the antihistamine doxylamine and vitamin B_6 with or without dicyclomine) had been used for ~25% of all pregnant women since 1958. After the removal of Bendectin from the market, fear of litigation, combined with a legitimate awareness that there was insufficient evidence regarding safety and efficacy of antiemetic treatments during pregnancy, resulted in wide variation in the use of both pharmacological and other modalities to treat HG. Although case series and a few randomized trials have addressed the use of treatment for NVP, there is very little information on trends in the treatment of HG. The aim of this study is to describe general trends in the treatment of HG during the past two decades, based on patient reports, and to describe patient perceptions of the effectiveness of these treatments.

MATERIALS AND METHODS

The nonprofit Hyperemesis Education and Research (HER) Foundation was established in 2000 and is run by health professionals. Its main goals are (1) to minimize the suffering and complications related to HG through education, (2) to develop an effective HG treatment protocol, (3) to eliminate the need to terminate pregnancy due to ineffective HG treatment, and (4) to raise awareness of the debilitating effects of HG. As part of its mission, it has produced a registry for women with HG and undertaken a variety of online surveys regarding their experiences. One survey, which was offered from 2003 to 2005, questioned women regarding the treatments used for their HG pregnancies and the effectiveness of these treatments.

Women searching for information regarding HG on the Internet located the HER Foundation website and were asked to participate in the survey if they had HG with any of their pregnancies. HG was defined as significant weight loss and debility secondary to NVP, typically requiring medications and/or intravenous (IV) fluids for treatment. For purposes of this study, pregnancies were considered independently and were included only if they resulted in the delivery of a newborn of at least 27 weeks of gestation. Medications were classified according to their pharmacological groups. Diclectin (Duchesnay Inc., Laval, Quebec, Canada) was grouped with antihistamines, and vitamin B_6 was grouped with vitamins. Alternative approaches included acupuncture, herbal medicine, homeopathy, sea bands, and chiropractic. Treatments that have characteristics of more than one category (e.g., promethazine, which is both an antihistamine and a phenothiazine) were grouped according to the presumed predominant mechanism of action. Women who reported that the treatments were "effective" or "maybe effective" were combined and compared with those who reported the treatments as "ineffective." We described the usage of the treatments by country of residence at the time of treatment and grouped them by 5-year periods starting from 1985 and ending in 2004. The questions regarding treatment as they appeared in the survey are listed in the appendix. Chi-square testing was used to compare differences across countries and across time periods. All calculations were performed in SAS (version 9.0; SAS Institute, Cary, NC). The study was approved through the institutional review board of the University of Southern California Health Sciences Campus.

RESULTS

Overall, 765 women from 26 countries participated in the survey. These women reported 1193 pregnancies between 1985 and 2004, 80% of which occurred in the United States. These patients reported the use of treatments in 25 different pharmacological and nonpharmacological categories (Table 1). During the past two decades, IV hydration and antihistamines were the most commonly used treatment modalities, with usage in 6 out of 10 pregnancies. Bed rest, alternative approaches, dietary changes, serotonin inhibitors, and vitamins were the other most frequent treatments. The frequency of the various treatments differed across the countries of residence. Women who resided in the United States during their pregnancy were the most likely to use IV hydration, serotonin inhibitors, vitamins, H_2 blockers, parenteral nutrition (PN), trimethobenzamide, and lansoprazole. Women who resided in Canada reported the highest usage of antihistamines and the lowest usage of IV therapy, promotility agents, and phenothiazines. The usage of any major medications other than antihistamines did not exceed the rate of 20% in these women. Women who reported that their pregnancy occurred in the United Kingdom were the most likely to have been treated with phenothiazines and anticholinergics and the least likely to have been treated with vitamins, antihistamines, and PN. The highest reported usage of promotility agents and the lowest reported usage of anticholinergics were among women from Australia/New Zealand. Although reported usage of bed rest, alternative approaches and dietary changes

Table 1 Hyperemesis Gravidarum Treatments by Country of Residence (in Order of Frequency)

		United States N = 952 (79.8%)	United Kingdom N = 81 (6.8%)	Australia/ New Zealand N = 80 (6.7%)	Canada N = 40 (3.4%)	Other N = 40 (3.4%)	Total N = 1193 (100%)	p
1*	**Intravenous hydration**	595 (62.5%)	46 (56.8%)	42 (52.5%)	16 (40.0%)	21 (52.5%)	720 (60.4%)	0.015
2*	**Antihistamines**	619 (65.0%)	15 (18.5%)	21 (26.3%)	35 (87.5%)	18 (45.0%)	708 (59.4%)	< 0.001
3	**Bed rest**	549 (57.7%)	50 (61.7%)	55 (68.8%)	22 (55.0%)	24 (60.0%)	700 (58.7%)	0.900
4	**Alternative approaches**	524 (55.0%)	48 (59.3%)	51 (63.8%)	25 (62.5%)	20 (50.0%)	668 (56.0%)	0.416
5	**Dietary changes**	536 (56.3%)	35 (43.2%)	41 (51.3%)	22 (55.0%)	21 (52.5%)	655 (54.9%)	0.721
6*	**Serotonin inhibitors**	466 (49.0%)	5 (6.2%)	20 (25.0%)	4 (10.0%)	6 (15.0%)	501 (42.0%)	< 0.001
7*	**Vitamins**	312 (32.8%)	8 (9.9%)	26 (32.5%)	10 (25.0%)	8 (20.0%)	364 (30.5%)	< 0.001
8*	**Promotility agents**†	282 (29.6%)	13 (16.1%)	52 (65.0%)	3 (7.5%)	6 (15.0%)	356 (29.8%)	< 0.001
9*	**H_2 blockers**	252 (26.5%)	11 (13.6%)	14 (17.5%)	7 (17.5%)	5 (2.5%)	289 (24.2%)	0.008
10*	**Phenothiazines**	209 (22.0%)	31 (38.3%)	24 (30.0%)	3 (7.5%)	4 (10.0%)	271 (22.7%)	< 0.001
11*	**Anticholinergics**	211 (22.2%)	31 (38.3%)	7 (8.8%)	7 (17.6%)	10 (25.1%)	266 (22.4%)	< 0.001
12*	**Total parenteral nutrition**	164 (17.2%)	2 (2.5%)	4 (5.0%)	2 (5.0%)	5 (12.5%)	177 (14.9%)	< 0.001
13	**Massage**	107 (11.2%)	4 (4.9%)	10 (12.5%)	3 (7.5%)	8 (20.0%)	132 (11.1%)	0.280
14*	**Trimethobenzamide**	93 (9.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.5%)	94 (7.9%)	< 0.001
15	**Antidepressants**	84 (8.8%)	1 (1.2%)	4 (5.0%)	2 (5.0%)	2 (5.0%)	93 (7.8%)	0.091
16	**Corticosteroids**	57 (6.0%)	2 (2.5%)	4 (5.0%)	0 (0.0%)	3 (7.5%)	66 (5.5%)	0.340
17*	**Lansoprazole**	61 (6.4%)	0 (0.0%)	0 (0.0%)	1 (2.5%)	2 (5.0%)	64 (5.4%)	0.018
18	**Psychological therapies**	53 (5.6%)	1 (1.2%)	1 (1.3%)	3 (7.5%)	5 (12.5%)	63 (5.3%)	0.076
19	**Enteral nutrition**	24 (2.5%)	1 (1.2%)	2 (2.5%)	0 (0.0%)	0 (0.0%)	27 (2.3%)	0.636
20	**Gastric pacing**	21 (2.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (5.0%)	23 (1.9%)	0.175
21	**Droperidol**	21 (2.2%)	0 (0.0%)	1 (1.3%)	0 (0.0%)	0 (0.0%)	22 (1.9%)	0.424
22	**Antibiotics**	17 (1.8%)	0 (0.0%)	1 (1.3%)	0 (0.0%)	0 (0.0%)	18 (1.5%)	0.558
23	**Physical therapy**	10 (1.1%)	0 (0.0%)	0 (0.0%)	1 (2.5%)	1 (2.5%)	12 (1.0%)	0.485
24	**Cannabis**	7 (0.7%)	1 (1.2%)	1 (1.3%)	0 (0.0%)	0 (0.0%)	9 (0.8%)	0.918
25	**Allergy injection**	3 (0.3%)	1 (1.2%)	0 (0.0%)	0 (0.0%)	1 (2.5%)	5 (0.4%)	0.185

*Use of the highlighted treatments varied statistically across countries ($p < 0.05$)
†This group includes metoclopramide

appeared to differ across the countries, these differences were not statistically significant.

Table 2 summarizes the usage of these treatment modalities during the years 1985–1989 to 2000–2004. The usage of IV therapy, antihistamines, bed rest, and vitamins almost doubled during years 1985–1989 to 2000–2004, whereas the usage of alternative approaches, anticholinergics, and antidepressants increased twofold during this period. Use of dietary changes increased from > 30% to near 60%, and the usage of promotility agents increased 3.5 times during these years. The usage of serotonin inhibitors, H_2 blockers, corticosteroids, and lansoprazole started in the 1990s and showed an increasing trend thereafter. The usage of PN, trimethobenzamide, psychological therapies, and enteral nutrition appeared to increase from 1985 to 2004, but these changes did not reach statistical significance. The usage of phenothiazines remained the same throughout this period, whereas droperidol was used less frequently over time, probably related to safety concerns.

Table 2 also includes women's reported effectiveness of these treatments. Among more frequently used treatment modalities, 80% of women reported that IV hydration, serotonin inhibitors, and PN may have been effective. More than half of those women who tried bed rest, H_2 blockers, massage, and corticosteroids, and nearly half of those who were treated with antihistamines, reported at least some level of effectiveness. The least effective treatments were trimethobenzamide and the majority of alternative approaches, with reported potential effectiveness of < 20%.

DISCUSSION

This study demonstrates that during the past two decades conventional therapies such as intravenous hydration, antihistamines, bed rest, and dietary changes have been the mainstays of HG treatment in this population. The primary exception is ondansetron, which was first reported as used during the early 1990s. By the years 2000 to 2004, it was reported as being used by ~50% of the women in this registry. Although Bendectin was removed from the U.S. market in 1983, Diclectin, its near equivalent (doxylamine/pyridoxine), has remained available in Canada.[15] Our data confirm that during the first years after Bendectin removal from the

Table 2 Secular Trends in Treatment of Hyperemesis Gravidarum, 1995 to 2004 (in Order of Frequency)

	Treatment Modality	1985–1989 N = 36	1990–1994 N = 82	1995–1999 N = 283	2000–2004 N = 792	Total N = 1193	*p*	Effective or Maybe Effective
1*	Intravenous hydration	11 (30.6)	36 (43.9)	160 (56.5)	513 (64.8)	720 (60.4%)	< 0.001	603 (83.8%)
2*	Antihistamines†	14 (38.9)	30 (36.6)	149 (52.7)	515 (65.0)	708 (59.4%)	< 0.001	349 (49.3%)
	Antihistamines (nonspecified)	7 (19.4)	19 (23.2)	68 (24.0)	246 (31.1)			
	Doxylamine/pyridoxine ± dicycloverine	1 (2. 8)	1 (1.2)	9 (3.2)	54 (6.8)			
	Prochlorperazine	9 (25.0)	24 (29.3)	121 (42.8)	429 (54.2)			
3*	Bed rest	11 (30.6)	38 (46.3)	152 (53.7)	499 (63.0)	700 (58.7%)	< 0.001	375 (53.6%)
4*	Alternative approaches†	7 (19.4)	28 (34.2)	146 (51.6)	487 (61.5)	668 (56.0%)	< 0.001	118 (17.7%)
	Acupuncture	1 (2.8)	5 (6.1)	28 (9.9)	108 (13.6)			
	Herbal medicine	2 (5.6)	11 (13.4)	34 (12.0)	141 (17.8)			
	Homeopathy	1 (2.8)	10 (12.2)	22 (7.8)	95 (12.0)			
	Seabands	3 (8.3)	23 (28.6)	123 (43.5)	415 (52.4)			
	Chiropractic	1 (2.8)	3 (3.7)	19 (6.7)	57 (7.2)			
5*	Dietary change	12 (33.3)	35 (42.7)	142 (50.2)	466 (58.8)	655 (54.9%)	0.001	147 (22.4%)
6*	Serotonin inhibitors†	0 (0.0)	4 (4.9)	58 (20.5)	439 (55.4)	501 (42.0%)	< 0.001	416 (83.0%)
	Ondansetron	0 (0.0)	4 (4.9)	57 (20.1)	436 (55.1)			
	Granisetron	0 (0.0)	0 (0.0)	0 (0.0)	10 (1.3)			
	Dolasetron	0 (0.0)	0 (0.0)	2(0.7)	25 (3.2)			
7*	Vitamins	6(16.7)	16 (19.5)	81 (28.6)	261 (33.0)	364 (30.5%)	< 0.001	102 (28.0%)
8*	Promotility agents†	3 (8.3)	12 (14.6)	52 (18.4)	289 (36.5)	356 (29.8%)	< 0.001	108 (30.3%)
	Metoclopramide	3 (8.3)	12 (14.6)	51 (18.0)	283 (35.7)			
	Cisapride	0 (0.0)	1 (1.2)	3 (1.1)	10 (1.3)			
	Domperidone	0 (0.0)	2 (2.4)	3 (1.1)	19 (2.4)			
9*	H_2 histaminic receptor blockers†	0 (0.0)	7 (8.5)	41 (14.5)	241 (30.4)	289 (24.2%)	< 0.001	149 (51.6%)
	Ranitidine	0 (0.0)	2 (2.4)	23 (8.1)	125 (15.8)			
	Cimetidine	0 (0.0)	1 (1.2)	10 (3.5)	59 (7.5)			
	Famotidine	0 (0.0)	4 (4.9)	20 (7.1)	157 (19.8)			
10	Phenothiazines†	8 (22.2)	17 (20.7)	71 (25.1)	175 (22.1)	271 (22.7%)	0.736	100 (36.9%)
	Prochlorperazine	6 (16.7)	17 (20.7)	65 (23.0)	160 (20.2)			
	Chlorpromazine	3 (8.3)	4 (4.9)	12 (4.2)	32 (4.0)			
11*	Anticholinergics†	3 (8.3)	15 (18.3)	54 (19.1)	194 (24.5)	266 (22.3%)	0.033	60 (22.6%)
	Scopolamine	1 (2.8)	1 (1.2)	3 (1.1)	11 (1.4)			
	Anticholinergics (nonspecified)	0 (0.0)	15 (18.3)	53 (18.7)	187 (23.6)			
12	Total parenteral nutrition	2 (5.6)	7 (8.5)	36 (12.72)	132 (16.7)	177 (14.4%)	0.081	139 (78.5%)
13	Massage	2 (5.6)	7 (8.5)	23 (8.1)	100 (12.6)	132 (11.1%)	0.110	74 (56.1%)
14	Trimethobenzamide	1 (2.8)	9 (11.0)	23 (8.1)	61 (7.7)	94 (7.9%)	0.487	15 (16.0%)
15*	Antidepressants	1 (2.8)	4 (4.9)	9 (3.2)	79 (10.0)	93 (7.8%)	0.001	38 (40.9%)
16*	Corticosteroids	0 (0.0)	2(2.4)	10 (3.5)	54 (6.8)	66 (5.5%)	0.040	36 (54.6%)
17*	Lansoprazole	0 (0.0)	1 (1.2)	6 (2.1)	57 (7.20)	64 (5.4%)	0.001	27 (47.4%)
18	Psychological therapies	3 (8.3)	3 (3.7)	11 (3.9)	46 (5.8)	63 (5.3%)	0.488	13 (20.6%)
19	Enteral nutrition	0 (0.0)	3(3.7)	6 (2.1)	18 (2.3)	27 (2.3%)	0.663	7 (25.9%)
20	Gastric pacing	2 (5.6)	1 (1.2)	5 (1.8)	15 (1.9)	23 (1.9%)	0.428	10 (43.5%)
21	Droperidol	1 (2.8)	2 (2.4)	4(1.4)	15 (1.9)	22 (1.9%)	0.888	8 (36.4%)
22	Antibiotics	0 (0.0)	1 (1.2)	4 (1.4)	13 (1.6)	18 (1.5%)	0.068	4 (22.2%)
23	Physical therapy	0 (0.0)	1 (1.2)	4 (1.4)	7 (0.9)	12 (1.0%)	0.802	7 (58.3%)
24	Cannabis	0 (0.0)	1 (1.2)	0 (0. 0)	8 (1.0)	9 (0.8%)	0.340	7 (77.8%)
25	Allergy injection	0 (0.0)	1 (1.2)	0 (0. 0)	4 (0.5)	5 (0.4%)	0.433	3 (60.08%)

*Use of the highlighted treatments varied statistically between time periods ($p < 0.05$)
†Numbers in subcategories may not add up to total due to usage of multiple drugs in the same category by some patients

U.S. market, women with HG were more likely to have been treated with nonpharmacological treatment modalities such as bed rest, dietary changes, and alternative approaches.

Of particular concern, 67% of women with HG in the United States, and as many as 90% of women with HG in the United Kingdom, did not report being prescribed vitamins such as pyridoxine and thiamine during the critical period of fetal development when HG commonly presents. Pyridoxine is known to be safe and one of the few agents for which randomized controlled trials have confirmed its efficacy in reducing symptoms in general NVP.[17,18] Thiamine has been recommended for all women with >3 weeks of daily vomiting because this is associated with Wernicke's encephalopathy,[11] which can lead to permanent maternal neurological dysfunction and death of the fetus or mother.[8] Although we found an increasing use of these vitamins from 17% in 1985–1989 to 33% in 2000–2004, there is still significant underutilization.

Although the use of nonpharmacological measures has stayed almost the same over time, the use of the antiemetic medications such as antihistamines has increased at least by 100% in the 2000 to 2004 period. This may be attributed to the increased body of evidence regarding the safety of most of the antihistamines in particular.[15]

Our study also shows that whereas nonpharmacological treatment modalities were used in equivalent proportions in the various countries represented in this survey, the usage of various medications for HG treatment differed according to country of residence. It has been suggested that the availability of Diclectin in Canada has enabled physicians to treat NVP effectively in earlier stages of the disease,[19] reducing the rate of severe NVP and HG and the need for hospitalization. Our data may be consistent with this view in that they demonstrate that use of IV hydration and PN was significantly less among Canadian women compared with Americans. Nevertheless, from these data we cannot distinguish whether Canadian women were indeed treated earlier with less invasive modalities, thus preventing more serious disease, or whether Canadian women were undertreated. American women, in contrast, seem to have been treated primarily with ondansetron, which is more expensive than conventional antiemetics. Our understanding of the effectiveness of antiemetic medications for the treatment of HG remains limited. Although several comparisons of antiemetic medications have been conducted, including some randomized controlled trials,[20,21] these have yielded conflicting results with no regimen demonstrating clear benefit over any other. Several studies have shown a benefit of various formulations of ginger in NVP and, in one trial, in HG.[21–24] With respect to pyridoxine, randomized trials have shown a benefit in the treatment of NVP when it is used alone[17,18] or in combination with antihistamine doxylamine.[25] Trials of antihistamines alone suggest efficacy in NVP, but the data are heterogeneous.[15] The weight of the randomized trials of acupressure or acustimulation suggests a benefit in NVP with no apparent risk.[13] Among anticholinergics, dicyclomine failed to show effectiveness in decreasing nausea in one study,[25] whereas phenothiazines have been shown to decrease the symptoms of NVP significantly.[26,27] Despite its relatively common usage, metoclopramide has never been subjected to an efficacy trial in NVP or HG. The status of ondansetron as the most commonly prescribed medication for women with HG is in contrast to the evidence, a single study, which showed that ondansetron is not superior to promethazine in decreasing the severity of nausea.[28] In our study, possible effectiveness was reported with ondansetron in 80% of women's pregnancies, a proportion equivalent to that reported for IV hydration and PN. However, possible effectiveness of antihistamines, including promethazine, was reported in fewer than half of women's pregnancies. Interestingly, although corticosteroids have been the subject of more randomized trials than any other pharmacological regimen for HG; they were infrequently reported in this survey. This may be due to the inconclusive results of the trials or to concerns related to teratogenicity.

Serious complications of parenteral nutrition, including maternal death, have been reported;[29] such complications are seen even with peripherally inserted catheter (PIC) lines.[30] In our report, use of PN increased significantly over the years, but use of enteral nutrition remained low. Enteral feeding has very few adverse effects,[31] and although placement of the enteral feeding tube may not be well tolerated by women with HG, access to and adaptation of this treatment option warrants further exploration.

Women with HG may suffer from oropharyngeal and dental lesions due to increased exposure of mucosa to corrosive gastric contents. This study shows that although the usage of H_2 blockers has increased recently, still more than half of women with HG have not being treated with these agents.

Our results are based on women's self-reports of the treatments used to improve the symptoms of HG, and consequently we acknowledge the inherent limitations in the accuracy and generalizability of our findings. We wish to note that many of the women used these treatments in combination, and for this reason, the reported effectiveness of any individual treatment may be influenced. Because of the large number of treatments analyzed, the interpretability of statistical significance may be limited. Nevertheless, we believe that these findings contribute to our understanding of women's perception of their treatment for HG, and that they suggest further opportunities for

maximizing the effectiveness of current treatment modalities.

The pharmacological treatment of HG appears to have become more frequent during recent years and may potentially be attributed to more evidence regarding the safety of most of the antiemetic medications during pregnancy. However, the concern of teratogenicity of medications and lack of evidence-based HG management guidelines may be contributing to the low and heterogeneous use of antiemetic drugs to treat HG internationally. More research regarding the safety and effectiveness of different medications for HG treatment and more education about the prevention of severe complications of HG with administration of vitamins/B_6 therapy is warranted.

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APPENDIX

Did the following treatments decrease or eliminate your nausea and vomiting? (Please answer: "Not offered" for all treatments that were not offered to you, "Effective" for all treatments that helped your symptoms, "Not effective" for treatments you tried that did not help, "Maybe" for all treatments you tried that might have helped, and "Not tried" for all treatments you did not try but were offered. Using the option of "Not tried" allows us to know if a treatment is being offered, but women are not trying it.)

List of Medications and Treatments: These are equivalent to the medications and treatments listed in Tables 1 and 2.

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