OBSTETRICS

Prepregnancy metformin use associated with lower risk of severe nausea and vomiting of pregnancy and hyperemesis gravidarum

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BACKGROUND: Severe nausea and vomiting of pregnancy and hyperemesis gravidarum are associated with adverse maternal, fetal, and child outcomes. The recurrence risk is reported to be as high as 89%. Identifying an effective, safe, and affordable method to prevent hyperemesis gravidarum is critical to reducing the risk for reoccurrence and improving maternal, fetal, and child health. We recently demonstrated that a genetic predisposition to hyperemesis gravidarum is mediated by low prepregnancy levels of the emetogenic hormone, growth and differentiation factor 15, which leads to hypersensitivity to its rapid rise during pregnancy. Because metformin increases circulating levels of growth and differentiation factor 15, we hypothesized that the use of metformin before pregnancy will desensitize patients to the hormone and lower the risk for severe nausea and vomiting in pregnancy and hyperemesis gravidarum.

OBJECTIVE: The objective of the study was to determine whether daily use of metformin is associated with a lower risk for severe nausea and vomiting of pregnancy and hyperemesis gravidarum.

STUDY DESIGN: Through means of a structured questionnaire, visitors to the Hyperemesis Gravidarum Education and Research Foundation social media sites from January 2023 to September 2024 reported daily use of 32 common substances in the month before each pregnancy and the level of nausea and vomiting of pregnancy. Crude and multivariate associations between the use of each substance and severe nausea and vomiting of pregnancy and hyperemesis gravidarum in the subsequent pregnancy were estimated using a logistic regression. The final multivariate models included tobacco use and maternal age; the number and type of additional drugs used and race and ethnicity had little influence and were not retained.

RESULTS: A total of 5414 participants reported their daily medication and substance use in the month before pregnancy and the level of nausea and vomiting during pregnancy. Using metformin before the first pregnancy was associated with a >70% reduction in the risk for hyperemesis gravidarum (adjusted relative risk, 0.29; 95% confidence interval, 0.12–0.71; P=.007). Tobacco use was also associated with a significant reduction in the risk (adjusted relative risk, 0.51; 95% confidence interval, 0.30–0.86; P=.011). Conversely, selective serotonin reuptake inhibitors were associated with an increased risk for hyperemesis gravidarum (adjusted relative risk, 2.41; 95% confidence interval, 1.33–4.38; P=.004). The use of metformin was also associated with an 82% reduction in the risk for severe nausea and vomiting of pregnancy and hyperemesis gravidarum (adjusted odds ratio, 0.18; 0.06–0.59; P=.005) in the second pregnancy, even after adjustment for the 86% reoccurrence risk identified in this study. Conversely, the use of cannabis or selective serotonin reuptake inhibitors before the second pregnancy were each associated with increased risk (adjusted odds ratio, 3.48; 1.80–6.75; P<.001; and adjusted odds ratio, 1.84; 1.12–3.04; P=.016, respectively).

CONCLUSION: Prepregnancy metformin treatment may decrease the risk for severe nausea and vomiting, whereas prepregnancy cannabis use and selective serotonin reuptake inhibitors may increase the risk. Metformin, which is routinely used before and after conception, may be a safe and affordable treatment to offer patients with a history of hyperemesis gravidarum to decrease the chance of reoccurrence. Clinical trials are warranted to investigate metformin use before pregnancy to lower the risk for hyperemesis gravidarum, thereby mitigating the associated adverse maternal and offspring outcomes.

Key words: cannabis, GDF15, growth and differentiation factor 15, hyperemesis gravidarum, metformin, morning sickness, nausea, pregnancy, prevention, selective serotonin reuptake inhibitors, vomiting

Introduction

During pregnancy, 70% of people are affected by nausea and vomiting.[1] The most severe form, hyperemesis gravidarum, is associated with adverse physical and psychological maternal, fetal, and child outcomes and even maternal and fetal death.[1,2] Suicide, pregnancy termination, and fear of subsequent pregnancy are common considerations for patients with hyperemesis gravidarum, particularly among those who report poorer quality of care.[3,4] Families often change their reproductive plans because of the condition.[5,6]

The greatest risk factors for hyperemesis gravidarum are having a previously affected pregnancy and having an affected family member, which supports a genetic etiology.[5–7] We discovered associations between hyperemesis gravidarum and genetic variants in growth and differentiation factor 15 (GDF15) and subsequently showed that a main cause of hyperemesis gravidarum is a genetic predisposition for increased sensitivity to high circulating levels of GDF15, an emetogenic hormone released by the placenta.[8–10] We also discovered that desensitization to GDF15 before pregnancy may be a strategy to prevent the disease.[10] Genetic risk variants at the *GDF15* gene locus are associated with lower GDF15 levels in the nonpregnant state, likely

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AJOG at a Glance

Why was this study conducted?

The risk for severe nausea and vomiting of pregnancy and hyperemesis gravidarum may be reduced by increasing growth and differentiation factor 15 (GDF15) before pregnancy to desensitize against the rise of the emetogenic hormone during pregnancy. Metformin increases circulating GDF15. This study was conducted to determine whether prepregnancy metformin treatment is associated with a decreased risk for severe nausea and vomiting of pregnancy and hyperemesis gravidarum.

Key findings

Daily use of metformin in the month before pregnancy was associated with >70% reduction in the risk for severe nausea and vomiting of pregnancy and hyperemesis gravidarum. Cannabis and selective serotonin reuptake inhibitors were associated with increased risk.

What does this add to what is known?

The recurrence risk for severe nausea and vomiting of pregnancy and hyperemesis gravidarum is high. This study provides support for the hypothesis that prepregnancy metformin treatment may reduce the risk for severe nausea and vomiting of pregnancy and hyperemesis gravidarum. This study identified medications and substances associated with increased risk.

contributing to acute sensitivity to the rise in GDF15 in early pregnancy.[10] This mechanism is supported by a murine model and observation in humans.[10] Mice were desensitized to an acute dose of GDF15 by low-dose GDF15 pretreatment. GDF15 is a stress-response hormone that is not only expressed by the placenta but also in nonpregnant individuals by cells and tissues under stress, which leads to higher circulating levels in people with chronic diseases and in chronic smokers from damaged lung tissue.[10–12] Accordingly, people with conditions or substance use associated with elevated GDF15 before pregnancy (thalassemia and tobacco) experienced a markedly reduced risk for developing hyperemesis gravidarum.[10]

An effective, safe, and affordable method to prevent hyperemesis gravidarum would decrease complications associated with the condition.[1] Metformin is a rational candidate for lowering hyperemesis gravidarum risk because it induces the endogenous production of GDF15.[13,14] We hypothesized that metformin use before pregnancy may desensitize patients to the rise in GDF15 during pregnancy, thereby providing an affordable and effective pathway to lower hyperemesis gravidarum risk (Figure).[10] Metformin use before and during pregnancy is generally well-tolerated and considered to be safe and may improve fertility and reduce maternal complications in patients with polycystic ovary syndrome.[15–17] Metformin has a reassuring safety profile in pregnancy, in addition to a long-term safety profile in children exposed during gestation as treatment for mothers' with type 2 diabetes.[18,19] Because metformin is an inexpensive generic medication, if effective, it may provide an equitable solution to lower the risk for hyperemesis gravidarum. This study aimed to study nausea and vomiting of pregnancy levels in patients exposed to medications and substances before pregnancy to gain insight into the use of metformin as a method to reduce the risk for severe nausea and vomiting of pregnancy and hyperemesis gravidarum.

Materials and methods

Source population and study design

A retrospective online survey was conducted by the Hyperemesis Education and Research Foundation and the University of Southern California using a structured questionnaire that was disseminated via the Hyperemesis Education and Research Foundation social media platforms from January 2023 to September 2024. This survey was open to those with 1 or more live birth(s) who have and have not had hyperemesis gravidarum. Of the 5613 participants who took part in the survey, 23 were excluded because of logically incompatible sets of responses to key variables, leading to a total of 5590 participants included in the final analysis. The survey was anonymous and allowed 1 response per Internet Protocol address. This institutional review board–approved study was exempt from review because survey responses were anonymous, and no identifiers were obtained during the survey.

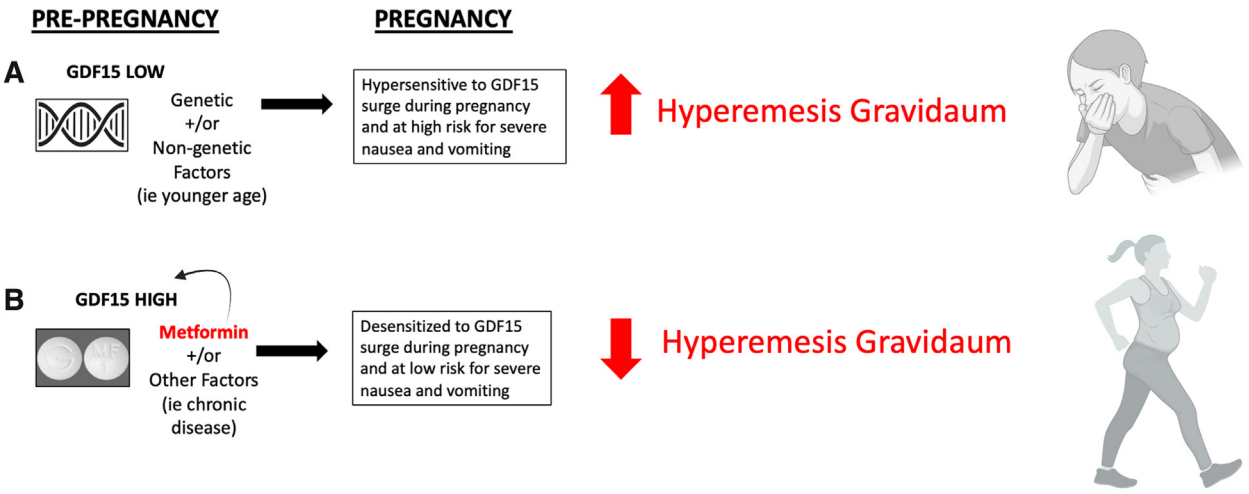
Data collection measures

The online questionnaire included 18 questions. The initial section queried the number of pregnancies (1–6, >6, unknown and prefer not to answer, or never pregnant). The subsequent section queried the participant on the number of pregnancies that ended in a live birth (with similar response options). The third section inquired about the participant's age at the time of the survey. The fourth and fifth sections requested information on the age at first live birth and the country of residence during the first live birth. Another section gathered data on race or ethnicity or ancestry. Two final sections inquired about daily intake of certain medications and substances for 1 month before each pregnancy and the intensity of nausea and vomiting of pregnancy per pregnancy. The medications and substances queried appears in the Supplemental methods.

Exposure

We requested information on the exposure to metformin and tobacco, which we hypothesized would be linked to the outcome because of their association with elevated GDF15 levels, and cannabis because of its self-reported effectiveness in mitigating symptoms and improving weight gain during pregnancies affected by hyperemesis gravidarum.[10–14,20,21] We titled the survey "Daily medication prior to

FIGURE
Model and potential prevention strategy



A, When GDF15 levels are low before pregnancy because of genetics and other factors, then the patient may be hypersensitive to the rise in GDF15 during pregnancy and at increased risk for severe nausea and vomiting and hyperemesis gravidarum. **B,** When GDF15 levels are high before pregnancy because of prepregnancy metformin treatment and other factors, then the patient may be desensitized to the rise in GDF15 during pregnancy and at low risk for severe nausea and vomiting and hyperemesis gravidarum.

GDF15, growth and differentiation factor 15.

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pregnancy" and queried participants about the use of a broad spectrum of additional, frequently used medications to conceal our hypotheses and minimize the influence of the research process on participants' reporting of accurate and unbiased data. Our hypothesis was published in January 2024,[10] and survey participation was closed in September 2024, giving participants little time to test it and become pregnant in the short time frame. Regardless, we performed a subanalysis with removal of those who participated after posting the hypothesis, and the results were comparable.

Outcome

The primary outcome variable, namely nausea and vomiting of pregnancy experienced during each pregnancy, was reported by participants who selected 1 of 5 order levels of severity specified by detailed descriptions published previously. Although the 5-point scale has not been validated in a clinical setting, it has been used in research settings in at least 3 separate studies that have had substantial findings, supporting its use. More detail about the 5-point scale is provided in the Supplemental methods.[7,8,22]

Statistical analysis

For the descriptive analyses, we tabulated the values of the 5-level nausea and vomiting of pregnancy variable reported by each participant for each of the first 6 pregnancies and reported these as count data and percentages (Supplemental Table 1). We also reported the distributions of values for categorical demographic and clinical variables of the participants during the first pregnancy (Table 1). We used chi-square tests to assess the differences in distribution of these categorical variables in terms of dichotomous nausea and vomiting of pregnancy status (no nausea and vomiting of pregnancy, mild nausea and vomiting of pregnancy, or moderate nausea and vomiting of pregnancy vs severe nausea and vomiting of pregnancy or hyperemesis gravidarum).

We used a multinomial logistic regression to determine the point estimate and 95% confidence interval (95% CI) estimates of the relative risk (RR), assessed as the odds ratios (ORs) for the association between use of each medication or substance and nausea and vomiting of pregnancy level. A multivariate analytical model was built by introducing terms for candidate covariates one-by-one and retaining those that produced a $\geq$10% difference in the effect size. Candidate covariates were clinical and demographic variables and terms for use of each medication or substance, except for selective serotonin reuptake inhibitors (selective serotonin reuptake inhibitors) and corticosteroids and derived variables that captured the total number of reported medications and substances used and the number of drug categories used for 30 days before pregnancy. The derived selective serotonin reuptake inhibitor variable was scored as yes for each participant who reported using either sertraline or escitalopram and as no for all others. The corticosteroid variable was scored as yes for participants who reported using prednisone or triamcinolone acetonide and as no for others. The final models included terms for use of tobacco (yes or no), metformin (yes or

TABLE 1
Clinical and demographic characteristics of the study population[a] according to severity of nausea and vomiting of pregnancy reported for first pregnancy

	First pregnancy		
	None and Mild and Moderate nausea and vomiting of pregnancy	Severe nausea and vomiting of pregnancy and hyperemesis gravidarum	
Clinical and demographic variables	N (%) or mean±standard deviation	N (%) or mean±standard deviation	*P* value
Age at first live birth (y)	880 (27.6±5.7)	4424 (27.7±4.9)	.42
Country where first live birth was delivered	881/881 (100)	4432 (100)	
United States	534/881 (60.6)	2520/4432 (56.9)	.01
United Kingdom	171/881 (19.4)	806/4432 (18.2)	
Australia	33/881 (3.8)	239/4432 (5.4)	
Others	143/811 (16.2)	867/4432 (19.6)	
Race or ethnicity or ancestry	881 (100)	4432 (100)	.82
White	719/881 (81.6)	3670/4432 (82.8)	
Hispanic and Latino	63/881 (7.2)	281/4432 (6.3)	
Other	30/881 (3.4)	162/4432 (3.7)	
Black and African American	30/881 (3.4)	131/4432 (3.0)	
Asian	27/881 (3.1)	119/4432 (2.7)	
Prefer not to answer	6/881 (0.7)	40/4432 (0.9)	
American Indian and Alaska Native	2/881 (0.2)	17/4432 (0.4)	
Native Hawaiian or Other Pacific Islander	4/881 (0.5)	12/4432 (0.3)	

[a] Data not provided for participants with missing values for clinical and demographic variables.

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no), cyclobenzaprine (yes or no), and derived variables for selective serotonin reuptake inhibitors and for corticosteroids. Some key variables, including maternal age at first live birth, number and types of additional drugs used, and race and ethnicity, that demonstrated minimal influence were not included in the final model. Maternal age at the time of the first pregnancy was missing for 105 participants. To evaluate whether including these individuals in the analyses were likely to introduce confounding, the analyses were repeated in the subset of participants who did report their age at the first live birth. No differences were noted, and so we reported on the full set. In addition, a linear-by-linear test was conducted to evaluate the trend across different levels of the outcome.

In an initial set of multivariate analyses, we estimated associations between the reported use of each medication or substance before each of the first and second pregnancies and severe nausea and vomiting of pregnancy and hyperemesis gravidarum (vs none and mild and moderate nausea and vomiting of pregnancy) reported in the corresponding pregnancy (Supplemental materials). We regarded the investigation of metformin, tobacco, and cannabis as the primary analyses that addressed specific hypotheses, and we planned, a priori, to interpret any corresponding association for which $P<.05$ as statistically significant. However, we regarded the investigation of all other medications as agnostic, thus requiring correction of the nominal level of significance for multiple comparisons (Supplemental Table 2).

We subsequently estimated the associations of selected medications and substances with the 5-level outcome variable, specifying no nausea and vomiting of pregnancy as the reference level against which each other level was individually compared (Table 2). In these analyses, we investigated the 3 hypothesized medications and substances and the derived variables for 2 classes of agnostically investigated medications that satisfied the prespecified criteria for inclusion in the multivariate analyses, namely selective serotonin reuptake inhibitors and corticosteroids.

To estimate the burden of hyperemesis gravidarum that may have been prevented by metformin among those who took metformin before the first pregnancy, we calculated point estimates and the 95% CI estimates of the attributable fraction among the exposed[23] from the multivariate estimate of the RR association between prepregnancy use of metformin and hyperemesis gravidarum (Table 2). Owing to the inverse association between these variables, the calculated estimate represents hyperemesis

TABLE 2
Association[a] between the prepregnancy use of selected medications and substances and the level of nausea and vomiting of pregnancy in the first pregnancy using multinomial logistic regression

	Level of nausea and vomiting reported for the first pregnancy										
	None[b]		Very Little[c]		Typical[d]		Severe[e]		Hyperemesis gravidarum[f]		Trend
Medication or substance	No.	Relative risk (95 % CI)	No.	Relative risk (95 % CI)	No.	Relative risk (95 % CI)	No.	Relative risk (95 % CI)	No.	Relative risk (95 % CI)	*P* value
Metformin											
No	216	1	228	0.32	420	0.8	720	0.25	3676	0.29	.006
		(Ref)		(0.06–1.63)		(0.28–2.28)		(0.08–0.84)		(0.12–0.71)	
Yes	6		2	*P*=.17	9	*P*=.67	5	*P*=.025	31	*P*=.007	
Tobacco											
No	205	1	211	1.11	396	1.01	695	0.53	3555	0.51	<.001
		(Ref)		(0.56–2.20)		(0.55–1.87)		(0.29–0.99)		(0.30–0.86)	
Yes	17		19	*P*=.77	33	*P*=.97	30	*P*=.046	152	*P*=.011	
Cannabis											
No	208	1	212	1.28	405	0.88	685	1.03	3439	1.35	.35
		(Ref)		(0.60–2.73)		(0.44–1.80)		(0.54–1.99)		(0.75–2.41)	
Yes	14		18	*P*=.53	24	*P*=.73	40	*P*=.92	268	*P*=.32	
Selective serotonin reuptake inhibitor[g]											
No	210	1	219	0.93	403	1.17	669	1.64	3293	2.41	<.001
		(Ref)		(0.40–2.17)		(0.58–2.38)		(0.86–3.14)		(1.33–4.38)	
Yes	12		11	*P*=.87	26	*P*=.66	56	*P*=.14	414	*P*=.004	

CI, confidence interval.

[a] Adjusted as appropriate for the use of tobacco, metformin, cyclobenzaprine, and derived variables for selective serotonin reuptake inhibitors and for corticosteroids; [b] No nausea and vomiting; [c] Very little nausea and vomiting (1–7 days); [d] Typical nausea and vomiting—no weight loss, mostly normal daily routine, and no need for medical treatment because of nausea and vomiting; [e] More severe morning sickness—interfered with routine but did not require intravenous hydration, may have taken medication and lost a few pounds or 1 kg; [f] Hyperemesis gravidarum—persistent nausea and vomiting with weight loss; a few pounds or 1 kg that interfered substantially with daily routine and led to the need for IV hydration and prescription medications; [g] The derived selective serotonin reuptake inhibitor variable was scored as yes for each participant who reported using either sertraline or escitalopram and as no for all others.

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gravidarum that was likely averted by participants who took metformin before pregnancy.

In further analyses we evaluated whether the association between prepregnancy use of each of these medications and substances with nausea and vomiting of pregnancy severity during the first pregnancy differed between subgroups of participants who reported having or not having a second pregnancy (Supplemental Table 3). For these analyses, we returned to using the 2-level nausea and vomiting of pregnancy variable as the outcome.

Finally, we investigated determinants of the nausea and vomiting of pregnancy level reported for the second pregnancy, again using a multivariate logistic regression analysis to calculate the adjusted ORs (aORs) and 95% CIs for the association between the use of individual medications and substances and severe nausea and vomiting of pregnancy and hyperemesis gravidarum. However, in addition to the covariates used in earlier analyses, in this analysis, we controlled for nausea and vomiting of pregnancy level experienced during the first pregnancy.

We elected to limit the multivariate analyses to the first 2 pregnancies because of more limited data available for ≥3 pregnancies and the consequent potential for random error. All *P* values were 2-sided, and the results were considered statistically significant at a *P* value of <.05 for hypothesized medications and substances. For all other medications, we accounted for multiple comparisons using Bonferroni correction, setting the nominal level of significance at 0.0017 (0.05 out of 29). All analyses were performed using Stata, version 18.0 (Stata Corporation, College Station, TX).

Results

Population characteristics

The clinical and demographic characteristics are shown in Table 1 according to 2 nausea and vomiting of pregnancy levels in the first pregnancy, namely none and mild and moderate nausea and

vomiting of pregnancy vs severe nausea and vomiting of pregnancy and hyperemesis gravidarum. Participants in both groups had a mean age of 28 years at the first live birth and evinced no substantial differences in race or ethnicity or ancestry. Although more than half of the participants were living in the United States when their first birth was delivered, overall, there were marked differences in the country of delivery between those with more severe and those with less severe symptoms. The severity of nausea and vomiting of pregnancy was reported by 5414 participants for up to 6 pregnancies (Supplemental Table 1). Most participants (>80%) reported severe nausea and vomiting of pregnancy and hyperemesis gravidarum and, conversely, reports of none and very little nausea and vomiting of pregnancy were rare (<10%) for the first 4 pregnancies.

Prepregnancy use of metformin, tobacco, and selective serotonin reuptake inhibitors was independently associated with an altered risk across different levels of nausea and vomiting of pregnancy

Our initial analysis estimated the associations between daily use of each medication and substance in the 30 days before the first pregnancy and severe nausea and vomiting of pregnancy and hyperemesis gravidarum vs mild and moderate nausea and vomiting of pregnancy during the first pregnancy (Supplemental Table 2). This multivariate analysis identified 4 medications and substances (metformin, tobacco, and the selective serotonin reuptake inhibitors escitalopram and setraline) that were markedly associated with this measure of nausea and vomiting of pregnancy severity. Among these 4 medications and substances, 2—metformin and tobacco—were inversely associated with the risk as expected for these prepregnancy exposures that reduce the risk. Daily use of metformin in the month before the first pregnancy was associated with a 75% lower frequency of severe nausea and vomiting of pregnancy and a 71% lower frequency of hyperemesis gravidarum, and a highly significant trend in the effect size was observed over the 5 levels of severity (P=.006) (Table 2). The estimate of the prevented fraction among the exposed indicates that participants who used metformin before the first pregnancy may have been spared (71%; 95% CI, 29%−88%) of hyperemesis gravidarum that would otherwise have complicated pregnancies in this group. Daily use of tobacco was associated with a nearly 50% lower frequency of both severe nausea and vomiting of pregnancy and hyperemesis gravidarum with a similar significant trend across the levels of severity (P<.001). However, selective serotonin reuptake inhibitor use was associated with a significant trend of increasing severity (P<.001) for which the composite measure was associated with a 1.64-fold more frequent severe nausea and vomiting of pregnancy and a 2.41-fold greater frequency of hyperemesis gravidarum.

We also investigated whether the associations between prepregnancy use of medications and substances before the first pregnancy and the severity of nausea and vomiting of pregnancy during the first pregnancy differed between subgroups of participants who reported having a second pregnancy and those who reported not having a second pregnancy and did not identify substantial differences (Supplemental methods).

Prepregnancy use of metformin was associated with an 82% reduction in severe nausea and vomiting of pregnancy and hyperemesis gravidarum in the second pregnancy, whereas cannabis and selective serotonin reuptake inhibitors were associated with increased risk

Hyperemesis gravidarum is associated with a high reoccurrence rate and a consequent reduction in family size because of the fear for reoccurrence.[5,6] Therefore, we used multivariate analyses to investigate joint associations between the outcome of the second pregnancies and both the outcome of the first pregnancies and use before the second pregnancies of key drugs and substances found to be associated with the first pregnancy outcome. We found that those who experienced hyperemesis gravidarum in the first pregnancy had an 85-fold greater frequency of either severe nausea and vomiting of pregnancy or hyperemesis gravidarum in the second pregnancy, even after controlling for the use of key substances and drugs in the 30 days before the second pregnancy (Table 3). Moreover, after accounting for this recurrence risk, severe nausea and vomiting of pregnancy and hyperemesis gravidarum was 82% less frequent among those who took metformin before the second pregnancy (aOR, 0.18; 0.06−0.59; P=.005), more than 3-fold more frequent among those who used cannabis before pregnancy (aOR, 3.48; 1.80−6.75; P<.001), and nearly twice as frequent among those who took selective serotonin reuptake inhibitors (aOR, 1.84; 1.12−3.04; P<.016) (Table 3).

Comment

Principal findings

This study demonstrated that both severe nausea and vomiting of pregnancy and hyperemesis gravidarum was less than 30% as frequent among those who took metformin for 30 days before the first pregnancy and identified an 85% risk for severe nausea and vomiting of pregnancy and hyperemesis gravidarum in the second pregnancies of patients who had their first pregnancies affected by hyperemesis gravidarum and an 82% lower risk for severe nausea and vomiting of pregnancy and hyperemesis gravidarum following daily use of metformin before the second pregnancy, even after adjusting for the high risk of reoccurrence from the first to the second pregnancy. These findings support the hypothesis that metformin, a medication associated with elevated circulating GDF15 levels, may desensitize women to the rapid rise of GDF15 in early pregnancy and thereby mitigate their risk for severe nausea and vomiting of pregnancy symptoms.[10] Additional novel findings included an increased risk for severe nausea and vomiting of pregnancy and hyperemesis gravidarum among people who reported prepregnancy use of cannabis and selective serotonin reuptake inhibitors.

TABLE 3
Association[a] (95% confidence intervals) between the prepregnancy use of selected medications and substances and the level of nausea and vomiting during the second pregnancy

Medications and substance	Level of nausea and vomiting of pregnancy reported in the second pregnancy		
	No nausea and vomiting of pregnancy, mild nausea and vomiting of pregnancy, or moderate nausea and vomiting of pregnancy	Severe nausea and vomiting of pregnancy or hyperemesis gravidarum	Adjusted odds ratio[a] (95 % confidence interval)
Metformin			
No	402	2555	1.00 (ref)
Yes	8	14	0.18 (0.06–0.59)
			P=.005
Tobacco			
No	389	2511	1.00 (ref)
Yes	21	58	0.79 (0.41–1.50)
			P=.47
Cannabis			
No	394	2404	1.00 (ref)
Yes	16	165	3.48 (1.80–6.75)
			P<.001
Selective serotonin reuptake inhibitor derived			
No	385	2271	1.00 (ref)
Yes	25	298	1.84 (1.12–3.04)
			P=.016
Nausea and vomiting of pregnancy status in the first pregnancy			
None	80	32	1.00 (ref)
Very Little	87	63	1.75 (1.03–2.96)
			P=.038
Typical	134	179	3.35 (1.09–5.36)
			P<.001
Severe	51	428	20.41 (12.31–33.88)
			P<.001
Hyperemesis gravidarum	53	1842	85.82 (52.14–141.27)
			P<.001
Other	5	25	—

[a] Adjusted, as appropriate, for the use of tobacco, metformin, cyclobenzaprine, derived variables for selective serotonin reuptake inhibitors and corticosteroids, and nausea and vomiting of pregnancy status in the first pregnancy.

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Results in the context of what is known

We found a reduction in the risk for severe nausea and vomiting of pregnancy and hyperemesis gravidarum among people who used metformin before pregnancy, which is consistent with a recent study that reported a lower rate of hyperemesis gravidarum among patients exposed to metformin in the preconception period.[24] Little is known about the influence of cannabis use and selective serotonin reuptake inhibitors on circulating GDF15 levels. The association between hyperemesis gravidarum risk and prepregnancy cannabis use and selective serotonin reuptake inhibitors may be because of mechanisms unrelated to GDF15. Chronic cannabis use can lead to cannabis hyperemesis syndrome (CHS) and the association of nausea and vomiting of pregnancy severity with prepregnancy cannabis use identified here may be because of a misdiagnosis of hyperemesis gravidarum in pregnancies affected by CHS.[21] In the case of selective serotonin reuptake inhibitors, it seems plausible that the increased availability of serotonin (the mechanism of selective serotonin reuptake inhibitor action) may oppose the effectiveness of serotonin inhibitors that are commonly used to treat severe nausea and vomiting of pregnancy and hyperemesis gravidarum. In addition, if the placental serotonin system plays a role in placental development, selective serotonin reuptake inhibitors taken before conception and in early pregnancy may augment early placentation, leading to a greater rise in GDF15 levels in early pregnancy and an increased risk for hyperemesis gravidarum.[25]

Clinical Implications

This study may have considerable clinical implications. People who are planning to conceive who have a family history of hyperemesis gravidarum and those with a previous hyperemesis gravidarum pregnancy may benefit from prepregnancy treatment with

metformin. Metformin is an inexpensive medication, making it an equitable and economical approach to lower the risk for severe nausea and vomiting of pregnancy and hyperemesis gravidarum, which has been estimated to cost more than 2.2 billion dollars in the United States annually.[26,27] Metformin use before and during pregnancy is generally well-tolerated and considered to be safe and potentially effective in improving fertility and reducing maternal complications, including gestational diabetes and preeclampsia.[15–17] In addition, metformin has a reassuring long-term safety profile in pregnancy and in children who were exposed in utero during the treatment of mothers with type 2 diabetes.[18,19] Metformin has a United States category B classification and rare side-effects, including mild erythema and decreased vitamin B-12 absorption.[19] Common side effects are nausea and diarrhea, which may be reduced with extended-release formulation and slow dose increases. Conversely, patients at risk for hyperemesis gravidarum and who are using cannabis or are treated with selective serotonin reuptake inhibitors may benefit from counseling on whether a potential benefit of cessation before conception to lower hyperemesis gravidarum risk outweighs the risk of discontinuation during the preconception period (eg, return of depression and anxiety symptoms upon cessation of selective serotonin reuptake inhibitor treatment).[20,28]

Research implications

This retrospective study that showed a large reduction in the risk for hyperemesis gravidarum associated with prepregnancy metformin treatment supports the recent discovery that the major mechanism behind nausea and vomiting of pregnancy is tolerance to the rapid rise in GDF15 during pregnancy. A prospective clinical trial is now warranted to determine the dose and timing required to potentially reduce the risk for severe nausea and vomiting of pregnancy and hyperemesis gravidarum. Additional work should focus on identifying the circulating prepregnancy GDF15 levels required to reduce risk.

Strengths and limitations

A strength of this study is that the survey was promoted at sites that focused on hyperemesis gravidarum, and so a large sample size could be identified rapidly. This would have been difficult to achieve in a general population without surveying many thousands of women given the relatively low prevalence of both metformin use before pregnancy and of hyperemesis gravidarum. Indeed, low power that was a consequence of surveying a general pregnant population was reportedly a caveat in another study of metformin to prevent hyperemesis gravidarum.[24] That study also identified a reduced rate of hyperemesis gravidarum in the preconception metformin-exposed group, but their findings did not reach statistical significance. That being said, our hyperemesis gravidarum-enriched approach also has a potential caveat. People may have been more likely to participate if they had hyperemesis gravidarum more than once, which may have contributed to the high reoccurrence risk identified in this study. Nonetheless, any consequent bias is likely to be minor given that similar rates of reoccurrence were reported in previous prospective studies.[5,6] So, if this occurred, we would expect reoccurrence risk to be only slightly lower in the general obstetrical population. Regardless, the reduction in risk was substantial in our model, with and without adjusting for reoccurrence. It seems unlikely that participation would be influenced by both the use of metformin and a history of hyperemesis gravidarum in advance of or shortly following public dissemination of the hypothesis, making participation bias an unlikely explanation for the observed association. Another limitation is that the indication, timing, and dose for each medication and substance is unknown. It is possible that an observed association may be related to indication rather than medication and substance used to treat it. However, conditions commonly treated with metformin, namely diabetes and polycystic ovary syndrome, have been reported to be associated with an increase in the risk for hyperemesis gravidarum.[29,30] So, any confounding by indication for metformin should bias the results upward and could not explain the inverse associations observed. However, we cannot rule out that patients who were taking metformin for other indications may respond differently to metformin, which is why we now recommend a prospective study in healthy patients with a history of hyperemesis gravidarum. Finally, with respect to cannabis, its use during pregnancy is associated with a decrease in symptoms, and thus chronic users who continue use during pregnancy would be expected to have a lower, not higher, risk for severe nausea and vomiting of pregnancy and hyperemesis gravidarum.[20,21]

Conclusion

Preventing severe nausea and vomiting and hyperemesis gravidarum in patients at high risk would benefit patients and decrease healthcare costs. This retrospective study supports the hypothesis that daily use of metformin before pregnancy may reduce the risk for severe nausea and vomiting of pregnancy and hyperemesis gravidarum by desensitizing patients to the rapid rise of the emetogenic pregnancy hormone GDF15. A prospective clinical trial is warranted to determine whether the strong inverse association between prepregnancy use of metformin and severe nausea and vomiting of pregnancy and hyperemesis gravidarum reflects prevention rather than a form of systematic error that was not recognized in this observational study. We suggest that trial(s) enroll healthy, nonpregnant patients with a history of hyperemesis gravidarum who are planning to conceive and treat cases with an escalating dose of extended-release metformin (which has a better side-effect profile).[31] Although the effective dose is unknown, we suggest starting at 500 mg per day and slowly increasing the dose up to 2000 mg per day or the highest tolerated dose that does not interfere with prepregnancy nutrition. Patients can likely wean off metformin treatment within 2 weeks following a positive pregnancy test. The level of nausea and vomiting in the first trimester should be assessed using validated screening tools

GLOSSARY

aOR: adjusted odds ratio
AC: after meals
CHS: cannabis hyperemesis syndrome
CI: confidence interval
Desensitization: a treatment that aims to reduce reactions (in this case nausea and vomiting) by gradually exposing the body to increasing amounts of the substance (in this case GDF15 via metformin).
Emetogenic: a substance that has the ability to cause nausea and vomiting
Growth and differentiation factor 15 (GDF15): a hormone that causes nausea and vomiting and is produced by the placenta and tissues under conditions of stress, including infection, chronic disease, and undernutrition
HFA: hydrofluoroalkane
HELP: hyperemesis level prediction
Hyperemesis gravidarum: defined here as persistent nausea and vomiting with weight loss exceeding a few pounds or 1 kg that interfered markedly with daily routine and led to the need for intravenous hydration and prescription medications
Murine model: use of mice or rats in biomedical research studies
OR: odds ratio
Prevented fraction among the exposed: a measure in epidemiology that quantifies the proportion of disease or risk factors prevented by a specific exposure or intervention
PUQE: pregnancy unique quantification of emesis and nausea
RR: relative risk
Severe nausea and vomiting of pregnancy: defined here as more severe morning sickness that interfered with routine but did not require intravenous hydration, may take medication, and lost a few pounds or 1 kg.
XR or XL: extended release

(eg PUQE, HELP)[32] and compared with an untreated, well-matched control group to determine the effectiveness of the approach in reducing nausea and vomiting of pregnancy symptoms. The result could be much-needed progress in limiting adverse maternal, fetal, and child outcomes associated with hyperemesis gravidarum. ■

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Supplemental methods

Medications and substances queried

Participants were asked to provide a yes or no response to indicate whether each of the following substances or medications were used daily for the 30 days before each pregnancy: none, albuterol sulfate hydrofluoroalkane (HFA) (Ventolin HFA, Proair HFA, Proventil HFA), alprazolam (Xanax), amlodipine (Norvasc), amphetamine and dextroamphetamine (Adderall, Adderall XR), armour thyroid, cannabis (marijuana), cetirizine (Zyrtec), clonazepam (Klonopin), cyclobenzaprine (Flexeril), diazepam (Valium), doxycycline hyclate (Vibramycin), escitalopram (Lexapro), famotidine (Pepcid, Pepcid AC), Ferosul (ferrous sulfate), folic acid, gabapentin (Neurontin), hydrochlorothiazide (Microzide), ibuprofen (Advil, Motrin, Nuprin, Midol), levothyroxine (Synthroid, Levoxyl), loratadine (Claritin), lorazepam (Ativan), metformin (Glucophage), methocarbamol (Robaxin), metoprolol (Toprol XL)(Lopressor), naproxen (Naprosyn), prednisone (Deltasone), sertraline (Zoloft), synthroid (levothyroxine), tobacco (smoke nicotine cigarettes), trazodone (Desyrel), triamcinolone acetonide (Nasacort allergy 24 hour), vitamin D (Drisdol), zolpidem (Ambien), other, do not remember and prefer not to answer.

Nausea and vomiting of pregnancy 5-level severity scale

1) No nausea and vomiting
2) Very little nausea and vomiting (1−7 days)
3) Typical nausea and vomiting—no weight loss, mostly normal daily routine, and no need for medical treatment because of nausea and vomiting
4) More severe morning sickness—interfered with routine but did not require intravenous hydration, may take medication, and lost a few pounds or 1 kg
5) Hyperemesis gravidarum—persistent nausea and vomiting with weight loss exceeding a few pounds or 1 kg that interfered markedly with daily routine, and led to the need for intravenous hydration and prescription medications
6) Other
7) Do not remember and prefer not to answer

For pregnancies with nausea and vomiting of pregnancy status reported as other, we reviewed additional information provided by the participants that could reveal the level of nausea and vomiting of pregnancy. If warranted by this information, we reassigned the nausea and vomiting of pregnancy level to a specific value (1-none, 2-very little, 3-typical, 4-severe, 5-hyperemesis). Of note, 3 separate studies have used the 5-point scale and have had substantial findings, supporting its use.[7,8,22] One study identified familial aggregation of hyperemesis gravidarum using the scale, another was a classic twin study that identified high heritability of hyperemesis gravidarum in a study of 2 separate populations and showed "the twin correlations and (genetic and environmental) sources of variance were equivalent between cohorts," providing support for reproducibility of the scale. The third study used it to identify genes associated with the condition that led to the identification of the major mechanism that contributed to hyperemesis gravidarum. Of note, in the third study, there were 2 scans; 1 that used only the extreme ends of the clinical spectrum, hyperemesis gravidarum vs no nausea and vomiting, and a second that used the same 5-point scale used in this study (3 additional points in addition to the extreme ends of the clinical spectrum) and the integration of the 5-point scale led to an enormous increase in the significance of the association with the risk genes (eg the GDF15 locus had a $P=7\ 10^{-15}$ when no nausea and vomiting in pregnancy was compared with hyperemesis gravidarum and a $P=2\ 10^{-41}$ when each of the 5 steps were compared. This provides biologic support for the validity of the 5-point scale.

Comparisons of the first pregnancy outcomes according to whether there was a second pregnancy

We investigated whether associations between prepregnancy use of the medications and substances in the first pregnancy and severity of nausea and vomiting of pregnancy (none and mild and moderate nausea and vomiting vs severe nausea and vomiting of pregnancy and hyperemesis gravidarum) during the first pregnancy differed between subgroups of participants who reported having a second pregnancy and those who did not. In both groups, the use of metformin and tobacco were both inversely associated with severity and the use of selective serotonin reuptake inhibitors was positively associated with severity. However, the use of cannabis was not associated with severity among those who did have a second pregnancy but was positively associated, albeit without achieving statistical significance, with severity among those who did not have a second pregnancy. For each exposure, the results were less substantial in the group without a second pregnancy, likely owing to a lower number of participants in this group (supplemental Table 3).

SUPPLEMENTAL TABLE 1

Frequency of nausea and vomiting of pregnancy reported by 5414 participants for each pregnancy

Level of NVP	First Pregnancy		Second Pregnancy		Third Pregnancy		Fourth Pregnancy		Fifth Pregnancy		Sixth Pregnancy	
	N	%	N	%	N	%	N	%	N	%	N	%
No nausea and vomiting of pregnancy[1]	222	4.1%	94	3.1%	35	3.6%	15	5.3%	5	5.4%	6	17.1%
Very little nausea and vomiting of pregnancy[2]	230	4.3%	110	3.6%	26	2.7%	7	2.5%	6	6.4%	2	5.7%
Typical nausea and vomiting of pregnancy[3]	429	7.9%	206	6.9%	64	6.7%	24	8.4%	10	10.8%	3	8.6%
Severe nausea and vomiting of pregnancy[4]	725	13.4%	368	12.2%	127	13.2%	38	13.3%	12	12.9%	5	14.3%
Hyperemesis gravidarum[5]	3707	68.5%	2201	73.2%	700	72.8%	197	69.1%	57	61.3%	18	51.4%
Other[6]	93	1.7%	29	1.0%	10	1.0%	4	1.4%	3	3.2%	1	2.9%
No answer[7]	8	0.1%	0	0%	0	0%	0	0%	0	0%	0	0%
Total	**5414**	100%	**3008**	100%	**962**	100%	**285**	100%	**93**	100%	**35**	100%

[1]No nausea and vomiting.
[2]Very little nausea and vomiting (1-7 days).
[3]Typical nausea and vomiting- no weight loss, mostly normal daily routine, and no need for medical treatment due to nausea/vomiting.
[4]More severe morning sickness-interfered with routine but did NOT require intravenous hydration, may have taken medication and lost a few pounds or one kilogram.
[5]Hyperemesis Gravidarum-persistent nausea and vomiting with weight loss > a few pounds/1 kilogram, that interfered significantly with daily routine and led to need for intravenous hydration and/or prescription medications.
[6]Other, excluding pregnancies reclassified based on additional information (First pregnancy-43, Second pregnancy-18, Third pregnancy-9, Fourth pregnancy-2)
[7]Don't remember/prefer not to answer

Sharma. Prepregnancy metformin associated with lower hyperemesis gravidarum risk. Am J Obstet Gynecol 2025.

SUPPLEMENTAL TABLE 2

Crude and adjusted* associations (95% confidence intervals [CIs]) between the prepregnancy use of selected medications and substance and the level of nausea and vomiting of pregnancy during first and second pregnancies

Medication/substance	First Pregnancy				Second Pregnancy			
	Crude OR (95%CI)	p-value	Adjusted OR* (95 % CI)	p-value	Crude OR (95%CI)	p-value	Adjusted OR* (95 % CI)	p-value
Hypothesized[1] associations								
Metformin (Glucophage)	**0.42 (0.23-0.74)**	**0.003**	**0.39 (0.22-0.71)**	**0.002**	**0.27 (0.11-0.66)**	**0.004**	**0.27 (0.11-0.64)**	**0.003**
Tobacco (Smoke nicotine cigarettes)	**0.50 (0.38-0.67)**	**<0.001**	**0.49 (0.37-0.66)**	**<0.001**	**0.43 (0.26-0.71)**	**0.001**	**0.39 (0.23-0.65)**	**<0.001**
Cannabis (Marijuana)	1.10 (0.82-1.48)	0.53	1.28 (0.93-1.74)	0.125	1.69 (1.00-2.85)	0.05	**2.07 (1.19-3.63)**	0.01
Agnostically estimated[2] associations								
Adrenergic agonist								
Amphetamine/dextroamphetamine (Adderall, Adderall XR)	0.76 (0.42-1.38)	0.37	0.74 (0.41-1.36)	0.33	1.23 (0.37-4.10)	0.74	1.05 (0.31-3.55)	0.94
Beta-1-adrenergic receptor antagonist								
Metoprolol (Toprol XL) (Lopressor)	0.79 (0.22-2.82)	0.72	0.90 (0.25-3.27)	0.87	0.64 (0.07-5.72)	0.69	0.98 (0.09-10.18)	0.98
Beta-2-adrenergic receptor agonist								
Albuterol sulfate HFA^ (Ventolin HFA, Proair HFA, Proventil HFA)	0.92 (o.63-1.35)	0.67	0.92 (0.62-1.36)	0.66	1.12 (0.59-2.12)	0.73	1.11 (0.58-2.15)	0.75
Calcium antagonist								
Amlodipine (Norvasc)	0.60 (0.06-5.74)	0.66	0.59 (0.06-5.72)	0.65	0.16 (0.02-1.13)	0.067	0.13 (0.02-0.98)	0.048
Gamma-aminobutyric acid (GABA) analog								
Gabapentin (Neurontin)	2.19 (0.51-9.34)	0.29	3.00 (0.68-13.19)	0.145	-		-	
GABA receptor agonists								
Alprazolam (Xanax)	1.14 (0.51-2.55)	0.76	1.18 (0.52-2.68)	0.69	1.76 (0.41-7.52)	0.44	1.56 (0.36-6.82)	0.55
Clonazepam (Klonopin)	1.85 (0.66-5.19)	0.25	1.69 (0.59-4.83)	0.33	2.08 (0.27-15.94)	0.48	1.84 (0.23-14.43)	0.56
Cyclobenzaprine (Flexeril)	0.40 (0.14-1.16)	0.09	0.39 (0.13-1.19)	0.098	0.64 (0.07-5.72)	0.69	0.74 (0.08-7.07)	0.79
Diazepam (Valium)	0.93 (0.27-3.23)	0.91	0.86 (0.24-3.12)	0.82	1.12 (0.14-9.11)	0.92	1.52 (0.18-13.19)	0.70
Lorazepam (Ativan)	4.20 (1.02-17.40)	0.047	3.87 (0.92-16.29)	0.07	-		-	
Zolpidem (Ambien)	0.93 (0.27-3.23)	0.91	0.94 (0.26-3.34)	0.92	0.96 (0.11-7.97)	0.97	0.90 (0.11-7.67)	0.93
Glucocorticoids								
Prednisone (Deltasone)	0.42 (0.18-0.98)	0.04	0.44 (0.18-1.04)	0.06	-		-	
Triamcinolone acetonide (Nasacort allergy 24 hour)	0.65 (0.21-1.98)	0.44	0.60 (0.19-1.89)	0.38	0.24 (0.04-1.43)	0.12	0.21 (0.03-1.35)	0.10
Histamine-1 receptor antagonist								
Cetirizine (Zyrtec)	0.98 (0.72-1.35)	0.90	0.97 (0.70-1.34)	0.86	1.13 (0.68-1.88)	0.63	1.09 (0.65-1.82)	0.74
Loratadine (Claritin)	0.65 (0.46-0.91)	0.012	0.65 (0.46-0.92)	0.015	1.09 (0.59-2.02)	0.78	1.12 (0.60-2.10)	0.73
Histamine-2 receptor antagonist								
Famotidine (Pepcid, Pepcid AC)	1.02 (0.56-1.86)	0.94	1.11 (0.60-2.06)	0.73	1.38 (0.54-3.50)	0.50	1.39 (0.54-3.60)	0.49
Nutritional supplements								
Ferosul (Ferrous sulfate)	1.23 (0.48-3.18)	0.66	1.38 (0.53-3.61)	0.51	1.76 (0.41-7.52)	0.44	1.82 (0.42-7.91)	0.43
Folic acid	1.14 (0.97-1.34)	0.12	1.12 (0.95-1.32)	0.19	1.18 (0.92-1.51)	0.19	1.19 (0.92-1.52)	0.18
Vitamin D (Drisdol)	0.94 (0.72-1.21)	0.62	0.93 (0.72-1.21)	0.60	0.90 (0.60-1.35)	0.62	0.92 (0.61-1.39)	0.69
Non-steroidal anti-inflammatory drugs (NSAIDs)								
Ibuprofen (Advil, Motrin, Nuprin, Midol)	0.89 (0.73-1.07)	0.21	0.93 (0.76-1.13)	0.47	1.07 (0.78-1.48)	0.65	1.1 (0.78-1.49)	0.63
Naproxen (Naprosyn)	1.06 (0.52-2.17)	0.87	1.20 (0.58-2.49)	0.63	1.92 (0.45-8.17)	0.38	1.77 (0.41-7.60)	0.44
Thyroid analogs								
Armour thyroid	-		-		0.56 (0.12-2.69)	0.47	0.46 (0.09-2.24)	0.33
Levothyroxine (Synthroid, Levoxyl)	1.32 (0.85-2.04)	0.21	1.28 (0.82-1.99)	0.27	1.22 (0.62-2.24)	0.53	1.20 (0.65-2.23)	0.56
Serotonin receptor antagonists and reuptake inhibitors (SARIs)								
Trazodone (Desyrel)	3.59 (0.48-26.91)	0.21	2.82 (0.37-21.43)	0.32	-		-	
Selective serotonin re-uptake inhibitors (SSRIs)								
Escitalopram (Lexapro)	**2.58 (1.49-4.46)**	**0.001**	**2.77 (1.59-4.83)**	**<0.001**	3.47 (1.27-9.52)	0.016	3.73 (1.35-10.29)	0.01
Sertraline (Zoloft)	**1.74 (1.22-2.49)**	**0.002**	**1.83 (1.27-2.62)**	**0.001**	1.68 (1.06-2.67)	0.027	1.73 (1.1-2.76)	0.02

1 nominal level of significance p<0.05
2 nominal level of significance p<0.05/30=0.002
*Adjusted as appropriate for use of tobacco, metformin, cyclobenzaprine, and derived variables for SSRIs and for corticosteroids
^Hydrofluoroalkane
Sparse data on Doxycycline hyclate (Vibramycin), Hydrochlorothiazide Microzide, Methocarbamol (Robaxin)

Sharma. Prepregnancy metformin associated with lower hyperemesis gravidarum risk. Am J Obstet Gynecol 2025.

SUPPLEMENTAL TABLE 3

Association[1] (95% confidence intervals) between the prepregnancy use of selected medication or substances and the level of nausea and vomiting during the first pregnancy for participants who reported having a second pregnancy vs those who did not

Nausea and Vomiting of Pregnancy Status in First Pregnancy						
Medications/ Substance	Among women who had a second pregnancy			Among women who did not have a second pregnancy		
	None/Mild/ Moderate nausea and vomiting of pregnancy	Severe Nausea and vomiting of pregnancy/ Hyperemesis Gravidarum	Odds Ratio (adjusted) (95 % Confidence Interval)	None/Mild/ Moderate nausea and vomiting of pregnancy	Severe Nausea and vomiting of pregnancy/ Hyperemesis Gravidarum	Odds Ratio (adjusted) (95 % Confidence Interval)
Metformin						
No	740	3152	1.00 (Ref)	124	1244	1.00 (Ref)
Yes	13	25	**0.42 (0.21-0.82) P=0.01**	4	11	**0.29 (0.09-0.99) P=0.047**
Tobacco						
No	692	3056	1.00 (Ref)	120	1194	1.00 (Ref)
Yes	61	121	**0.44 (0.32-0.61) P<0.001**	8	61	0.74 (0.34-1.60) P=0.44
Cannabis						
No	704	2980	1.00 (Ref)	121	1144	1.00 (Ref)
Yes	49	197	1.13 (0.80-1.59) P=0.50	7	111	1.83 (0.80-4.20) P=0.15
Selective Serotonin Reuptake Inhibitor						
No	711	2878	1.00 (Ref)	121	1084	1.00 (Ref)
Yes	42	299	**1.86 (1.33-2.61) P<0.001**	7	171	**2.90 (1.32-6.37) P=0.008**
Corticosteroid						
No	744	3159	1.00 (Ref)	126	1243	1.00 (Ref)
Yes	9	18	0.48 (0.21-1.09) P=0.08	2	12	0.46 (0.10-2.23) P=0.34
Cyclobenzaprine						
No	749	3169	1.00 (Ref)	127	1253	1.00 (Ref)
Yes	4	8	0.48 (0.14-1.67) P=0.25	1	2	0.26 (0.02-3.76) P=0.32

[1] Adjusted as appropriate for use of tobacco, metformin, cyclobenzaprine, and derived variables for selective serotonin reuptake inhibitors and corticosteroids

Sharma. Prepregnancy metformin associated with lower hyperemesis gravidarum risk. Am J Obstet Gynecol 2025.