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Research Submissions

Association of Migraine Headaches With Suicidal Ideation Among Pregnant Women in Lima, Peru

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Background.—Suicide is a leading cause of maternal death globally, and suicide prevalence rates have been shown to be increased in those with migraine. No previous study has examined the association between migraine and suicidal ideation during pregnancy.

Objective.—To examine the association between migraine and suicidal ideation among a cohort of pregnant women.

Methods.—A cross-sectional study was conducted among 3372 pregnant women attending prenatal care clinics in Lima, Peru. Suicidal ideation and depression were assessed using the Patient Health Questionnaire-9 (PHQ-9) scale during early pregnancy. Migraine classification (including migraine and probable migraine) was based on International Classification of Headache Disorders-III beta criteria. Multivariable logistic regression analyses were performed to estimate odds ratios (OR) and 95% confidence intervals (95%CI).

Results.—Suicidal ideation was more common among those with migraine (25.6%) as compared to those with probable migraine (22.1%, $P < .001$) or non-migraineurs (12.3%, $P < .001$). After adjusting for confounders, including depression, those with migraine or probable migraine had a 78% increased odds of suicidal ideation (OR = 1.78; 95% CI: 1.46-2.17), as compared with non-migraineurs. Women with both migraine and depression had a 4.14-fold increased odds of suicidal ideation (OR = 4.14; 95% CI: 3.17-5.42) compared to those with neither condition.

Conclusion.—Migraine is associated with increased odds of suicidal ideation in pregnant women even when controlling for depression. These findings support the consideration of screening women with comorbid migraine and depression for suicidal behavior during pregnancy.

Key words: migraine, depression, suicidal ideation, pregnancy

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INTRODUCTION

Migraine headaches are an often debilitating neurologic disorder with an estimated worldwide prevalence of 10-15%.[1,2] Migraine is most common among adults 18-49 years old[3,4] as compared to those at either ends of the age distribution, and among women as compared to men.[5,6] Additionally migraine has been shown to be comorbid with

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several psychiatric disorders including depression and suicide.[7–9] Suicide is currently a leading cause of maternal death in developed countries[10,11] and in low and middle income countries.[12,13] Estimated rates of suicide vary widely between countries.[14] Suicidal behaviors, including suicidal ideation, having a suicide plan, and unsuccessful suicide attempts, are the strongest predictors of suicide. While suicidal ideation is often a defining symptom of depressive disorders, suicidal ideation may occur *without* accompanying depression.[15,16] Notably, recent studies have demonstrated that a substantial proportion of pregnant women with suicidal ideation do not meet clinical thresholds for depressive disorders.[17,18]

There is limited evidence concerning the association of migraine with suicidal ideation in pregnancy.[19] Therefore, we sought to examine the extent to which migraine is associated with suicidal ideation among a cohort of pregnant women in Peru. Furthermore, we sought to explore the independent and joint effects of migraine and depression on the odds of suicidal ideation.

METHODS

Study Population.—The study population was a cohort of 3372 participants from a larger ongoing cohort of the Pregnancy Outcomes, Maternal and Infant Study (PrOMIS). The PrOMIS cohort was designed to examine maternal social and behavioral risk factors of preterm birth and adverse pregnancy outcomes among Peruvian women.[20–23] The study population includes women attending prenatal care clinics enrolled in the Instituto Nacional Materno Perinatal (INMP) in Lima, Peru. The INMP is the primary reference establishment for both maternal and perinatal care operated by the Ministry of Health of the Peruvian government. Recruitment began in February 2012. Pregnant women were eligible for inclusion if they were between the ages of 18 and 49 years, with a gestational age $\leq$16 weeks, and who spoke and understood Spanish. All participants provided written informed consent, and all study procedures were approved by Institutional Review Boards from the INMP, Lima, Peru and the Human Research Administration Office at the Harvard T. H. Chan School of Public Health, Boston, Massachusetts, USA.

Analytical Population.—The study population for this report is derived from information collected from participants who enrolled in the PrOMIS Study between February 2012 and March 2014. During this period 3775 eligible women were approached, and 3372 (89.3%) agreed to participate. Forty-three (1.2%) women were excluded for missing information on the suicide ideation question on the Patient Health Questionnaire-9 (PHQ-9) (thoughts that you would be better off dead or of hurting yourself in some way). Of the 43 participants with missing information on the suicidal ideation question, 35 participants had missing information on other items of the PHQ-9. Twenty-two women were excluded for missing information on their migraine history. Thus, a total of 3323 pregnant women remained for analysis. The excluded participants did not differ from the rest of the cohort in regards to sociodemographic or lifestyle characteristics.

Migraine Assessment.—Migraine was classified by trained interviewers using a Spanish-language questionnaire administered during early pregnancy and based on the International Classification of Headache Disorders (ICHD)-III beta criteria.[24] Probable migraine was classified as those fulfilling all but one of the migraine diagnostic criteria.

Suicidal Ideation and Depression Assessment.—Depression and suicidal ideation were assessed using a Spanish-language version of the PHQ-9.[25,26] The PHQ-9 is a 9 item depression screening tool that has been validated in this population.[17,27] The questionnaire assesses 9 depressive symptoms on the 14 days prior to evaluation. The PHQ-9 score is calculated by assigning a score of 0-3 to the response categories "not at all," "several days," "more than half the days," and "nearly every day." Suicidal ideation was assessed based on the PHQ-9 question inquiring as to patients having "thoughts that you would be better off dead or of hurting yourself in some way." Participants who responded to this question with "several days," "more than half the days," and "nearly every day" were categorized as affirmative for suicidal ideation. The question asking about suicidal ideation was not considered in the total score for depression. The first 8 questions (PHQ-8) were used to calculate a

Table 1.—Characteristics of the Study Population According to Migraine Status (N = 3323)

	All participants (N = 3323)		No migraine (N = 2200)		Probable migraine (N = 716)		Migraine (N = 407)		
Characteristics	n	%	n	%	n	%	n	%	*P* value
Age (years)†	28.19 ± 6.30		28.35 ± 6.29		27.82 ± 6.34		27.92 ± 6.28		.099
Age (years)									
18-19	172	5.2	114	5.2	38	5.3	20	4.9	.43
20-29	1848	55.6	1196	54.4	417	58.2	235	57.7	
30-34	700	21.1	477	21.7	135	18.9	88	21.6	
≥35	603	18.1	413	18.8	126	17.6	64	15.7	
Education (years)									
≤6	145	4.4	92	4.2	32	4.5	21	5.2	.135
7-12	1806	54.5	1180	53.7	416	58.3	210	51.9	
>12	1363	41.1	924	42.1	265	37.2	174	43.0	
Pre-pregnancy self-reported BMI									
<18.5 kg/m^2	33	1.2	19	1.0	11	1.8	3	0.9	.488
18.5-24.9	1471	53.1	985	54.2	307	50.9	179	51.1	
25-29.9	962	34.7	613	33.7	220	36.5	129	36.9	
>30	305	11.0	201	11.1	65	10.8	39	11.1	
Early pregnancy measured BMI									
<18.5 kg/m^2	63	1.9	30	1.4	27	3.8	6	1.5	.001
18.5-24.9	1582	48.2	1053	48.5	322	45.5	207	51.4	
25-29.9	1210	36.9	792	36.5	277	39.1	141	35.0	
>30	428	13.0	297	13.7	82	11.6	49	12.2	
Mestizo ethnicity	2501	75.4	1650	75.1	576	80.4	275	67.7	<.001
Married/living with a partner	2679	81.0	1764	80.6	584	81.9	331	81.5	.705
Employed	1525	45.9	1069	48.6	286	39.9	170	41.8	<.001
Difficulty paying for basics									
Hard	1649	49.7	1016	46.2	397	55.4	236	58.0	<.001
Not very hard	1672	50.3	1182	53.8	319	44.6	171	42.0	
Difficulty paying for medical care									
Hard	1760	53.1	1067	48.7	438	61.2	255	62.8	<.001
Not very hard	1554	46.9	1125	51.3	278	38.8	151	37.2	
Nulliparous	1621	48.9	1103	50.3	340	47.6	178	43.8	.04
Planned pregnancy	1390	42.1	948	43.3	291	40.9	151	37.4	.063
Gestational age at interview†	9.24 ± 3.46		9.25 ± 3.47		9.27 ± 3.41		9.18 ± 3.45		.903
Thoughts that you would be better off dead or of hurting yourself in some way									
No	2790	84.0	1929	87.7	558	77.9	303	74.4	<.001
Yes	533	16.0	271	12.3	158	22.1	104	25.6	
Depression (PHQ-8)	865	26.2	472	21.6	213	30.0	180	44.8	<.001

Due to missing data, percentages may not add up to 100%.
†Mean ± SD (standard deviation): How many weeks pregnant were you during your first prenatal care visit?
For continuous variables, *P* value was calculated using the one-way ANOVA; for categorical variables, *P* value was calculated using the chi-square test.

depression score. Participants were categorized as "yes" for depression with a PHQ-8 score ≥10, similar to the cutoff for the PHQ-9. The use of the PHQ-8 depression questionnaire has been demonstrated to minimally influence overall scale performance, mean scores or diagnostic cut points as compared with use of PHQ-9.[28,29]

Other Covariates.—All subjects participated in structured interviews that included a questionnaire with information about sociodemographic,

Table 2.—Association of Migraine with Suicidal Ideation During Pregnancy (N = 3323)

	No suicidal ideation (N = 2790)		Suicidal ideation (N = 533)				
Migraine	n	%	n	%	Unadjusted OR (95% CI)	Adjusted OR (95% CI)†	Adjusted OR (95% CI)‡
No migraine	1929	69.1	271	50.8	Reference	Reference	Reference
Any migraine	861	30.9	262	49.2	2.17 (1.80-2.61)	1.99 (1.64-2.41)	1.78 (1.46-2.17)
Types of migraine							
No migraine	1929	69.1	271	50.8	Reference	Reference	Reference
Probable migraine	558	20.0	158	29.6	2.02 (1.62-2.51)	1.88 (1.50-2.34)	1.74 (1.39-2.19)
Migraine	303	10.9	104	19.5	2.44 (1.89-3.16)	2.20 (1.69-2.86)	1.84 (1.41-2.42)

OR, odds ratio; CI, confidence interval.
†Adjusted for age, marital status, difficulty paying for the very basics, difficulty paying for medical care.
‡Adjusted for age, marital status, difficulty paying for the very basics, difficulty paying for medical care, and depression.

headache characteristics, and depression. Participants were also interviewed regarding sociodemographic characteristics. Participants' age was categorized as: 18-19, 20-29, 30-34, and ≥35 years old. Other covariates include education (≤6, 7-12, >12 years of education); pre-pregnancy self-reported body mass index (BMI) and early pregnancy measured BMI (<18.5, 18.5-24.9, 25-29.9, >30); ethnicity (Mestizo vs others); marital status (married/living with partner vs others); employment status (employed vs not employed); difficulty paying for the very basics (hard vs not very hard); difficulty paying for medical care (hard vs not very hard); parity (nulliparous vs multiparous); planned pregnancy (yes vs no); and gestational age at interview.

Statistical Analysis.—Participants' demographic and reproductive characteristics were first examined. Continuous variables were presented as mean ± standard deviations (SD). Categorical variables were expressed as number (percent, %). Chi-square tests were used to evaluate differences in the distribution of categorical variables. Student's *t*-tests were used to evaluate differences in means. Multivariable logistic regression procedures were used to estimate odds ratios (OR) and 95% confidence intervals (95% CI) for suicidal ideation in relation to migraine diagnosis. Covariates were entered into each model individually, and adjusted and unadjusted ORs were compared to assess confounding. The final adjusted models included variables that were previously identified as potential confounders or altered the adjusted OR by at least 10%. Given that depression has been implicated as an important comorbid disorder with migraine, we repeated the analyses stratified by maternal depression status. We also explored the independent and joint effects of migraine and depression on the odds of suicidal ideation by categorizing participants into four groups based on the combination of depression and migraine status. The four categories examined were: (1) no migraine and no depression, (2) depression only, (3) migraine only, and (4) both migraine and depression. Pregnant women with no migraine and no depression were considered as the reference group and compared with women in the other three categories. All reported *P* values are two sided with a statistical significance set at .05. Statistical analyses were performed using SPSS (IBM SPSS v22.0, Chicago, IL, USA).

RESULTS

The sociodemographic and reproductive characteristics of the study population are presented in Table 1. The average age of study participants was 28.2 years (SD = 6.3); and the average gestational

Table 3.—Independent and Joint Associations of Migraine and Depression with Odds of Suicidal Ideation

	No suicidal ideation (N = 2773)		Suicidal ideation (N = 524)			
Migraine and depression status	n	%	n	%	Unadjusted OR (95% CI)	Adjusted OR (95% CI)†
(−) Migraine, (−) Depression	1544	55.7	168	32.1	Reference	Reference
(−) Migraine, (+) Depression	373	13.5	99	18.9	2.44 (1.86-3.21)	2.44 (1.85-3.22)
(+) Migraine, (−) Depression	593	21.4	127	24.2	1.97 (1.53-2.53)	1.84 (1.43-2.36)
(+) Migraine, (+) Depression	263	9.5	130	24.8	4.54 (3.49-5.91)	4.14 (3.17-5.42)
P value for interaction term					.783	.706

OR, odds ratio; CI, confidence interval.
†Adjusted for age, marital status, difficulty paying for the very basics, and difficulty paying for medical care.

age at the interview was 9.2 weeks (SD = 3.5). The majority of participants were Mestizos of mixed European and Amerindian descent (75.4%), married or living with a partner (81%), and multiparous (51.1%). Overall, compared to women without migraine, migraineurs were more likely to be unemployed, have difficulty paying for the basics and for medical care, have multiparous pregnancies, and do not identify as Mestizo (Table 1).

Suicidal ideation was endorsed by 16.0% of the cohort, and 26.2% of the cohort fulfilled criteria for depression. Participants with migraine or probable migraine (any migraine) had more than a 2-fold increase odds of suicidal ideation (OR = 2.17; 95% CI: 1.80-2.61) as compared with non-migraineurs (Table 2). After adjusting for confounders including age, marital status, difficulty paying for the basics, and difficulty paying for medical care, there was still an almost 2-fold increase in suicidal ideation (OR = 1.99; 95% CI: 1.64-2.41). Further adjustment for depression attenuated the association (OR = 1.78; 95% CI: 1.46-2.17), although the association remained statistically significant. Separate analyses for women with migraine or probable migraine diagnosis also showed a consistent increased odds of suicidal ideation (probable migraine: OR = 1.74; 95% CI: 1.39-2.19; migraine: OR = 1.84; 95% CI: 1.41-2.42) when compared with non-migraineurs after adjusting for all of the above confounders. The magnitude and direction of associations remained similar after stratifying analyses by maternal depression status (Supporting Information Table). For instance, after adjusting for confounders among participants with depression, migraineurs had a 1.75-fold increased odds of suicidal ideation as compared to non-migraineurs (95% CI: 1.28-2.39). Among participants without depression, migraineurs had a 1.80-fold increased odds of suicidal ideation (95% CI: 1.40-2.32) as compared with non-migraineurs.

We next explored the independent and joint effect of migraine and depression on the odds of suicidal ideation (Table 3). In a fully adjusted model, women with depression and no migraine had a 2.44-fold increased odds of suicidal ideation (95% CI: 1.85-3.22) as compared with women who had no migraine and no depression (referent group). Those with migraine but no depression had a 1.84-fold increased odds of suicidal ideation (95% CI: 1.43-2.36) when compared with the referent group. Pregnant women with comorbid migraine and depression had a 4.14-fold increased odds of suicidal ideation (95% CI: 3.17-5.42) compared with those who had neither condition, although the interaction term did not reach statistical significance ($P = .706$).

DISCUSSION

In this study of pregnant women, those with migraine had increased odds of suicidal ideation even after controlling for depression. Specifically, after

adjusting for confounders including depression, migraineurs had almost a 2-fold increased odds (OR = 1.78; 95% CI: 1.46-2.17) of suicidal ideation compared with non-migraineurs. Women with both migraine and depression had a 4.14-fold increased odds (95% CI: 3.17-5.42) of suicidal ideation compared with those who had neither condition.

Given this is the first study to examine the relation between migraine and suicidal ideation in pregnancy, the results can be tentatively compared with studies that included men and non-pregnant women.[30–32] In a previous study among 1007 members of a large Health Maintenance Organization in Michigan, Breslau et al found a significant association between migraine and thoughts of committing suicide in patients with migraine.[31] Similarly, Fuller-Thomson et al in their 2005 Canadian Community Health Survey (a general community-based population) found migraine was associated with increased odds of suicidal ideation in both men and women (men: OR = 1.70; 95% CI: 1.55-1.96; women: OR = 1.72; 95% CI: 1.59-1.86) although comorbid depression was not taken into account in this analysis.[32] In contrast to these studies, a tertiary care hospital-based study of Korean patients (N = 238) reported that migraine patients had a 5-fold increased odds of suicidal ideation (OR = 5.09; 95% CI: 1.17-22.1) compared with non-migraine patients; however after adjusting for comorbid depression and anxiety, the authors did not find a statistically significant association of suicidal ideation with migraine (OR = 1.51; 95% CI: 0.31-7.50).[30]

Our study is the first to find evidence of an association between migraine and suicidal ideation among a cohort of pregnant women. The burden of migraine is particularly high among pregnant women, since migraine headaches are more prevalent among women of childbearing age.[6,33] The prevalence and frequency of headaches, including migraines, can also be altered during pregnancy and is thought to be influenced by hormonal changes across the menstrual cycle and during pregnancy.[34] In addition to migraine, additional risk factors make women in low- and middle-income countries particularly vulnerable to suicidal behaviors during pregnancy.[35] In our study, the association between migraine and suicidal ideation remained even when we adjusted for multiple confounders including depression.

There are plausible biological mechanisms for the association between migraine and suicidal ideation including shared genetic and neurochemical pathophysiological pathways.[36] Genetic and environmental risk factors have been identified for migraine headaches, depression, and suicidal behaviors.[37,38] Studies have linked migraine, depression, and suicidal behaviors to polymorphic alleles of serotonin and dopamine, for example. A recent review of meta-analyses supports the association of serotonin transporter gene-linked polymorphic region (5-HTTLPR) with stress and depression symptoms,[39] although this conclusion is controversial.[40] The distribution of polymorphism frequencies in 5-HTTLPR is significantly different among migraine and control patients.[41] Another study found 5-HTTLPR polymorphisms do not predispose individuals to develop migraines but may affect the frequency of attacks in migraine patients.[42] Studies have also found some evidence of an association between serotonin-related polymorphisms and suicidal behaviors, but the association is far from conclusive.[43,44] The associations of serotonin transporter 5-HTTLPR with affective disorders may be mediated by fluctuations in estradiol and progesterone hormones.[45] Polymorphisms in the transcription initiation site of a serotonin transporter (5-HTT) show frequencies of the short allele are increased in migraine with aura patients but not in migraine without aura patients or controls, and this functional polymorphism is hypothesized to be related to migraine.[46] There is a significant association between alleles of the serotonin 5-HT2A receptor and both depression and suicide ideation.[47] Serotonin transporter function has been shown to be associated to suicidal behavior and depression.[48] Neural activity patterns also suggest differences in brain morphology in patients with a history of suicidal behaviors compared to patients without suicidal behavior.[49,50]

There is also evidence suggestive of genetic variations in the dopamine receptor gene associated

with migraine, depression, and suicidal behaviors. One study showed increased incidence of migraine, depression, and anxiety disorders in individuals with the dopamine receptor DRD2 *Nco*I C allele in comparison to an DRD2 *Nco*I T allele in exon 6.[51] Other studies, however, do not support this association.[52] In summary, suicidal behaviors have been associated with variants in genes known to regulate both dopamine and serotonin metabolism.[44] Future studies are needed to more fully explore these associations and further elucidate hypothesized mechanisms.

The strengths of our study include a relatively large sample size, the use of well-trained interviewers, and rigorous statistical analytic approaches that included controls for confounding. However, there are some limitations that must be considered. First, because of the cross-sectional study design, we cannot be certain of the temporal relation between migraine and risk of suicidal ideation. Longitudinal studies with more detailed assessment of lifetime and recurrent episodes of suicidal ideation and suicidal behaviors with concomitant assessments of migraine and depression will enhance causal inferences in this area of research. Second, migraine diagnosis was made using a well-established structured questionnaire based on ICHD-III criteria.[24] Use of structured interviews is the most feasible method of data collection for large scale epidemiologic studies. Additionally, this study is also subject to recall bias, as subjects are asked about past painful or traumatic experiences, including suicidal thoughts.[53] However, the effect of this non-differential bias would most likely lead to an attenuation of the true association towards the null value. Lastly, our analysis did not distinguish between migraine with aura and migraine without aura. Migraine subtypes have been shown in previous studies to vary in the strength of their relationship with suicidal ideation, and this may also have attenuated the association reported in our study.

In conclusion, our study suggests that the risk of suicide ideation is increased among pregnant women with migraine. Pending replication, these findings have potential important clinical and public health implications. Specifically our findings suggest it may be important that clinicians treating pregnant women are aware of the comorbidity between migraine, depression, and suicidal behaviors and consider screening pregnant migraineurs for suicidal ideation.[32,54,55]

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article.