Published in final edited form as:
Clin Auton Res. 2013 June ; 23(3): 117–122. doi:10.1007/s10286-013-0190-1.

Gynecological and Menstrual Disorders in Women with Vasovagal Syncope

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Abstract

PURPOSE—Vasovagal syncope (VVS) is a chronic debilitating condition seen mostly in young women of reproductive age. There are anecdotal reports of increased syncope and presyncope around menstruation. This case-control study assessed the effects of the menstrual cycle on lightheadedness episodes and compared the gynecological and pregnancy history of VVS patients to healthy subjects.

METHODS—A custom-designed gynecological and menstrual cycle questionnaire was previously developed for patients with orthostatic intolerance. This questionnaire was administered to female patients with VVS (n=128) as a part of the multicenter Second Prevention of Syncope Trial, and to gender-matched healthy subjects (n=92).

RESULTS—VVS patients and healthy subjects reported significant variability in self-reported lightheadedness throughout the menstrual cycle. Both cohorts experienced greatest lightheadedness during menses (53±2 vs. 56±4), which decreased during the follicular phase (44±2 vs. 41±4). VVS patients reported less severity in premenstrual symptoms (Fisher's Method p=2.7E-06) compared to healthy controls. There is no difference in the incidence of gynecological abnormalities (Fisher's Exact p=0.193) and pregnancy complications (p=1.0) between the two cohorts. VVS patients have similar pregnancy rates compared to healthy subjects (p=0.674).

CONCLUSION—The severity of lightheadedness varies during the menstrual cycle and is similar in both VVS patients and healthy controls. VVS patients have no greater risk of gynecological abnormalities and pregnancy complications than healthy subjects.

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Conflict of Interest

The authors declare that they have no conflict of interest.

Keywords

Syncope; menstrual cycle; lightheadedness; vasovagal; gynecological

Introduction

Vasovagal syncope (VVS) is a reflex disorder of autonomic regulation, in which transient global cerebral hypoperfusion leads to transient loss of consciousness [1]. Its characteristic symptoms include acute visual disturbance, auditory disturbance, cognitive slowing, followed by loss of consciousness. With recumbence, these symptoms rapidly resolve without neurological sequelae. The most remarkable physiological manifestations include vasodilation with or without bradycardia resulting in hypotension with lightheadedness to loss of consciousness. VVS can be a debilitating disorder and it is associated with a poor quality of life [2]. These episodes can be triggered by either central triggers (e.g. emotions or pain) or peripheral triggers (e.g. prolonged orthostasis or carotid sinus afferent activity) [3].

VVS disproportionately affects more females than males [3, 4]. Female patients are known to have a greater number of syncopal episodes, and these occur over longer periods of their lifetime compared to male patients [4, 5]. In 1935, Soma Weiss noted that females tend to faint during menstruation [6]. Since then, several other researchers have suggested that menstruation is a trigger for syncope [7, 8], while there are case reports of familial history of menstruation triggering VVS [9]. Despite a strong prevalence of VVS in females, there are no data about whether recurrent VVS is associated with more frequent gynecological disorders or pregnancy complications. We tested the hypothesis that self-perceived lightheadedness varied during different phases of menstrual cycle using a self-administered questionnaire completed by female VVS patients and healthy subjects.

Methods

Subjects

VVS patients and healthy subjects between 18 to 65 years of age were recruited for this study. Female VVS patients were drawn from the Second Prevention of Syncope Trial [10] (POST2; clinicaltrials.gov number NCT00118482), an international, multicenter, randomized controlled trial conducted between 2006 and 2011. Syncope patients had at least three prior syncopal spells and a score of ≤ 2 on the Calgary Syncope Symptom Score [11], which suggests VVS. Patients with structural cardiac problems, glaucoma, diabetes mellitus, hepatic diseases, renal diseases, seizure disorders, hypertension, orthostatic hypotension, or orthostatic tachycardia were excluded.

Healthy female subjects were recruited via broadcast in the Vanderbilt community. Control subjects self-described themselves as healthy and with no history of fainting (no physical assessment was performed). Token monetary compensation was offered for participating control subjects.

Investigational Review Board (IRB) Approval

This study was a pre-specified sub-study of POST2 trial. Written informed consent was obtained from each subject prior to their participation in the study. The questionnaire administered to the VVS patients through the POST2 study was approved by the local IRB at each study site. The healthy subjects completed this questionnaire within a separate study, which was approved by the Vanderbilt University IRB. The comparison between VVS

patients and healthy subjects was a pres-specified analysis in the protocol for the POST2 Women's Reproductive Health sub-study.

Structure of the Questionnaire

We developed a self-administered questionnaire to assess the gynecological symptoms and reproductive histories of VVS patients and healthy subjects. This questionnaire was previously used to study the prevalence of gynecological disorders and menstrual cycle lightheadedness in women with postural tachycardia syndrome (POTS) [12]. The questionnaire asks subjects about the following five subject categories: 1) current reproductive status; 2) detailed menstrual cycle history with information about the length and heaviness of the flow, irregularity in bleeding patterns, faintness during various phases of the cycle, and the intensity of premenstrual symptoms; 3) preexisting gynecological disorders; 4) medication history with special emphasis on the use of hormonal contraceptives, hormone replacement therapy (HRT), and changes in fainting while on medication; and 5) detailed obstetrics history encompassing pregnancy abnormalities, complications, and history of fainting during the pregnancy trimesters. The questionnaire used in this study is included as Online Resource 1.

VVS patients in the POST2 study completed a paper questionnaire and the data were then entered into a secure web-based study database. Healthy subjects completed an electronic questionnaire via Research Electronic Data Capture (REDCap) application, which is a secure web-based database designed to capture data for clinical studies [13]. The two questionnaires used slightly different Likert scales when assessing faintness during different phases of the menstrual cycle. To remedy this difference, we mapped the responses for this one question onto a uniform 100-point scale (1 is best and 100 is worst). The intensity of ten premenstrual (defined as 5 days before menses) symptoms in both VVS and healthy subjects were measured with a six-point Likert scale ranging from not present (1) to most intense (6).

Statistical Data Analysis

Data from the two questionnaires was combined and transcoded into Microsoft Excel spreadsheets (Microsoft Corp, Washington). All the data was kept on password protected servers to ensure patient privacy. The transcoded data was exported into IBM SPSS statistics software (version 19.0, IBM Corp, New York) for further analysis. We analyzed the continuous variables with Student's t-test and presented them as mean ± standard deviation. Categorical variables were analyzed with a Fisher's Exact test. Ordinal variables were analyzed with Mann-Whitney U test and presented as median and interquartile range. A probability (P) value of <0.05 was considered as significantly different between healthy subjects and VVS patients. A Bonferroni correction was applied to correct the p-value thresholds due to multiple comparisons (e.g. lightheadedness in three trimesters of pregnancy). We employed repeated measures of ANOVA for analyzing changes in lightheadedness over time.

Results

The mean age for VVS patients and healthy subjects was similar (Table 1), with a range of 18-57 years and 19-56 years, respectively. Women in both cohorts were also of similar age at menarche (12.8±0.1 years vs. 12.6±0.1 years; P=0.564). We observed no significant difference between the cohorts in the duration of bleeding, severity of heaviest blood flow, and length of irregular pattern of bleeding (Table 1). There was, however, a significant difference in the time gap between menstrual cycles and duration of heaviest menstrual blood flow. VVS patients had more frequent periods (22-26 days) compared to healthy subjects (>32 days; P=0.009). VVS patients reported longer duration of heaviest bleeding

during menstruation (Table 1). We queried both groups about other abnormal menstrual patterns and detected no significant differences (Table 2). There was a non-significant trend toward irregular periods in VVS patients (28.9%) compared to healthy subjects (18.5%; P=0.083).

VVS patients and healthy subjects self-reported their presyncope (measured as lightheadedness in the questionnaire) during different phases of menstrual cycle (Fig 1). Overall, the subjects experienced a significant change in the presyncope over time during the menstrual cycle (P<0.001). Subjects in both cohorts experienced a similar pattern of variability in the presyncope during the menstrual cycle (P=0.637), with the intensity of lightheadedness highest during the menstrual phase, decreasing during the follicular phase, to a nadir during the early luteal phase before increasing again during the late luteal phase (Fig 1). There were no “between-group” differences in self-reported presyncope between VVS patients and healthy subjects during the menstrual (53±2 vs. 56±4), follicular (44±2 vs. 41±4), early luteal (40±2 vs. 38±4), and late luteal (49±2 vs.49±5) phases.

We analyzed hormonal contraceptive usage in both cohorts to evaluate the possibility of effect of hormonal contraceptives or hormone replacement therapy (HRT) on lightheadedness. VVS patients and healthy subjects have similar current usage (35% vs. 46%; P=0.118) or lifetime usage (80% vs. 84%; P=0.487) of hormonal contraceptives. There was no significant difference in the use of HRT between VVS patients or healthy subjects in terms of either lifetime (5% vs. 9%; P=0.315) or current usage (2% vs. 3%; P=1.000), but overall utilization of HRT in the study population was very small (n=17).

The intensity of ten premenstrual symptoms in both VVS and healthy subjects was measured with a six-point Likert Scale ranging from less intense to most intense (Table 3). A majority of measured symptoms were significantly more intense in control subjects than VVS patients. Healthy subjects reported higher levels of breast pain (P=0.02), higher inability to cope with daily demands (P=0.005), more stress (P=0.038), feeling depressed (P=0.002), higher weight gain (P=0.015), and more edema (P=0.034) compared to that of VVS patients.

The prevalence of thirteen different gynecological abnormalities in VVS patients and healthy subjects were measured (Table 4). Only galactorrhea had a significantly higher incidence in VVS patients compared to that of control subjects (6% vs. 0%; P=0.043). VVS cohort also reported a slightly higher prevalence of dysfunctional bleeding (12% vs. 4%; P=0.086), endometriosis (11% vs. 5%; P=0.223), hirsutism (8% vs. 3%; P=0.246), and premature menopause (6% vs. 1%; P=0.143) (Table 4). There were no significant differences in the rates of anovulation, uterine fibroids, ovarian cysts, hyperprolactinemia, infertility, hypopituitarism, polycystic ovarian syndrome, and regular menopause.

VVS patients and healthy subjects had similar rates of pregnancy (41% vs. 38%; P=0.674). Among those participants who were pregnant, there were no differences in the incidence of difficulties getting pregnant or complications during pregnancy such as gestational diabetes, high blood pressure, preterm delivery, preeclampsia, miscarriages, or vaginal bleeding (Table 5). There were no significant differences in lightheadedness during the three trimesters of pregnancy between VVS patients and healthy subjects. Neither cohort reported a significant increase in presyncope during pregnancy compared to their non-pregnant state (data not shown).

Discussion

VVS is known to be more prevalent among women. Several studies have also indicated that menstruation could act as a trigger for these reflex faints [6-9]. In this study, we sought to analyze the association between menstrual cycle and incidence of presyncope or syncope.

We also measured the prevalence of various menstrual and gynecological disorders in women with VVS using a large cohort of female VVS patients (n=126) and age-matched healthy subjects (n=92). The key findings of this study are: 1) both VVS patients and healthy subjects experienced variability in lightheadedness during different phases of the menstrual cycle, with no difference between the two groups; 2) healthy subjects reported more intense premenstrual symptoms compared to VVS patients; and 3) VVS patients do not have increased gynecological or pregnancy related complications compared to healthy subjects.

Cyclical Lightheadedness

Subjects in VVS and healthy cohorts experienced similar pattern of variability in self-assessed lightheadedness during various phases of menstrual cycle (Fig 1). Both VVS patients and healthy subjects experienced peak lightheadedness during menses, which then decreased during the follicular phase and reached a nadir at the early luteal phase before increasing again in the late luteal phase (premenstrual; Fig 1). This variation can be attributed to cyclical changes in plasma volume [14] and relative ratio of estrogen-to-progesterone during the menstrual cycle. Another possibility might be the release of vasodilators like prostaglandin F_2 and prostacyclins during menstruation can cause pooling of blood leading to increased lightheadedness [15]. It is noteworthy that there was no significant difference between the intensity of lightheadedness experienced by the VVS patients and healthy subjects at any phase of the menstrual cycle (Fig 1). This is consistent with data from Fu *et al* which showed that the menstrual cycle does not affect the sympathetic baroreflex sensitivity [16]. A recent study by Zesko et al. showed that the results of tilt table tests are not affected by the phase of menstruation in premenopausal women[17]. In contrast to these data, a recent study by Peggs *et al* [12] showed that female POTS patients feel significantly more lightheaded during all phases of menstrual cycle compared to healthy subjects. The reason for POTS patients but not VVS patients feeling more lightheaded than healthy subjects may be due to an exaggerated sympathetic tone or more profound hypovolemia in POTS, which leads to increased tachycardia (a distinguishing feature of POTS).

Premenstrual Symptoms & Gynecological Disorders

There is a prevailing notion that VVS patients experience more intense premenstrual discomfort compared to healthy subjects. In our study, however, control subjects reported more intense premenstrual symptoms compared to VVS patients (Table 3). One possible explanation for this finding could be that VVS patients are generally more symptomatic with a poorer quality of life at baseline, such that the premenstrual symptoms do not have as much impact on their quality of life compared to a control subject free of basal symptoms.

There is no significant difference in the incidence of gynecological disorders between VVS patients and healthy subjects, with the exception of galactorrhea (Table 4). This stands in contrast to the Peggs *et al* [12] study in which female POTS patients reported a higher incidence of gynecological abnormalities like uterine bleeding, endometriosis, uterine fibroids, and ovarian cysts. This difference could be attributed to either different ratios of estrogen-to-progesterone or different levels of estradiol in VVS and POTS patients. A high level of progesterone acts as a protective agent against estrogen-related gynecological abnormalities, whereas high levels of estradiol may have the opposite effect. An in depth hormonal study with measurements throughout the menstrual cycle would be necessary to test this hypothesis. The pregnancy rates of VVS patients and healthy subjects are similar, with no difference in the rates of pregnancy complications (Table 5).

Limitations

This study is based on recall data from VVS patients and healthy subjects. It is conceivable that chronically affected VVS patients might have better recall about their symptoms compared to healthy controls. Our data argue against this possibility since the healthy subjects actually reported more intense premenstrual symptoms than VVS patients. The overall sample size of this study is fairly large for a syncope study, but some endpoints (such as HRT and pregnancy) had relatively few subjects, making it harder to draw strong conclusions about these specific end points.

Conclusion

In this study, we found cyclical variability in self-perceived presyncope during the menstrual cycle of both VVS patients and healthy subjects. Both cohorts experienced a similar degree of lightheadedness during all phases of menstrual cycle. Pregnancy rates are similar between VVS patients and healthy subjects. VVS patients also reported no increased gynecological abnormalities or pregnancy complications compared to controls.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

This study is supported in part by Canadian Institutes of Health Research grant 70319, National Institutes of Health grants UL1 RR024975, R01 HL102387 and P01 HL056693.

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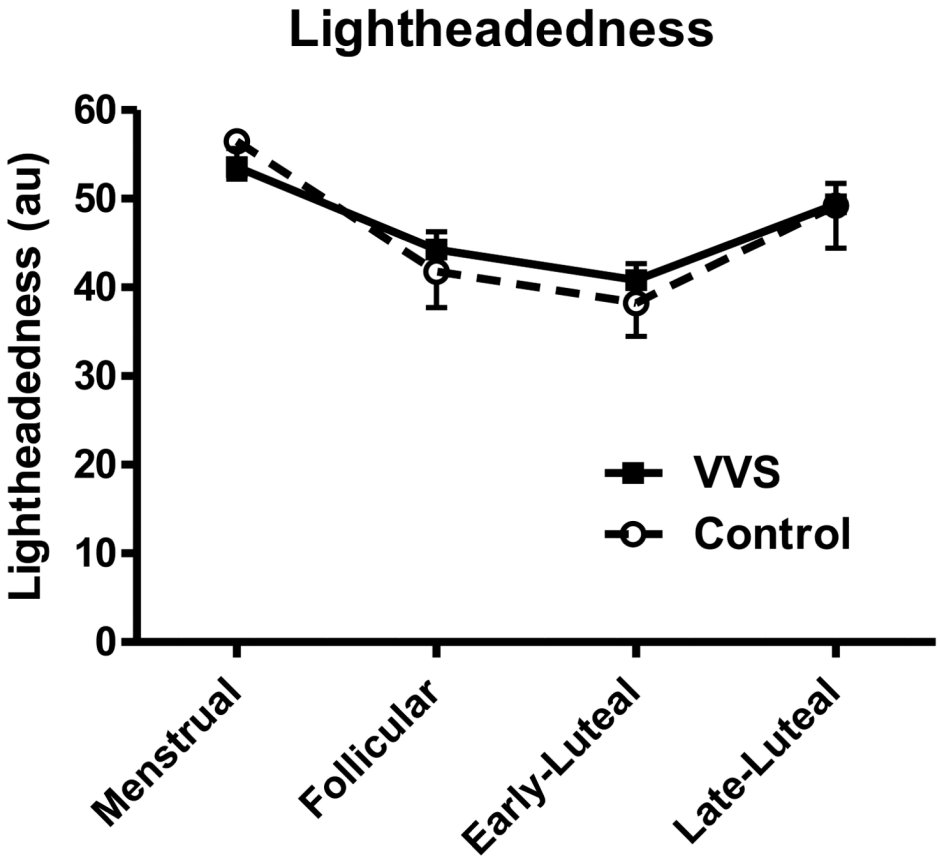

Fig 1. Menstrual Lightheadedness Profile of Vasovagal Syncope Patients and Healthy Subjects

The degree of self-reported lightheadedness (in arbitrary units [a.u.] with 100 being worst) during the four phases of menstrual cycle (menstrual, follicular, early luteal, and late luteal) is shown. Both vasovagal syncope (VVS) and healthy subjects perceive similar changes in lightheadedness during the menstrual cycle

Table 1
Menstrual history for Vasovagal Syncope Patients and Healthy Subjects

	VVS[a] (n=128)	Controls (n=92)	P-Value[b]
Age	31.4±12.4	32.6±10.6	0.45
Age at Menarche (Years)	12.8±0.2	12.6±0.1	0.564
How far apart are/were your periods? (days)	22-26 [22-26, >32]	>32 [22-26,>32]	0.009 *
Duration of bleeding (days)	6-9 [6-9,>10]	6-9 [6-9,>10]	0.083
Severity of heaviest blood flow[c]	2 [1.25,3.0]	2 [2.0,3.0]	0.475
Duration of heaviest blood flow (days)	3-5 [3-5,6-9]	3-5[3-5,3-5]	0.023 *
Length of irregular pattern of bleeding (months)	2-6 [1,7-12]	2-6 [1,>12]	0.429

[a] vasovagal syncope.

[b] Age and age at menarche are reported as mean ± SEM and analyzed with a Student t-test. Other data are presented as median [25th, 75th percentile] and analyzed with a Mann-Whitney U test.

[c] Severity of heaviest blood flow measured as light (1; small pads or tampons changed 3 times/day), medium (2; medium pads or tampons changed every 3-6 hours), and heavy (3; thick pads or tampons changed every 1-3 hours).

* Statistically significant difference.

Table 2
Menstruation and Bleeding Patterns in Vasovagal Syncope and Healthy Subjects

	VVS[a] (n=128)	Controls (n=92)	P-value[b]
Are/were your periods regular?	71.1%	81.5%	0.083
More than 1 period/month	35.2%	42.4%	0.325
Continuous spotting >10 days	25.8%	25.0%	1
Continuous moderate to heavy flow >10 days	13.3%	10.9%	0.679
Missed period (one month and not pregnant)	37.5%	40.2%	0.779
Amenorrhoea	21.1%	16.3%	0.391

[a] vasovagal syncope.

[b] Menstruation and bleeding patterns of VVS were compared to that of normal subjects and Fisher's Exact p-values are reported.

Table 3
Premenstrual Symptoms Compared Between Vasovagal Syncope and Healthy Subjects

Premenstrual Symptom[a]	VVS[b] (n=128)	Controls (n=92)	P Value
Breast Pain	2 (1,4)	3 (2,4)	0.02*
Unable to cope with ordinary demands	1 (1,3)	2 (1,3)	0.005*
Feel under stress	2 (1,3)	3 (2,4)	0.038*
Irritable/Bad Temper	3 (1,4)	3 (2,5)	0.093
Feel sad or blue	2 (1,4)	3 (2,4)	0.002*
Backache, Joint and muscle pain; Stiffness	2 (1,4)	3 (1,5)	0.865
Weight gain	2 (1,3)	3 (2,4)	0.015*
Abdominal heaviness, discomfort or pain	4 (2,5)	3 (2,5)	0.977
Edema, puffiness, swelling	2 (1,3)	2 (1,3)	0.034*
How long did you experience these symptoms?	2 (1,2)	2 (1,2)	0.08

[a] Severity of the symptoms was measured on a six-point Likert scale (six being the most severe). Responses from each group are summarized with mean and interquartile range (25^{th}, 75^{th} percentile).

[b] vasovagal syncope.

* Statistically significant difference.

Table 4

Gynecological Disorders Compared Between Vasovagal Syncope Patients and Healthy Subjects

Gynecological abnormalities[a]	VVS[b] (n=128)	Controls (n=92)	P-value
Anovulation	1.6%	2.2%	1
Dysfunctional Bleeding	11.7%	4.3%	0.086
Endometriosis	10.9%	5.4%	0.223
Uterine Fibroids	4.7%	9.8%	0.117
Galactorrhoea	5.5%	0%	0.043*
Hirsutism	7.8%	3.3%	0.246
Hyperprolactinemia	0%	1.1%	0.418
Hypopituitarism	0%	1.1%	0.418
Infertility	2.3%	3.3%	0.696
Ovarian Cyst	18%	13%	0.356
Polycystic Ovarian Syndrome	3.1%	3.3%	1
Premature Menopause	5.5%	1.1%	0.143
Regular Menopause	4.9%	6.5%	0.766

[a] Percentage and the number of gynecological disorders reported by VVS and healthy subjects are itemized here.

[b] vasovagal syncope.

* Statistically significant difference.

Table 5

Pregnancy Complications Compared Between Vasovagal Syncope Patients and Healthy Subjects

	VVS[a]	Controls	P-value
Pregnant at least once (n)	40.6%(52)	25%(23)	0.674
Any complications	53.8%	52.2%	1
Gestational Diabetes	5.8%	0%	0.548
High Blood pressure	13.5%	13%	0.1
Miscarriage	13.5%	26.1%	0.201
Preeclampsia	5.8%	13%	0.363
Preterm delivery	15.4%	4.3%	0.26
Vaginal bleeding	36.5%	17.4%	0.112

Percentage and the numbers of pregnancy complications reported by each group are summarized.

[a] vasovagal syncope.