

ORIGINAL RESEARCH

Evaluation of biochemical markers like thyroid function, serum beta-HCG, serum Calcium levels and psychological factors in Indian women with hyperemesis gravidarum attending a tertiary care hospital in West Bengal, India- A case control study

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Received: 27 September, 2023

Accepted: 30 October, 2023

ABSTRACT

Objective: Hyperemesis gravidarum (HG) represents an abnormal response of gravid women to pregnancy itself. The cause of hyperemesis is obscure, and there are conflicting data regarding the relationship between the disease itself with serum HCG levels and thyroid functions. Hyperparathyroidism, one of the reasons for intractable vomiting, can also be a differential diagnosis of hyperemesis and needs early identification. Additionally, women suffering from hyperemesis might have psychological counterparts. **Methods:** In this prospective case-control study, we have tried to evaluate the existence of any relationship between serum biochemical markers and depression scoring of pregnant women with the disease process of hyperemesis. **Result:** 33[66%] and 27[54%] women admitted with hyperemesis were found to possess high serum beta-HCG and abnormal thyroid function. Only one was detected with a high calcium level. A statistically higher number of women with hyperemesis were revealed to suffer from a low to severe form of depression. **Conclusion:** Though statistically higher numbers of women with hyperemesis were found to possess high serum beta-HCG and abnormal thyroid function in contrast to controls, more notably, a significant number of them do not show these aberrations implying the fact that these hormones cannot be considered as any form of universal straightway bio-marker for HG. Contrary to our speculation, serum calcium level estimation reveals no importance in women with hyperemesis. Depression score is found to be significantly higher in women presenting with hyperemesis. Thus, determining psychological status should remain an integral to evaluating this disease.

Key words: Hyperemesis Gravidarum; Thyroid Function Tests ; Depression;HCG BETA

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INTRODUCTION

Scientific background and explanation of rationale

Hyperemesis gravidarum [HG] is denoted by intractable vomiting during the first trimester of pregnancy, leading to weight loss, fluid depletion, ketonuria/and ketonemia¹. Almost 1% of all pregnancies might suffer from it, accounting for many hospital admissions in the first trimester². The causes of HG are multifactorial and often poorly associated. Maternal age, genetic susceptibility, stress,

depression, parity, ethnicity, marital status, body mass index, and previous history of hyperemesis correlate with the increased prevalence of HG³. Studies are there trying to evaluate the relationship of HG with serum hormones like estrogen, PAPP A, free HCG and thyroid. One observational study showed high levels of PAPP A and beta-HCG in HG women, in contrast to controls⁴. Another study showed an association with hyperthyroidism⁵. However, conflicting reports are also there, leading to a bar to

drawing a straightaway relationship and thus suggesting any prediction or prognostic competence with them⁶.

Clinically, HG is a diagnosis of exclusion, and hypercalcemia per-se can be a reason for excessive nausea and vomiting in early pregnancy⁷. Among the differential diagnosis for hypercalcemia, the most common cause is hyperparathyroidism, which can lead to diverse complications in pregnant women ranging from spontaneous abortion, stillbirth, neonatal death, or neonatal tetany⁸. After diabetes and thyroid disorders, primary hyperparathyroidism is the third most common endocrine disorder having a prevalence of 0.15 to 1.4% and affecting women twice as men⁹. In patients with hyperparathyroidism, excessive nausea and vomiting are symptoms of hypercalcemia mimicking HG¹⁰. This correlation has also been found in pregnant patients with undiagnosed hyperparathyroidism and thus assessment of serum calcium levels and symptom severity is considered in the management itself.

HG is an area of obstetrics with psychological aspects closely interacting with socio-cultural factors¹¹. Thus, apart from measuring the serum markers, evaluation of mental status and associated social factors can help the caregivers to link the association, if any, and formulate a plan accordingly. Therefore, this study tries to find out any linkage with the mental health symptoms of women presenting with HG.

Specific objectives or hypotheses

Considering these facts, in our present study, we have tried to assess and link the relationship of biochemical markers with the hyperemesis itself. Furthermore, we attempted to conclude whether these assessments are valuable in every hyperemesis case. This is considered a primary outcome.

Simultaneously, we investigate the levels of depression in women presenting with hyperemesis gravidarum. We have tried to correlate the effect of hyperemesis on quality of life and vice versa. This is considered a secondary outcome.

METHODS

Trial design

A prospective case-control study

Participants

Eligibility criteria for participants

Inclusion criteria

1. Antenatal women carrying singleton fetus less than 22 weeks gestation with the diagnosis of HG.

2. Willing to participate in the study.

Diagnosis of HG follows the most recent RCOG guideline, which describes HG as protracted nausea and vomiting of pregnancy [NVP] with the triad of more than 5% pre-pregnancy weight loss, features of dehydration and/or electrolyte imbalance¹².

Exclusion criteria

1. USG confirmed twin pregnancy, Hydatidiform mole.
2. Pregnancy is associated with other first-trimester complications or waiting for termination.
3. Pregnancy is associated with other medical and surgical comorbidities
4. Women with known psychiatric disorders

Settings and locations where the data was collected

The trial was conducted in the Department of Obstetrics and Gynaecology, College of Medicine Sagar Dutta Medical College, Kolkata, India from June 2018 to May 2019(1 year) over the women admitted with hyperemesis.

Interventions

The women diagnosed with HG were admitted following inclusion and exclusion criteria. Each control was chosen from the subsequent age, gravida and gestational age-matched pregnancy attending the emergency department for safe confinement without any comorbidity, when the previously enrolled one was diagnosed and admitted for HG.

The enrolled subjects had undergone the following tests along with necessary supportive care.

1. Blood for the total count, urea, creatinine[RFT], sugar, electrolytes, and viral marker screening.
2. Blood for amylase, lipase, calcium, beta-HCG, liver function test[LFT], and thyroid function tests [TFT].
3. Urine for routine and microscopic examination.
4. Ultrasonography[USG] of fetoplacental profile[if not done], USG of the whole abdomen

Similar tests were conducted over the controls.

The table (The American Pregnancy Association) below gives guidelines for the expected wide range of beta-HCG levels each week of pregnancy¹³. Beta-HCG levels are measured in milli-international units of beta-HCG hormone per millilitre of blood (mIU/mL).

Pregnancy week	Standard beta-HCG range
3 weeks	5–50 mIU/mL
4 weeks	5–426 mIU/mL
5 weeks	18–7,340 mIU/mL
6 weeks	1,080–56,500 mIU/mL
7–8 weeks	7,650–229,000 mIU/mL
9–12 weeks	25,700–288,000 mIU/mL
13–16 weeks	13,300–254,000 mIU/mL
17–24 weeks	4,060–165,400 mIU/mL
25–40 weeks	3,640–117,000 mIU/mL

Values more significant than the upper limit were considered deviated.

The respective institutional reference range was followed to comment on the serum levels of sodium, potassium, calcium and relevant abnormalities in liver and renal function tests.

Women further diagnosed with vomiting due to other causes [i.e. gallstone, pancreatitis] were excluded from the study.

Apart from detailed history taking, a patient health questionnaire [PHQ-9] was used to assess mental status; which comprises nine items¹⁴.

1. Little interest or pleasure in doing things
2. Feeling down, depressed, or hopeless
3. Trouble falling or staying asleep or sleeping too much
4. Feeling tired or having little energy
5. Poor appetite or overeating
6. Feeling bad about yourself or that you are a failure or have let yourself or your family down
7. Trouble concentrating on things, such as reading the newspaper or watching television
8. Moving or speaking so slowly that other people could have noticed. Or the opposite, being so fidgety or restless that you have been moving around a lot more than usual
9. Thoughts that you would be better off dead or hurting yourself

Each questionnaire can be scored from 0 (not at all), 1(several days), 2(more than half the days, or 3(nearly every day) regarding the feelings of subjects in the last two weeks.

Total added scores ranging from 0–4 would be considered minimal depression, 5–9 mild depression, 10–14 moderate depression, 15–19 moderately severe depression and 20–27 severe depression.

Informed written consent was taken from each of the patient. Necessary ethical approval was received from the institutional ethics committee.

Outcomes

1. Enumeration of the number of women among cases and controls having elevated/deviated/abnormal levels of beta-HCG, TFT, electrolytes, RFT and LFT tested at the time of admission and comparison among the groups accordingly.
2. Enumeration of the number of women and subgrouping them according to the severity of depression and comparison of the numbers among both groups.

Any changes to trial outcomes after the trial commenced, with reasons

As per the institutional ethical approval, the title of the project was ‘‘ Evaluation of Thyroid Function, Beta-HCG and Calcium in Patients with Hyperemesis Gravidarum Attending a Tertiary Care Hospital in West Bengal’’ [Memo no CMSDH/IEC/127/06-2018 dated 23.06.2018]

We found many women with HG needed psychiatric counselling during the trial. We thus incorporate a secondary outcome linking the level of depression with the disease process, which was not predefined in the initial stage of formulation of the study.

Sample size

The sample size calculation was based on EPI-INFO software. Keeping the confidence interval at 95%, fifty study subjects with hyperemesis and fifty age, parity and gestational age-matched healthy pregnant women were taken as control. The sample size closely correlated with a similar previous study by Al-Yatamaet al.¹⁵

Statistical Methods

Descriptive statistical analysis.

Categorical data have been expressed as percentages, and comparisons between two groups were made by Chi-square test with Yates' correction and Fisher's exact test, and $P \leq 0.05$ was considered significant. Continuous variables were expressed as mean +/- standard deviation (SD), and comparisons were made by Student t-test.

Software - SPSS 21

RESULTS

Most of the enrolled cases are primigravida [60%], and a majority [42%] are adolescents. 50% and 94% of women presented with symptoms of HG within 10 weeks and 14 weeks of gestation. 32[64%] women informed that their pregnancy was unplanned [Table-1].

Beta-HCG levels appear elevated in 33 HG cases. 27 and 25 women with HG were detected to have elevated fT4 levels and low TSH levels, respectively. All of these appear statistically significant [Table-2] Serum-electrolyte reports revealed that 21 and 24 women with HG had low sodium and potassium, respectively, compared to matched controls. These results are more significant than matched controls. In addition, one woman was detected to have a high calcium level [Table-2].

Fourteen women with HG were found to have deviated LFT reports in contrast to 4 among the controls. This appears statistically significant.[Table-2]

A statistically higher number of women with HG revealed to suffer from a low-severe form of depression, in contrast to control.[Table-3].

Table-1: Distribution of cases and controls as per the demographic characteristics

		Case [n=50]	Control [n=50]	p value
Gestational age	<10 weeks	25	24	0.97891
	10-14 weeks	22	23	
	>14 weeks	3	3	
Age	<= 19 years	21	22	0.935024
	19-30 years	24	24	
	>30 years	5	4	

Gravida	Primiparous	30	32	0.8369
	Multiparous	20	18	
Planned pregnancy	Yes	18	23	0.4162
	No	32	27	

Table 2: Distribution of cases and controls as per the results of biochemical markers

Hormones and electrolytes		Cases[n=50]	Controls[n=50]	p value
FT4	Elevated	27	1	<0.0001
	Normal/low	23	49	
TSH	Low	25	2	<0.0001
	Normal/high	25	48	
B HCG	Deviated	33	10	<0.0001
	Normal	17	40	
Sodium	Low	21	0	<0.0001
	Normal	29	50	
Potassium	Low	24	0	<0.0001
	Normal	26	50	
Calcium	High	1	0	1
	Normal	49	50	
LFT	Deviated	14	4	0.0174
	Normal	36	46	
RFT	Deviated	2	0	0.4949
	Normal	48	50	

Table 3: Association of cases and controls with the scale of depression

Presence of depression	Case [n=50]	Control [n=50]
No /minimal depression	20	36
Low to moderate depression	22	12
Severe depression	8	2

The chi-square statistic is 11.1126. The p-value is 0.003863

DISCUSSION

Our study findings revealed that adolescent primigravid women were more susceptible to developing HG, and their symptoms primarily developed within the first 14 weeks of gestation. Our study's findings are consistent with similar studies and literature^{15,16}.

However, as these demographic factors are unalterable, identifying other modifiable determinants of HG, if existing, can be essential to assess the disease process. The role of social determinants as predictors of HG is also not always universally specific; thus, serum biochemical markers can be regarded as of specific value and have been extensively studied in a few studies to evaluate their role^{16,17}. As because, the severity and clinical course of HG is often remain poorly understood, an ideal marker of the disease would be of value in this aspect. We aim to measure beta-HCG, TSH and free thyroxine in every case of HG to assess their link with the disease process and to conclude whether routine testing of them can be recommended in all cases of HG. Since beta-HCG is considered the prime hormone with emetic potential, studies have always tried to evaluate a linear relationship between the HG's severity and the beta-HCG level. However, there exists no consensus regarding the exact role of beta-HCG for the pathogenesis of HG. It is evident that

few conditions associated with high beta-HCG levels, like choriocarcinoma; do not typically reciprocate symptoms of nausea and vomiting. On the other hand, many pregnant women with documented high beta-HCG levels also do not show symptoms of HG. Thus, one must be cautious to conclude that the relationship is causal. In addition, the observations that symptoms continue in a substantial proportion of women beyond the first trimester when beta-HCG levels are actually falling, and symptoms of nausea and/or vomiting do not appear during beta-HCG administration as luteal phase support or to generate oocyte; put a question regarding the hypothesis of beta-HCG as the sole factor in the aetiology. In one study, it was found that human chorionic gonadotropin was higher among hyperemesis subjects compared to controls. Still, a weak correlation existed between beta-HCG and free T4 and TSH¹⁸. Mason et al. and Jarnfelt et al., in their respective studies, showed a linear relationship between symptoms severity and the serum levels of beta-HCG, concluding that it is higher in level in emetic women than the serum beta-HCG levels of non-emetic women^{19,20}. Kaupilla also confirmed this view observing that serum beta-HCG concentrations are substantially higher than average in women presenting with HG, especially between 7 to 14 weeks of gestation²¹. Keeping in mind about these results, our study result does not differ from the expected

outcomes revealing, though not in all but a statistically higher beta-HCG level in HG women in contrast to controls. We found 66% of participants amongst hyperemesis cases had elevated beta-HCG compared to 20% in the control group, which has been statistically significant. But more importantly, beta-HCG levels of 34% of HG women were found to be low in contrast to control pregnant which supports the theory of the existence of other factors apart from beta-HCG as a cause of HG.

Because beta-HCG closely resembles another glycoprotein hormone TSH, it has been postulated that it acts as a thyroid stimulator in pregnancy complicated with HG and raises thyroid hormone levels. A study conducted by B K Gill et al. showed statistically increased serum T(3) and T(4) levels and low TSH levels in HG women in contrast to the controls but without any features of clinical hyperthyroidism in them.²² Wilson, in a similar study conducted over 10 HG women, showed just reverse outcome, i.e. no consistent abnormalities of thyroid status and beta-HCG apart from some individual variations in HG women in contrast to controls²³. T M Goodwin again showed the existence of biochemical hyperthyroidism after evaluating the thyroid status of 57 HG women and concluded that beta-HCG acts as a thyroid stimulator in this state¹⁸. These data reflect the common cohabitation of biochemical hyperthyroidism in women with hyperemesis gravidarum and suggest that the beta-HCG plays the role of the thyroid stimulator in this state. Our study showed that HG women have statistically altered thyroid functions compared to the controls. However, as not all women with HG but only a percentage [54% with high T4 and 50% with low TSH] showed an altered thyroid state, we could not recommend altered thyroid function as a universal marker and thus, based on inconsistent findings from our study as well as from earlier researches; we could not recommend thyroid hormones as a marker or predictor for the clinical course of HG.

Electrolyte imbalance is a common feature of HG, and even a report of cardiac arrest is due to HG-induced profound hypokalaemia²⁴. Our study showed electrolyte [sodium and potassium] disturbances are statistically evident among women admitted with HG compared to the controls. However, at the same time, our study result showed unaltered renal function tests and calcium levels among HG women. Our initial search suggested these investigations as per our initial postulate that hypercalcemia in pregnancy may mimic these symptoms of HG and could have its own intrinsic maternal-fetal risks. Mild liver dysfunction is not uncommon among HG women, but studies suggest no need to intervene if the primary diagnosis is confirmed²⁵. Another study showed that mild elevation of LFT with hyperemesis and abnormal LFT is more common in HG women with higher body mass index²⁶. Our study result showed a statistically higher number of HG women with abnormal LFT

reports than the controls. However, these outcomes should be considered an effect rather than the cause of HG, and we recommend all HG women should undergo most of these tests as found to possess statistically abnormal results in contrast to controls that need to be treated.

Women with HG are thought to be more prone to anxiety and depression and can have relevant psychosocial issues. Gedife Ashebir, in their study, showed that pregnant women who are urban dwellers or have polygamous husbands are more prone to develop HG²⁷. However, there always exists controversy regarding the risk factors of HG. As predicted, the location of the habitation and the husband's faithfulness does not appear to correlate with the disease incidences in other similar studies done by the author Erginbas Kender E et al. and Senturk M et al. respectively^{28,29}. This is quite explainable as expectations about the quality of living and the level of tolerability about a polygamous relationship in marriage vary from country to country and might not cause any impact on the mindset of the gravid women. However, leaving these existing controversies regarding stress-generating factors, we have directly estimated the linkage of the mental status of the women with the disease severity, and it reflects that the odds of developing HG were four times higher among women experiencing some form of depression compared to having no such. Kuo SH et al. showed that the severity of nausea and vomiting is significantly associated with the level of depression as well as "acceptance of pregnancy"³⁰.

In our study, 64% of women with HG revealed that their pregnancy was unplanned, compared to 54% in the control group. In India, unplanned pregnancy does not appear as a risk factor for developing HG. This is quite explainable as unintended pregnancies are never considered a social taboo in India, provided the couple is married irrespective of their age³¹. All of our enrolled study objects were incidentally found married and did not wish for an abortion procedure as per our study protocol.

LIMITATIONS

The study has some limitations. Because this is a hospital-based study comprising a small group of women, neither the sample size is large enough nor could it represent the whole population with ethnic diversity.

Considering the protocol of this study, all the tests and the scores were individually assessed regarding the disease process itself, but no correlation was made among those results. A more robust study based on the framework of interlinked results of these biochemical and psychological markers could help to establish any causal relationship between these markers and the disease process.

CONCLUSION

A statistically higher number of women with HG is found to possess high serum beta-HCG and abnormal thyroid function compared to controls. But more importantly, a significant number of them do not show these aberrations, implying that these hormones cannot be considered as any form of universal marker for HG, either prognostic or diagnostic. Abnormal LFT and altered serum-level of sodium and potassium are found in a statistically higher number of women with HG. Our study results reinforce the recommendation of doing these tests in all women presenting with HG. Contrary to our speculation, serum calcium level estimation reveals no importance in women with HG. Depression score is found to be significantly higher in women presenting with HG. Therefore, determining the psychological status of women with HG should remain an integral part of evaluating this disease.

FUNDING

This trial received no specific grant from funding agencies from any sectors in the public, commercial, or not-for-profit one.

CONFLICT OF INTEREST

The authors declare they have no conflicts of interest.

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