

Maternal serum levels of interleukin-6 and β -hCG in women with hyperemesis gravidarum in the first trimester of pregnancy

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Article info

Received: 28 Dec 2016

Revised: 14 Jan 2017

Accepted: 20 Jan 2017

p-ISSN:2322-1895

e-ISSN: 2345-4334

Key Words:

Hyperemesis gravidarum
Interleukin-6
hCG

ABSTRACT

Background and Objective: Hyperemesis gravidarum (HG) is defined as vomiting sufficiently severe to produce weight loss, dehydration, electrolyte abnormalities. Interleukin-6 (IL-6), a pro-inflammatory and trophoblast-derived cytokine has ability to induce trophoblasts to secrete human chorionic gonadotropin (hCG). The purpose of our study was to assay the level of IL-6 and β -hCG in serum of pregnant women suffering from HG during the first trimester of pregnancy and compare with gestational age-matched controls and normal non pregnant women.

Materials and Methods: Plasma concentrations of IL-6 and β -hCG were measured in 30 healthy non pregnant women and 30 women with HG, 30 pregnant women with nausea and vomiting of pregnancy (NVP) and 30 normal pregnant women, matched for age, parity and gestational age .

Results: Mean serum levels of β -hCG were higher in women with HG. There was a significant difference between the three groups ($P < 0.001$) regarding IL-6 level.

Conclusion: IL-6 levels rise in women with HG and this could lead to higher levels of hCG seen in these patients. It appears that IL-6 does not have a primary role in etiology of HG.

1. Introduction

Nausea and vomiting in pregnancy (NVP) is the most common medical condition during gestation (1). Up to 75 percent of pregnant women experience nausea and vomiting before 20 weeks of gestation (2). HG is the extern form of NVP that

interferes with nutritional intake and metabolism, causes weight loss, fluid and electrolyte imbalances and malnutrition that can lead to hospitalization without coincidental medical conditions. It occurs in 0.3 to 3.6 percent of pregnancies (1). All forms of NVP exerts a huge burden on patients, caregivers and society (3-5).

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Activated lymphocytes and macrophages are the source of the cytokine with multiplex biological functions like inflammation, cell growth and differentiation, and immune responses (6). Trophoblast-derived cytokines, IL-6 and interleukin-1 have the capability to induce trophoblast to secrete HCG through a different pathway used by a GnRH analogue (7-11).

Numerous researches have established that immunological factors are higher in HG patients and had positive correlations with variations in hormone levels. In HG patients, a positive correlation between IL-6 levels and HCG and higher level of TNF α had been observed (12-14). The other researches demonstrated no association between IL-6 and HG (15).

The purpose of the present research was to assay the level of IL-6 and β -hCG in pregnant women suffering from HG during the first trimester of pregnancy and compare it with gestational age-matched control including normal pregnancy and pregnant women with nausea and vomiting and normal non-pregnant women.

2. Materials and Methods

The present study was approved by the Ethics Committee of Shahed University. Subjects were selected consecutively from the Obstetrics clinics of the Shahied Mustafa Khomeini hospital, Tehran, Iran.

The subjects were divided into four groups. The first group was 30 healthy non-pregnant women. The second, third and fourth groups consisted of 30 pregnant women with nausea and vomiting of pregnancy (NVP), 30 pregnant women with hyperemesis gravidarum (HG), and 30 healthy pregnant women, matched for age, parity and gestational age, respectively.

The (HG) group had at least the two following conditions at 6-16 weeks of gestation:

- A) Vomiting at least two times a day.
- B) The nausea was so severe that could not tolerate oral nutrition
- C) Weight loss of more than 5% of pre-pregnancy weight

D) Ketonuria <80 mg/dl in a random urinary sample

E) Hypokalemia (serum potassium level <3 meq/dl) or hyponatremia (serum sodium level <134 meq/dl) that need replacement therapy.

All patients had onset of vomiting in the first trimester and no other identifiable cause for the vomiting. The selected women were healthy before the start of nausea and vomiting of pregnancy. The pregnancy-unique quantification of emesis and nausea (PUQE) system was used for grading the severity of nausea and vomiting.

Inclusion criteria for the study were well-established gestational age verified by ultrasonography, a singleton fetus, no medication, no history of thyroid disease and other medical diseases.

Eligibility for the study was determined by a single physician. All participants were informed about the aim study and they will not directly benefit from this research, and written informed consent was given by all women.

Before starting treatment, blood samples were taken, serum was isolated and kept at -70°C.

After collection of all samples, serum levels of β -hCG and IL-6 were measured using HCG and IL ELISA kits from R&D company (Diacclone, France).

Mann-Whitney-U and Pearson's correlation analysis were used for statistical analysis. $p < 0.05$ was accepted as significant. All data are expressed as mean \pm SEM.

3. Results

Table 1 shows demographic data of the four study groups. There was no difference regarding the maternal age, body mass index, and parity.

Table 1. The study groups characteristics

Characteristic	Non pregnant women (n=30)	Healthy pregnant women (n=30)	Pregnant women with nausea and vomiting (n=30)	Pregnant women with hyperemesis gravidarum; (n=30)	P value
Age (year)	3.29±28.80	5.09±28.73	4.43±26.53	3.69±28.23	NS
Body mass index (kg/m ²)	2.35±24.12	1.44±25.31	1.68±24.75	2.42±24.11	NS
Parity (range)	(3-0)1	(3-0)1	(3-0)1	(3-0)1	NS
Gestational age (week)	–	0.84±7.68	0.848±7.91	0.75±7.82	NS

Table 2 shows cytokine and β -hCG levels in the study groups. Levels of interleukin-6 did not significantly differ among the groups. Median levels of interleukin-6 were higher in the (*HG*) group than pregnant women with (*NVP*) (79.82pg/mL) [range, 0–840 pg/mL] and healthy pregnant women (72.4pg/mL [range, 0–610 pg/mL]).

Mean serum β -hCG (817±210 mIU/ml) was significantly higher in the (*HG*) group than pregnant women with (*NVP*) (601±170.4 mIU/ml) and healthy pregnant women (486.2±150 mIU/ml).

Table 2. Values of hCG and IL-6 in four study groups

Characteristic	Non pregnant women (n=30)	Healthy pregnant women (n=30)	Pregnant women with nausea and vomiting (n=30)	Pregnant women with hyperemesis gravidarum; (n=30)	P value
IL-6 (pg/ml)	51.17±93.52	136.95±72.40	157.7±79.82	234.93±115.91	NS
hCG (mIU/ml)	12.35±9.7	150±486.2	170.4±601	210.8±817	P0.001>

4. Discussion

The aim of this research was to clarify the difference between the HCG and IL-6 serum levels in pregnant women suffering from HG during the first trimester of pregnancy and compare it with gestational age-matched control including normal pregnant women and pregnant women with nausea and vomiting and normal non-pregnant women.

Although IL-6 levels were higher than other 3 groups, it did not reach a significant level. Also, our findings showed that serum levels of interleukin-6 were higher in healthy pregnant women than in non-pregnant women. Serum levels of β -hCG was significantly higher in the (*HG*) group than pregnant women with (*NVP*) and healthy pregnant women.

In normal pregnancy, placental tissues are extensively infiltrated with mononuclear phagocytes and lymphocytes (18). Trophoblast is the main origin of IL-6 during pregnancy. The secretion of hCG is controlled by IL-1, IL-6 and TNF- α which originate from trophoblast (6-9). Excessive activity of granulocytes and high concentration of trophoblast-derived cytokines might be involved in hyperemesis gravidarum (19). The impact of elevated levels of hCG in zones of the brain involved in nausea directly or upper gastrointestinal tract or can rise thyroid hormone and estradiol which has the ability to affect nausea (11).

Our results showed that serum levels of interleukin-6 were higher in healthy pregnant women than in nonpregnant women. NVP and HG is associated with elevated serum hCG levels due to trophoblastic activity. Nevertheless, in women with HG, different levels of hCG have been reported. The findings of many studies indicated significant association between raised hCG levels and the occurrence of NVP or HG (11). Three other studies showed a lower hCG in women with HG or NVP and the other authors did not report a significant association (12-14). HCG isoforms or hCG receptor mutations may explain differences in symptoms. Efficacy of corticosteroids in the treatment of HG is an evidence of inflammation basis for NVP or HG. Suppress of the TNF- α and IL-6 by corticosteroids may inhibit inflammation responses and finally lead to relieve the symptom of HG.

The peak of hCG secretion in the first trimester coincides with the time of hyperemesis gravidarum that is generally seen. In women with twin and molar pregnancy which is associated with high HCG levels, HG is more common than normal pregnant women.

To conclude, IL-6 levels rise in women with HG and this could lead to higher levels of hCG seen in these patients. It appears that IL-6 does not have a primary role in etiology of HG.

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