

# The thiol/disulfide balance in ketone positive and ketone negative pregnant women with nausea and vomiting — a prospective study in a tertiary center

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## ABSTRACT

**Objectives:** We aimed to investigate the thiol/disulfide balance in ketone positive (hyperemesis gravidarum) and ketone negative pregnant women with nausea and vomiting.

**Material and methods:** A total of 60 patients under the 14<sup>th</sup> week of pregnancy were included in this study, and they were divided into two groups. Group 1 included 30 pregnant women with ketone positive, group 2 included 30 ketone negative pregnant women with nausea, and vomiting.

**Results:** The native thiol, disulfide, and total thiol concentrations were measured using an automated method and compared among the two groups. There were also three indexes that are derived from disulfide, native and total thiol (Index 1 =  $100 \times \text{disulfide/native thiol}$ ); (Index 2 =  $100 \times \text{disulfide/total thiol}$ ); (Index 3 =  $100 \times \text{native thiol/total thiol}$ ). When compared with Group 1 and Group 2, total thiol was high, native thiol was low but not statistically significant. Disulphide ( $p = 0.046$ ), index 1 ( $p = 0.036$ ) and index 3 ( $p = 0.034$ ) were statistically significant.

**Conclusions:** Patients with ketone positive are shifting to OS direction due to lack of nutrients and electrolytes. This study emphasizes the therapeutic potential of antioxidant supplementation, which is becoming an increasingly used approach in treating the symptoms of women with ketone positive.

**Key words:** hyperemesis gravidarum; nausea and vomiting; thiol/disulfide homeostasis; oxidative stress

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## INTRODUCTION

Nausea and/or vomiting is a common problem for pregnant women affecting approximately 80% of all pregnant women [1]. Hyperemesis gravidarum (HG), which is a severe form of nausea and/or vomiting, is diagnosed with ketonuria and more than 5% weight loss and occurs in 0.3–3% of all pregnant women [2, 3].

Thiols containing sulfhydryl groups [(R-SH)] are antioxidants that play an important role in the elimination of reactive oxygen species (ROS) that occur during oxidative stress (OS) [4]. With the separation of hydrogen from natural thiols, disulfide bonds [(R-S-S-R)] are formed, and with the

release of this hydrogen, excess oxygen is bound in the environment and the cells are protected from oxidative damage. Conversely, disulfides can turn into native thiols, which is called dynamic thiol/disulfide homeostasis [5, 6].

In this study, we aimed to investigate the thiol/disulfide balance in ketone positive and ketone negative pregnant women with nausea and/or vomiting.

## MATERIAL AND METHODS

A prospective study was performed with a total of 60 women with a history of nausea and/or vomiting, normal body mass index (20–25 kg/m<sup>2</sup>) and aged between

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18–35 years at the department of obstetrics and gynaecology. Patients were evaluated in two groups: Group 1 consisted of 30 patients with ketone positive (HG). Group 2 consisted of 30 patients having nausea and/or vomiting more than three times per day during pregnancy and did not have ketonuria.

Patients with trophoblastic diseases, diabetes, preeclampsia, thyroid diseases, inflammatory diseases, kidney diseases, liver diseases, smoking or alcohol habits and pregnancies older than 14 weeks were excluded from the study. Gestational weeks were determined by the last menstrual period and ultrasonography.

Blood samples were taken and centrifuged for 10 minutes at 4,000 rpm. The serum portion was separated and stored at  $-80^{\circ}\text{C}$  until assessment of thiol/disulfide homeostasis.

Serum thiol/disulfide homeostasis was evaluated with a new and automated measurement technique by Erel [7]. Thiol/disulfide homeostasis results were calculated  $\mu\text{mol/L}$ .

The study protocol was approved by a regional committee (number 3).

### Statistical analysis

All statistical analyses were done with SPSS 20.0 (IBM, New York, USA), MS Office Excel. The continuous variables were expressed as median (min–max); categorical variables were expressed as n (%). The difference of continuous variables between groups was calculated by the Mann Whitney U-test.  $p \leq 0.05$  was regarded as significant.

## RESULTS

There were also three indexes that are derived from disulfide, native and total thiol (Index 1 =  $100 \times \text{disulfide}/\text{native thiol}$ ); Index 2 =  $100 \times \text{disulfide}/\text{total thiol}$ ); Index 3 =  $100 \times \text{native thiol}/\text{total thiol}$ ). When compared with Group 1 and Group 2; total thiol was high, native thiol was low but not statistically significant. Disulphide ( $p = 0.046$ ), index 1 ( $p = 0.036$ ) and index 3 ( $p = 0.034$ ) were statistically significant (Tab. 1).

## DISCUSSION

Dynamic thiol/disulfide homeostasis is an essential predictor of OS in our body. Strengthening the enzyme mechanism and immune system depends on changes in thiol/disulfide balance [8, 9]. It is thought that HG is caused by the imbalance between free ROS that are formed by OS and antioxidants, and it has been found that antioxidant balance was low and the OS index was higher in the HG group [10]. Previously OS has been investigated in HG and healthy pregnant women. However, ketone positive and ketone negative pregnant women were compared for the first time. In this study, we investigated OS related changes due to malnutrition by compar-

ing thiol/disulfide balance between ketone positive and ketone negative pregnant women with nausea and/or vomiting. The findings were in favor of OS in ketone positive patients.

There are strong relationships between HG and OS [4]. First, a decrease in the antioxidant system is observed as a result of insufficient intake of vitamins and other energy sources taken as a result of reduced nutrition [11, 12]. Many antioxidant enzymes have been shown to decrease due to HG. Another important mechanism is the increase in the synthesis of ROS in the presence of *H. pylori* [13].

Onaran et al. [14] and Güney et al. [15] found a deficiency in the antioxidant system in HG. There is limited information about the importance of antioxidant effect in early fetus development. However, it increases the importance of antioxidants to free radical damage later in the fetus [16].

Ketonuria shows its carnage at the adipose site as a marker for HG, and it is widely used as HG-defined. Due to this carnage, there is correlation between the degree of ketonuria and HG [17]. While there is a negative correlation between disease severity and native thiol and total thiol, a positive correlation is detected between disulfide [18]. The American College of Obstetricians and Gynecologists (ACOG) currently recommends that a combination of oral pyridoxine hydrochloride (vitamin B6) and doxylamine succinate be used as first-line treatment for nausea and/or vomiting during pregnancy if pyridoxine monotherapy does not relieve symptoms [19]. Ege et al. [20] it has been shown that malnutrition in HG patients suppresses the antioxidant system and consequently the immune system is affected. Based on our results, in additional supplementa-

**Table 1. Demographic and laboratory results and comparison of two groups**

	Grup 1 (n = 30)	Grup 2 (n = 30)	p* value
	median (min–max)		
Age [years]	28 (18–34)	28 (20–35)	0.672
Fasting Glucose [mg/dL]	94 (73–123)	85.5 (66–122)	0.139
Native Thiol [ $\mu\text{mol/L}$ ]	598.7 511.3–695.6)	627.7 (510.9–772.1)	0.062
Total Thiol [Umol/L]	632.3 (556.5–740.4)	655.4 (536.1–802.3)	0.089
Disulfide	21 (11.4–45.3)	19.3 (12.2–26.8)	<b>0.048</b>
Index 1	3.51 (1.89–8.45)	2.87 (1.76–4.61)	<b>0.036</b>
Index 2	3.33 (1.82–7.23)	2.82 (1.7–23)	0.082
Index 3	93.35 85.54–96.36)	94.58 (91.56–96.61)	<b>0.034</b>

Index 1 —  $100 \times \text{disulfide}/\text{native thiol}$ ; Index 2 —  $100 \times \text{disulfide}/\text{total thiol}$ ;  
Index 3 —  $100 \times \text{native thiol}/\text{total thiol}$

\*Mann–Whitney–U test

tion of — SH-containing compounds can be discussed in ketone positive group.

The limitation of this study was the small number of patients having participated. Secondly, we were unable to measure the pre-pregnancy thiol/disulfide status of the forementioned pregnant women. Finally, we did not look at the level of H.pylori that causes of HG.

## CONCLUSIONS

In conclusion, patients with HG are shifting to OS direction due to lack of nutrients and electrolytes. A significant difference between the ketone positive and ketone negative groups shows that all nausea and/or vomiting will not cause OS and that the body can tolerate OS by considering a precise balance. This study emphasizes the importance of therapeutic support in the treatment of symptoms in ketone positive patients, where antioxidant supplements are gaining importance day by day.

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