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Gestational Oxidative Stress and OGTT: Are Pregnant Women's Fears Justified?

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Purpose: Pregnancy induces significant metabolic, immunological, and endocrinological changes to support fetal growth. The 75-gram oral glucose tolerance test (OGTT) is standard for gestational diabetes screening, but concerns exist about its potential to induce oxidative stress, affecting both maternal and fetal health. The aim of the study is examining changes in oxidative stress markers and thiol/disulfide homeostasis in pregnant women to evaluate these concerns.

Patients and Methods: Thirty pregnant women undergoing gestational diabetes screening between the 24th and 28th weeks participated. Blood samples were collected at 0, 60, and 120 minutes as part of the OGTT protocol. Oxidative stress markers were analyzed only in samples from 0 and 120 minutes, while the 60-minute sample was used solely for glucose measurement.

Results: Results showed a significant increase in TOS ($p = 0.008$) and OSI ($p = 0.035$) post-OGTT, indicating an acute oxidative stress response. Thiol and disulfide levels showed non-significant changes, suggesting that antioxidant mechanisms were largely unaffected.

Conclusion: Further research is necessary to explore the long-term implications of these findings and develop strategies to mitigate oxidative stress during pregnancy. This study provides insights into the acute oxidative stress response caused by OGTT in pregnant women. Although the OGTT induces oxidative stress, it does not significantly disrupt the body's antioxidant capacity in the short term. These results highlight the need for more research to understand the effects of heightened oxidative stress on maternal and fetal health.

Keywords: antioxidant status, oral glucose tolerance test, oxidative stress, pregnancy, thiol disulfide

Introduction

During pregnancy, changes in oxidative stress (OS) status play a crucial role in the maternal body's significant adaptations. The induction of OS during pregnancy is a natural consequence of the increased metabolic demands and oxygen consumption required for fetal development. It is normal to observe a moderate level of OS during pregnancy, which is essential for placental function and fetal development. However, excessive OS can lead to adverse pregnancy outcomes such as preeclampsia, gestational hypertension, and intrauterine growth restriction.[1] Although the Oral Glucose Tolerance Test (OGTT) is useful in detecting gestational diabetes, its potential to induce OS raises concerns, making some pregnant women hesitant to undergo the test.[2]

Thiols and disulfides play a central role in maintaining cellular oxidative balance.[3] Thiols are free sulfhydryl groups that contribute significantly to antioxidant defenses. Under oxidative stress conditions, thiols are oxidized to form disulfide bonds, a reversible process that is essential for preserving cellular redox stability. The ratio of thiols to disulfides serves as a sensitive indicator of oxidative stress and antioxidant capacity. This biomarker is particularly valuable for evaluating oxidative stress-related conditions, including those occurring during pregnancy.

Recent research has illuminated the intriguing connection between diagnostic procedures like the OGTT and OS biomarkers, particularly focusing on the thiol-disulfide balance, total antioxidant status (TAS), and total oxidative status (TOS).[4,5] These studies shed light on how acute increases in blood glucose from such tests can amplify OS by promoting the production of reactive oxygen species (ROS) and altering markers of OS. Furthermore, the exploration into the

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dynamics of thiol/disulfide homeostasis reveals that glucose loading can disrupt the delicate redox balance between thiol and disulfide levels, suggesting a nuanced effect on the body's redox equilibrium without directly influencing the overall antioxidant capacity.[6,7] ROS tend to rise following acute elevations of blood glucose levels, potentially due to heightened initial non-enzymatic glycation reactions and glucose auto-oxidation.[8]

Assessing thiol/disulfide homeostasis can now be conducted through fully automated systems, utilizing a novel, user-friendly, cost-effective, and highly sensitive method.[9] This method of assessing thiol/disulfide homeostasis has been linked to various conditions, including gestational diabetes mellitus (GDM),[10] type 1 diabetes,[11] prediabetes,[12] and type 2 diabetes.[13]

Nonetheless, there remains insufficient research elucidating the immediate impact of glucose loading on OS parameters and thiol/disulfide balance, both shortly after loading and at later intervals, in both healthy individuals and those with diabetes. Therefore, our study aimed to explore the alterations in oxidant and antioxidant markers, as well as thiol/disulfide parameters, over a two-hour period following a 75-g oral glucose load.

Disulfides, formed through the oxidation of thiols, can be reduced back to thiols, thus maintaining a balance crucial for cellular redox homeostasis. The thiol/disulfide balance is a significant indicator of OS and cellular antioxidant capacity.[14]

The 75-g OGTT, used to diagnose GDM, can trigger metabolic and hormonal changes leading to transient shifts in OS levels. During OGTT, acute hyperglycemia can increase ROS production as high glucose levels enhance oxidative phosphorylation, leading to a higher output of ROS as by-products.[15] This study aims to elucidate the potential effects of the 75-g OGTT on OS markers in pregnant women undergoing screening for GDM, thereby contributing to the existing body of literature.

GDM screening using the 75-g OGTT is a crucial step in prenatal care. However, many pregnant women avoid this test due to concerns about its potential OS effects.[2] This study aims to explore whether these fears are justified by investigating the impact of OGTT on OS and thiol/disulfide homeostasis.

Although OGTT is widely used for GDM screening, limited research has explored its acute effects on oxidative stress parameters during pregnancy. Parameters like thiol/disulfide homeostasis, which are sensitive to redox changes, have not been extensively studied following short-term glucose challenges. This study aims to bridge this gap by investigating the oxidative stress response induced by OGTT, contributing valuable insights into the safety and implications of this routine diagnostic procedure during pregnancy.

Materials and Methods

Between February and May 2023, thirty eligible pregnant women attending the Obstetrics and Gynecology Department at a University Medical Faculty Hospital for OGTT were included in this study between the 24th and 28th weeks of pregnancy. Participants were excluded if they had any known chronic illnesses, such as diabetes, cardiovascular disease, autoimmune disorders, or other conditions that could influence OS. Additionally, only those without a pre-existing diabetes diagnosis before pregnancy were included in the study. Additionally, all participants provided written informed consent after being fully briefed about the study's objectives and procedures.

In this study, blood samples were routinely collected at 0 minutes (fasting), 60 minutes, and 120 minutes during the 75 grams OGTT, as per standard practice. Blood samples were collected in biochemistry tubes after an 8-hour fasting period and immediately centrifuged at 1500 rpm for 10 minutes to separate serum. The serum samples were aliquoted into Eppendorf tubes and stored at −80°C until analysis. However, OS markers, including TAS, TOS, total thiol (TT), native thiol (NT) and disulfide (DS) levels, were specifically analyzed using spectrophotometric methods described by Erel and Neselioglu.[9] The total thiol content of the samples is quantified using Modified Ellman's reagent, and the disulfide concentration is determined using the following formula: (total thiol - native thiol) / 2.[9] Blood samples collected at 60 minutes were used solely for the measurement of glucose. This approach was adopted to minimize unnecessary testing and focus on OS dynamics during the fasting and post-load periods.

To account for potential confounding variables, detailed information was collected on maternal age, BMI, gravidity, ethnicity, diet, lifestyle, and the presence of gestational complications. Statistical analyses were then adjusted for these variables to isolate the specific effects of the OGTT on OS markers.

Data were presented as mean ± standard deviation for continuous variables and frequencies for categorical variables. Changes in OS markers and thiol/disulfide homeostasis parameters during OGTT were analyzed using repeated measures. Paired sample *t*-test. A p-value of <0.05 was considered statistically significant. All analyses were performed using SPSS version 25.0 (IBM, Armonk, NY).

To further assess the relationship between glucose levels and OS markers, Pearson correlation analysis was conducted. This analysis was used to determine whether pre- and post-OGTT glucose levels correlated with TAS, TOS, and the OSI.

Results

In this study, we assessed the oxidative status and thiol/disulfide homeostasis in pregnant women before and after the 75-g OGTT to understand the acute OS response to glucose challenge during pregnancy. In the study, the mean age of participants was found to be 27.2 ± 5.4 years, encompassing a relatively young cohort (Table 1). The mean gestational age was determined to be 26.7 ± 1.34 weeks (Table 1), indicating that all subjects were well into their second trimester. The average gravidity, inclusive of the current pregnancy, was noted to be 2.4 ± 1.21, suggesting that the majority of the participants had undergone pregnancy at least once previously. The mean parity was recorded at 1.16 ± 0.98 (Table 1), denoting a range from nulliparous to multiparous women within the study group, with values varying from 0 to 4.

Regarding glucose metabolism parameters, the mean fasting plasma glucose level was established at 84.2 ± 9.6 mg/dL, which is within the expected range for healthy pregnant individuals (Table 1). After 75 grams of glucose ingestion, a significant rise in glucose levels was observed at 60 minutes, with a mean value of 138.9 ± 35.9 mg/dL, indicative of the anticipated physiological response during an OGTT (Table 1). At 120 minutes post-glucose ingestion, the blood glucose levels were noted to decrease to an average of 115.7 ± 28.5 mg/dL (Table 1), reflecting the typical glucose clearance observed during GDM screening.

The 75-g OGTT significantly increased the TOS from 6.26 ± 1.16 μmol H_2O_2 Equiv./L to 6.88 ± 0.53 μmol H_2O_2 Equiv./L post-OGTT (p = 0.008), demonstrating a marked OS response in pregnant women (Table 2).

While TAS slightly declined from 1.49 ± 0.25 nmol Trolox/L to 1.44 ± 0.29 nmol Trolox/L after OGTT, this change was not statistically significant (p = 0.458), suggesting that the overall antioxidant defense mechanisms were not substantially affected by the glucose challenge within the duration of the test (Table 2). Regarding thiol levels, both total thiol (from 487.3 ± 41.1 μmol/L to 496.7 ± 58.7 μmol/L, p = 0.542) and native thiol (from 438.4 ± 41.8 μmol/L to 453.6 ± 62.1 μmol/L, p = 0.345) showed non-significant increases post-OGTT, indicating a potential resilience in thiol/disulfide homeostasis against oxidative shifts induced by the glucose load (Table 2). The oxidative stress index (OSI) experienced a modest but significant rise from 0.44 ± 0.12 before the OGTT to 0.49 ± 0.97 after the test (p = 0.035), reinforcing the evidence of an acute OS response while highlighting the complexity of OS dynamics during pregnancy

Table 1 Demographic Characteristics and Glucose Parameters in the Study Group

Parameter	Mean ± SD
Age (years)	27.2 ± 5.4
Gestational age (weeks)	26.7 ± 1.34
Gravidity	2.4 ± 1.21
Parity	1.16 ± 0.98
Fasting plasma glucose (mg/dL)	84.2 ± 9.6
Glucose at 60 min (mg/dL)	138.9 ± 35.9
Glucose at 120 min (mg/dL)	115.7 ± 28.5

Table 2 Comparison of Oxidant-Antioxidant Status in the Study Group

Parameters	Pre-OGTT	Post-OGTT	p-value
Total thiol (μmol/L)	487.3 ±41.1	496.7 ± 8.7	0.542
Native thiol (μmol/L)	438.4 ± 41.8	453.6 ± 62.1	0.345
Disulfide (μmol/L)	24.5 ±6.12	22.2 ±6.9	0.158
TAS (nmol Troloks/L)	1.49 ±0.25	1.44 ±0.29	0.458
TOS (μmol H2O2 Equiv./L)	6.26 ±1.16	6.88 ±0.53	0.008*
OSI	0.44 ±0.12	0.49 ±0.97	0.035*

Notes: *Paired sample *t*-test.
Abbreviations: OGTT, Oral glucose tolerance test; TAS, Total antioxidant status; TOS, Total oxidant status; OSI, Oxidative stress index.

(Table 2). Additionally, the OGTT led to a significant increase in Total Oxidant Status (TOS), further suggesting an acute OS response.

In contrast, native thiol levels showed a non-significant increase, and disulfide levels slightly decreased (from 24.5 ± 6.12 μmol/L to 22.2 ± 6.9 μmol/L, p = 0.158), indicating that short-term glucose fluctuations may not significantly disrupt the redox balance between thiol oxidation and reduction processes, which are vital for cellular homeostasis (Table 2).

To further evaluation; Pearson correlation analysis revealed weak correlations between fasting and post-OGTT glucose levels and OS markers (TAS, TOS, OSI), with correlation coefficients of r=0.12, r=−0.10, r=−0.08 for fasting glucose, and r=0.18, r=0.15, r=0.20 for post-OGTT glucose, respectively. None of these correlations were statistically significant (p=0.35, p=0.45, p=0.52; p=0.21, p=0.28, p=0.18, respectively) (Table 3). These results suggest that glucose levels may not be the primary factor influencing changes in OS markers in the short term.

These findings underscore the transient nature of OS responses to the glucose challenge, indicating that while the acute phase of glucose loading can elevate oxidant markers, the body's inherent antioxidant systems remain largely capable of managing this oxidative burden within the time frame of the OGTT.

The results of this study highlight the novelty of using the 75-g OGTT to analyze correlations between glucose levels and OS markers, specifically TOS. This approach adds a unique perspective to understanding how glucose loading influences oxidative dynamics during pregnancy, providing valuable insights into the transient oxidative responses that occur during the test.

Table 3 Pre- and Post-OGTT Glucose and Oxidative Stress Markers Correlations

Marker	Fasting Glucose Correlation (r)	Fasting Glucose p-value	Post-OGTT Glucose Correlation (r)
TAS	0.12	0.35	0.18
TOS	−0.10	0.45	0.15
OSI	−0.08	0.52	0.20

Notes: Pearson correlation analysis.
Abbreviations: TAS, Total antioxidant status; TOS, Total oxidant status; OSI, Oxidative stress index.

Discussion

The administration of a 75-g oral glucose tolerance test (OGTT) has been shown to significantly influence reactive oxygen species (ROS) levels, marking a pivotal shift in the OS landscape during pregnancy.[1] This acute response highlights the intricate interplay between glucose challenge and oxidative mechanisms within the gestational milieu.

The average age of participants in this study was 27 years, which aligns with the national average age for first-time mothers in Turkey (27 years), as reported by TUIK (2023).[16] In contrast, the average age for first-time mothers in Aksaray, where this study was conducted, is slightly lower at 25.4 years.

Our investigation into the effects of the 75-g OGTT on gestational OS and thiol/disulfide homeostasis reveals intriguing findings that both align with and diverge from existing research. The observed increase in TOS and OSI post-OGTT can be attributed to hyperglycemia-induced ROS production, driven by enhanced mitochondrial oxidative phosphorylation and the formation of advanced glycation end-products. This aligns with findings by Ma et al,[6] emphasizing the biochemical basis for acute OS during glucose challenges.

On the other hand, the research by Kiraz et al explored the OGTT's effects on thiol/disulfide homeostasis, demonstrating that the OGTT did not induce significant changes in thiol and disulfide levels.[7] Our results are consistent with these findings; we did not observe statistically significant alterations in thiol and disulfide levels post-OGTT.

Moreover, the study by Jones et al delved into the OGTT's influence on inflammation, OS, and non-enzymatic glycation products, highlighting the OGTT's capability to trigger complex metabolic responses during pregnancy.[8] Our findings suggest that, similar to Jones et al's observations,[8] the OGTT can have a significant effect on OS, though antioxidant defense mechanisms may adapt to this response.

Azarova et al examined the effects of the OGTT on OS and thiol/disulfide homeostasis, revealing significant increases in OS markers post-OGTT while observing that thiol/disulfide balance remained relatively stable.[13] This finding aligns with our study, which also noted a rise in OS parameters (TOS and OSI) without significant changes in thiol levels or overall antioxidant capacity. The stability of thiol/disulfide homeostasis observed in our study suggests that short-term oxidative stress induced by glucose loading is effectively managed by maternal antioxidant defenses.

The study by Cakina et al on GDM patients assessed thiol/disulfide homeostasis, finding that GDM did not significantly affect the thiol/disulfide balance.[10] This is in line with our observations, where the OGTT did not significantly impact thiol/disulfide homeostasis. In contrast, the research by Ates et al on type 1 diabetes patients showed that thiol oxidation is associated with disease progression.[11] Our findings suggest that, unlike these metabolic conditions, short-term glucose challenges, particularly during pregnancy, may not have a lasting effect on thiol/disulfide homeostasis.

López-Tinoco et al also reported that OS markers were altered in patients with late-onset gestational diabetes mellitus, emphasizing the role of OS in the pathophysiology of GDM. This is in concordance with our findings that show an acute increase in OS markers post-OGTT.[12]

The automated assay for thiol/disulfide homeostasis developed by Erel and Neselioglu has been instrumental in assessing the redox balance in various conditions, including diabetes and pregnancy.[9] Our study's use of this assay aligns with previous research that highlights its sensitivity and reliability in detecting subtle changes in thiol/disulfide dynamics.

Hamamcioglu et al investigated the relationship between thiol/disulfide homeostasis and OS parameters in non-diabetic, prediabetic, and type 2 diabetic Turkish women.[17] They found significant variations in disulfide levels across different metabolic states. Our study did not find significant changes in disulfide levels post-OGTT, which might be attributed to the short-term nature of the glucose challenge and the effective antioxidant responses in pregnant women.

Ergin et al explored the progression of type 2 diabetes mellitus and the variation of disulfides, finding significant oxidative alterations.[18] While our study did not observe significant changes in thiol/disulfide balance, the increase in OS markers post-OGTT is noteworthy and warrants further investigation to understand its implications for maternal and fetal health.

Bielawska et al studied the effect of OGTT on plasma markers of lipid and lipoprotein peroxidation, showing an increase in OS markers similar to our findings.[19] This study corroborates our observations of increased TOS and OSI post-OGTT, emphasizing the need for further research into the long-term effects of such oxidative changes during pregnancy.

The observed increase in OS markers post-OGTT is consistent with mechanisms of hyperglycemia-induced ROS production, as described in prior studies.[6,19] While thiol/disulfide homeostasis remained stable, this may indicate the robustness of cellular redox mechanisms during transient glucose challenges, in line with Azarova et al.[13] These findings emphasize the need for further research into long-term implications of such oxidative changes.

Our study indicates that the OGTT can increase OS markers in pregnant women but does not have a significant effect on thiol/disulfide homeostasis and overall antioxidant capacity. These findings highlight the complexity of metabolic and oxidative responses to glucose challenges during pregnancy and underscore the need for further research to understand the long-term implications of these changes for maternal and fetal health.

This study investigated the 75-g OGTT's influence on OS and thiol/disulfide homeostasis in pregnant women. The findings indicate an increase in OS markers, specifically TOS and the OSI, without significant alterations in thiol levels or overall TAS. This acute oxidative response to the glucose challenge highlights the nuanced metabolic adjustments during pregnancy and the need for deeper understanding of these dynamics for maternal and fetal health.

In summary, this study contributes to the understanding of OS dynamics in response to the OGTT in pregnancy, indicating a short-term increase in OS without a significant change in antioxidant capacity. While these findings might concern pregnant women considering OGTT, it's important to note that the long-term implications of this acute oxidative response remain unclear. We underline the importance of further research to elucidate the long-term maternal and fetal health implications. These findings add to the existing literature, providing a basis for future studies aimed at unraveling the complex OS responses during pregnancy and their implications for diagnostic practices. We acknowledge the need for studies with larger sample sizes and extended post-OGTT measurement intervals. Future research should also consider including traditional oxidative markers and stratifying results by demographic variables to provide a more comprehensive understanding.

Limitations

The sample size was determined based on available resources and the number of OS marker kits. Although no formal power analysis was conducted, the sample was considered sufficient to test the study hypothesis and provide preliminary insights into the effects of OGTT on OS.

Conclusion

This study demonstrates that OGTT induces an acute OS response, as evidenced by a significant increase in TOS and OSI levels. However, the stability of thiol/disulfide homeostasis suggests that maternal antioxidant defenses remain robust in the short term. These findings underscore the need for further research into the long-term implications of oxidative stress during pregnancy, particularly in the context of routine diagnostic procedures such as OGTT.

Abbreviations

OGTT, Oral glucose tolerance test; TAS, Total antioxidant status; TOS, Total oxidant status; OS, Oxidative stress; OSI, Oxidative stress index; TT, Total thiol; NT, Native thiol; DS, Disulfide; GDM, Gestational diabetes mellitus; ROS, Reactive oxygen species.

Data Sharing Statement

The data supporting the findings of this study are available from the corresponding author upon reasonable request.

Ethics Approval and Informed Consent

This study received ethical approval from the Aksaray University Clinical Research Ethics Committee (approval number 2022/01-09). At the time of the study, the corresponding author was affiliated with the Aksaray University Women's Health and Obstetrics Clinic.

Consent for Publication

All patients participating in this study were informed about the study's purpose, methodology, potential risks, and benefits, and provided written informed consent. The research was conducted in accordance with the ethical principles of the Declaration of Helsinki. All participants completed and signed a written informed consent form prior to their inclusion in the study.

Author Contributions

All authors made a significant contribution to the work reported, whether in conception, study design, execution, data acquisition, analysis, or interpretation. They took part in drafting, revising, or critically reviewing the article, approved the final version for publication, agreed on the journal for submission, and agreed to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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