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Gene Expression of Antioxidant Enzymes in Healthy and Aborted Women

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Abstract

Gene expression analysis is one of the most important tools for discovering the link between human disorders and the genes that control them. The primary purpose of this study is to identify the gene expression profile of antioxidant enzymes in healthy and aborted mothers. The study comprised fifty-five mothers who were admitted to Al-Khansa'a Hospital in Mosul City. Ten mothers were healthy and had normal births, while the remaining forty-five mothers were divided into four groups: women who had abortions, mothers who had normal deliveries but prior miscarriages, aborted women with hypertension, and aborted women without hypertension. Gene analysis of placentas and aborted foetuses was performed using quantitative real-time PCR (q-PCR). In contrast to other mothers without hypertension and normal labour who had previously miscarried, as well as healthy mothers who had normal labour, the results showed significant variations in the gene expression profile of antioxidant enzymes, indicating highly down regulation of Glutathione Peroxidase, Superoxide Dismutase, and Catalase genes in the placenta tissues of aborted mothers with hypertension. According to their regulatory genes, mothers who have had abortions have higher oxidative stress due to downregulation of antioxidant gene expression. The placentas of hypertensive moms who had abortions showed reduced Glutathione Peroxidase, Superoxide Dismutase, and Catalase capabilities. Due to our outcomes, oxidative stress intensifies due to lower antioxidant enzyme activity in aborted moms with and without hypertension. Antioxidant enzymes are required during pregnancy to protect mothers from abortion, and they have been linked to miscarriages.

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1. Introduction

The paradox of cell metabolism has a detrimental impact on live cells via the release of reactive oxygen species [1]. When body cells use oxygen to sustain themselves for food processing or environmental reactions, poisons known as free radicals containing unpaired electrons are created. Due to their negative responses to different cell components, they have a detrimental effect [2]. Biological and chemical compounds known as antioxidants, or "free-radical scavengers," mitigate cell damage spurred on by free radicals that generate in the body. These metabolites and enzymes remove free radicals from the body or prevent them from generating and damaging critical cell components like lipids, proteins, and DNA. [3]. The pathophysiology of pregnancy-related complications, endometriosis, polycystic ovarian disease, infertility that cannot be

explained, and gynecological malignancies is influenced by oxidative stress, which can impact various physiological mechanisms such as oocyte maturation, fertilization, implantation, and embryo development [4]. An abortion that ends before 20 weeks of gestation is referred to as a "spontaneous abortion" and happens between 10% and 15% of the time. Due to the fact that many abortions take place prior to pregnancy being clinically recognized, the actual incidence is unknown [5]. Spontaneous abortion arises out of an imbalance of the formation of reactive oxygen species (ROS) and antioxidant safeguarding. Despite the overexpression of antioxidants such as catalase, glutathione peroxidase, Cu/Zn, and Mn superoxide dismutase, placental tissue from early pregnancy losses showed an increase in oxidative stress indicators, such as MDA and lipid peroxides, compared with controls [6]. The most frequent ROS under physiological settings are superoxide anions (SOA). They are created when molecular oxygen receives an additional electron. In plasma, whole blood, and/or placental tissue of Recurrent Miscarriages (RM) patients, recent investigations have shown considerably lower activity levels of both enzymatic and non-enzymatic antioxidants, including glutathione peroxidase, catalase, glutathione reductase, reduced glutathione, and selenium [7]. Nevertheless, when ROS generation exceeds what is often seen in cells, uncontrolled attack on cellular organelles and shifts to the structure of macromolecules, including proteins, nuclear and mitochondrial DNA, and membrane lipids arise. [8]. Antioxidant-related genes are among those whose expression is altered, leading to cytotoxicity via different pathways [9]. Determining the gene expression of antioxidant enzymes in healthy and aborted women was the study's objective.

1. Research Method:

Ethical approval, patients, and sampling

An ethical permit has been issued under No. (6728 on 21 February 2022) by the Mosul City Health Department. In this study, fifty-five women were recruited at random. Ten of the patients introduced to Mosul's Al-Khansa'a Maternity Hospital were in good health and gave delivery normally. At the same time, forty-five women had been aborted (n=15), as well as women who had earlier miscarried but did not have hypertension (n=15 each). Placentas from aborted fetuses were obtained from study participants under the particular supervision of nurses and doctors. The specimens were placed on ice after having been rinsed with cold buffered saline to get rid of any remaining blood. Moreover, samples were stored at -80°C until they were processed for RT-PCR analysis to evaluate gene expression.

Processing quantitative real-time PCR (qPCR) for gene expression

Isolation of total RNA using a Promega RNA extraction kit (Promega, USA) in accordance with the manufacturer's instructions was the first step in the PCR process. The next step was using reverse transcriptase (RT) to transcribe the extracted RNA into cDNA. The cycle technique was as follows: priming at 25°C for 10 minutes, reverse transcription at 50°C for 60 minutes, RT inactivation at 80°C for 5 minutes, and holding at 12°C. The last step of qPCR was conducted by using Step-One Applied Biosystems tool system, USA on cDNA samples on selected genes, which were:

Primer		Sequence
GPx	Forward	5'-AACCAGTTTGGGCATCAGGAGA-3'
	Reverse	5'-TCTCGAAGAGCATGAAGTTGGG-3'
SOD	Forward	5'-GTGGAGAACCCAAAGGGGAGTT-3'
	Reverse	5'-TTTCATGGACCACCAGTGTGC-3'
CAT	Forward	5'-GTTACTCAGGTGCGGGCATTCTAT-3'
	Reverse	5'-GAAGTTCTTGACCGCTTTCTTCTG-3'
GAPDH	Forward	5'-ATGACATCAAGAAGGTGGTG-3'
	Reverse	5’-CATACCAGGAAAATGAGCTTG-3'

[10-12]. The mastermix reaction volume was 20 µl, 10µl SYBER green master mix, 2µl template, 2µl forward and reverse primers, and 6µl PCR water. The qPCR cycling was carried out using the following modes: initial denaturation at 95°C for 10 minutes, 35 cycles of cycling (95°C for 25 seconds, 60°C for 25 seconds, 72°C for 1 minute), and 72°C for the final extension. The 2^-(ΔΔCt) was used to extract the data as Ct values and calculate the fold change.

Statistical analysis

All data were given as mean ± SE using IBM's SPSS software version 26 (USA). A one-way ANOVA test was then run, with LSD used at P> 0.05, and was considered a significant difference value.

2. Results And Discussion:

Results:

1. Gene expression of *GPx, SOD,* and *CAT* in healthy and aborted women:

Clear variance in the cellular regulation of several antioxidants was found when the Ct values of these antioxidants were analyzed to determine their gene expression. Compared to women without chronic illness or hypertension, mothers who had previously experienced miscarriages, and healthy mothers who gave birth normally, GPx expression showed downregulation control in aborted mothers with hypertension.

Likewise, there was a downregulation in the gene expression of the antioxidant enzyme superoxide dismutase when comparing the placentas of aborted mothers with and without persistent hypertension to the placentas of mothers who had normal births but a history of miscarriage. There was no difference in SOD regulation between the two groups of mothers who gave birth spontaneously, irrespective of whether they had experienced previous miscarriages.

All study groups showed comparable levels of gene expression regulation for the antioxidant enzyme catalase, with the exception of the groups made up of mothers who had aborted fetuses and those who had hypertension, who showed a modest downregulation. Figures 1 and 2.

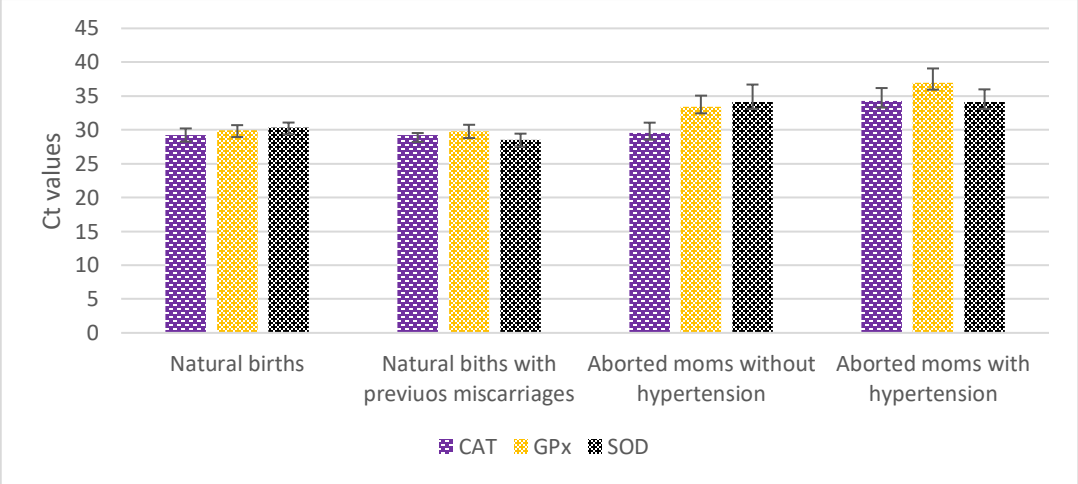

Figure 1: Calculated Ct values of antioxidant genes

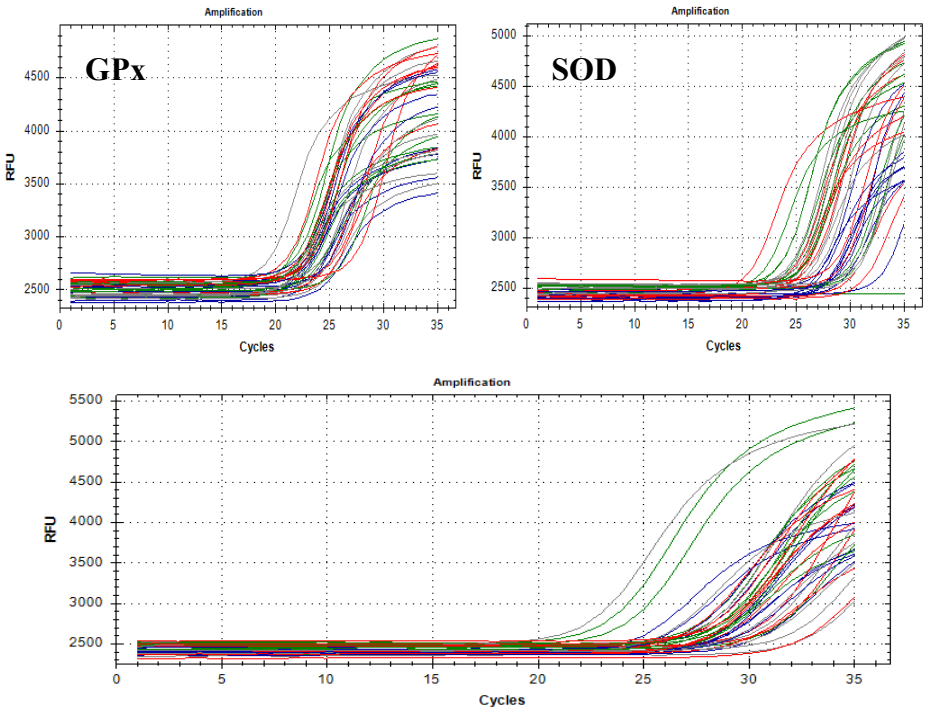

Figure 2: Antioxidant genes amplification curve

2. Fold change of investigated genes in miscarried and healthy women.

In the tissue samples of mothers who were aborted and had high blood pressure or low blood pressure, the GPX gene's calculated fold change from the Ct values of the expressed GPX gene revealed a highly and significantly higher fold change (598.9, 87.7, respectively) than 25.9, 5.1 in the cases of natural birth with and without previous miscarriages at *P* 0.001, as shown in figure 3.

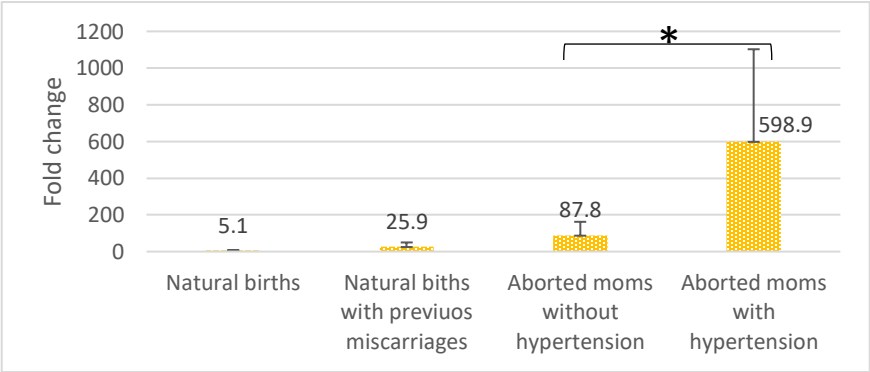

Figure 3: Calculated fold change of GPx gene

The calculated fold change of the SOD gene from Ct values of the expressed SOD gene in the tissue samples of aborted mothers with hypertension and aborted mothers without hypertension revealed high and significant fold changes of 1143.87, 632.67 respectively than 57.84, 4.39 in those with natural birth with and without previous miscarriages at *P* 0.001 as shown in Figure 4.

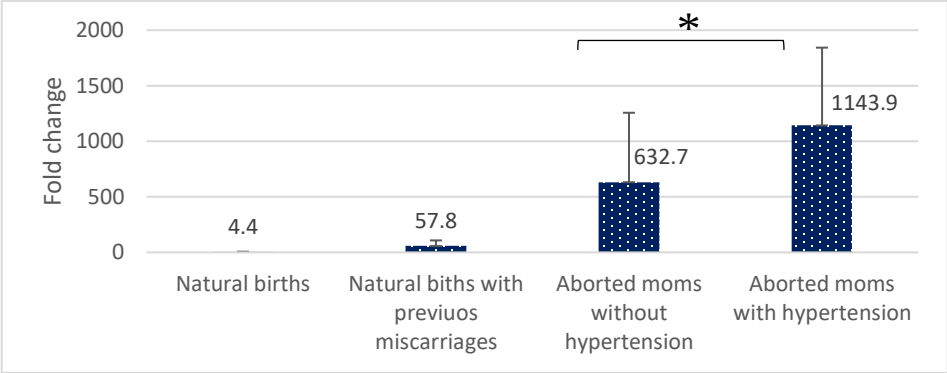

Figure 4: Calculated fold change of SOD gene

Figure 5 illustrates how the CAT gene's calculated fold change from the Ct values of the expressed CAT gene revealed a highly and significantly higher fold change (384.59) in the tissue samples of mothers who were aborted and had hypertension than 19.48, 2.37, and 4.99 in the other cases of aborted mothers without hypertension, natural birth with and without previous miscarriages at *P* 0.001.

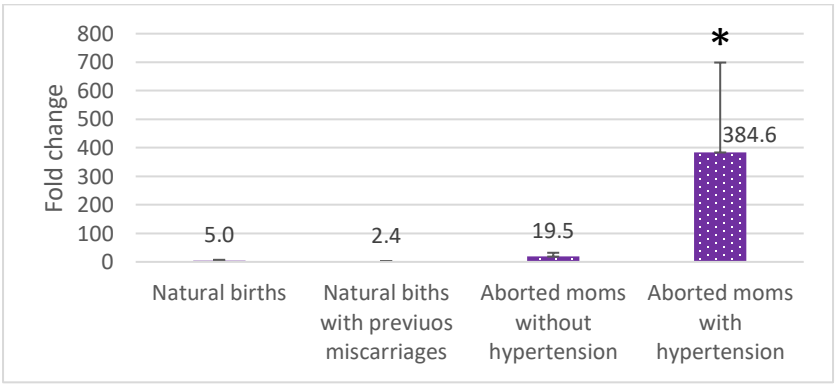

Figure 5: Calculated fold change of CAT gene

Discussion

Several factors collaborate and are co-regulated resulting in tissue and cellular regulation. Gene array analysis allows for the identification of many of the transcripts that comprise this complicated regulatory network. A review of the transcripts found that they were extensive. Oxidant and antioxidant-regulating genes are among the most frequently examined genes in the human body. [13]. Antioxidants, whether enzymes or not, play an important role in many physiological and pathological processes in the human body. Their balance with other oxidants is necessary for the regular functioning of all body organs.[14]. The results of the current study unequivocally demonstrate that there were moderate decreases in the GPx, SOD, and CAT expression in the placenta and tissues of aborted fetuses in both aborted mothers with and without hypertension and in mothers who gave birth normally after earlier abortion. These results were in agreement with other studies [15], whose indicate in mothers who experienced repeated miscarriages and had hypertension, oxidative stress may have played a significant role in their recurrent miscarriages (RM) by lowering their antioxidant GPx and CAT capacity. The decrease in GPx, SOD, and CAT activity observed in the placentas of mothers who are not in good health may be attributed to an increase in the production of free radicals as a result of oxidative stress brought on by pregnancy or high blood pressure. This opinion is in agreement with previous works [12-14]. The potential explanation for the large decreases in GPx and all other antioxidant enzymes observed in RM moms is a shift in these enzymes' gene expression levels, which is supported by the current data. We found a substantial proportion of downregulation in the GPx, CAT, and SOD gene expression levels in the placental tissue of RM individuals compared to healthy women. These genes are important for both mothers with and without hypertension when it comes to RM. This is in agreement with [15-18]. Oxidative stress is generated in the blood and placental tissue of RM mothers by the decrease in GPx, and CAT activities, which in turn causes extremely significant increases in H_2O_2 and MDA levels [22].

The present results indicate downregulation of studied genes plays an important role in enhancing the capacity of GPx, SOD, and CAT enzymes by depleting cellular GSH, which is crucial for all cellular vital activity such as cell cycle via redox cycle and leading to oxidative stress. Reduced gene expression or the inactivation of antioxidant enzymes generate NO radicals, which can be harmful during pregnancy and induce a variety of pathological changes in the placenta. This interpretation is compatible with [23], which proposes that the degree of nitration of enzymes, receptors, transporters, and structural proteins may have a major impact on placental cellular function in both healthy and diseased conditions. The generation of ROS and reactive nitrogen species (RNS), such as nitric oxide and peroxynitrite, can cause protein buildup and phosphorylation, impairing placental proliferation and embryo invasion and resulting in early embryonic mortality.[24]. This provides evidence to the idea that recurrent miscarriages are linked to abnormal placental development or partial degeneration; elevated levels of free radical production may also have negative consequences. We observed that [25] confirms our hypothesis that recurrent pregnancy loss correlates with the functional gene regulating the ROS promoter, possibly as a result of oxidative stress amplification and decreased antioxidant capability of GPx, SOD, and CAT enzymes.

The frequency of elevated oxidative stress is evident in this study, which may have led to toxicity and changed the expression of genes associated with apoptosis and antioxidants in RM patients, ultimately leading in miscarriage. H_2O_2, lipid peroxides, GSSG, and a drop in GSH/GSSG ratios are examples of ROS buildup [26]. RM showed higher amounts of catalase and glutathione reductase (GSR) mRNA expression than a normal placenta, according to a study by(author) [27]. There was no difference in the mRNA expression of glutathione peroxidase and superoxide dismutase. The hypothesis in this research is compatible with the current findings, prompting interpretation of the findings because inflammation and inflammatory mediators that regulate mRNA expression (TNFa, IL6, and IL8) are causally linked to higher ROS and reduced antioxidant defences. [25-27]. This conclusion confirms our findings indicating oxidative stress reduced the expression of the CAT and GPX genes.

3. Conclusion:

Oxidative stress worsens by downregulating antioxidant enzyme activity in mothers who have had abortions due to regulating genes. Mothers with hypertension who had abortions exhibited decreased levels of placental enzymatic antioxidant gene expression. Antioxidant enzymes are necessary during pregnancy to protect mothers from abortion and have been connected to miscarriages.

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دراسة التعبير الجيني للأنزيمات المضادة للأكسدة لدى النساء الصحيحات والمجهضات

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الخلاصة:

واحدة من أهم الطرق لتحديد العلاقة بين الأمراض البشرية والجينات التي تنظمها هي تحليل الجينات. تحديد ملف التعبير الجيني لمضادات الأكسدة الأنزيمية في الأمهات الصحيحات والمجهضات هو الهدف الأساسي لهذا البحث. في المجمل، تم تضمين خمس وخمسين أم تم إدخالهن إلى مستشفى الخنساء في مدينة الموصل في هذه الدراسة. كانت عشر من الأمهات ذات ولادة سليمة وبصحة جيدة، الخمسة وأربعون امرأة الباقية قسمت إلى ثلاث مجموعات وهي أمهات لها ولادات طبيعية ذات تاريخ مسبق بالإجهاض، وأمهات مجهضة تعاني من إرتفاع ضغط الدم، وأمهات مجهضة لا تعاني من إرتفاع ضغط الدم لها امراض مزمنة اخرى (العدد = 15 لكل منهم). تم إجراء تحليل الجينات باستخدام تقنية qPCR على المشيمة والأجنة المجهضة. وبالمقارنة مع الأمهات الأخريات غير المصابات بارتفاع ضغط الدم والولادات الطبيعية اللائي عانين سابقاً من الإجهاض، وكذلك الأمهات الصحيحات اللائي ولدن ولادة طبيعية، أظهرت النتائج إختلافات كبيرة في جانب التعبير الجيني للإنزيمات المضادة للأكسدة، مما يشير إلى إنخفاض كبير في تنظيم جينات الكلوتاثيون بيروكسيديز و سوبر أوكسيد ديسموتيز و الكاتاليز في أنسجة المشيمة للأمهات المجهضات المصابات بإرتفاع ضغط الدم. بناءً على جيناتهم التنظيمية، تبين أن الأمهات اللواتي خضعن للإجهاض لديهن إجهاد أكسدة مرتفع من خلال تقليل تنظيم نشاط الإنزيم المضاد للأكسدة. تم العثور على إنخفاض في نشاط وسعة الكلوتاثيون بيروكسيديز و سوبر أوكسيد ديسموتيز و الكاتاليز في مشيمة الأمهات المصابات بإرتفاع ضغط الدم واللواتي خضعن أيضاً للإجهاض. بالإعتماد على نتائج الدراسة لوحظ زيادة الإجهاد التاكسدي في الأمهات المجهضة نتيجة إنخفاض كفاءة مضادات الأكسدة التي تعاني والتي لا تعاني من إرتفاع ضغط الدم. إن مضادات الأكسدة ضرورية خلال الحمل لحماية الأمهات من الإجهاض والتي أثبتت الدراسة إرتباطها بالإجهاض.