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Association between Fluoride Toxicity, Oxidative Stress, and Pregnancy Complications in Women Living in Fluorosis Areas

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Abstract

The purpose of this study was to investigate the relationship between high plasma fluoride levels, oxidative stress, and pregnancy complications (abortion, intrauterine fetal death, preterm birth, and preeclampsia) in women living in Settat province, Morocco. Blood samples were collected from pregnant women with normal gestation (n=60), abortion (n=20), intrauterine fetal death (n=10), premature delivery (n=20), and preeclampsia (n=20). Afterwards, plasma fluoride levels and erythrocyte enzymatic activities of superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx) were determined. The results revealed that plasma fluoride levels were significantly lower in women who had normal pregnancies, with a concentration of 0.030±0.003 mg/l, compared to those presenting with abortion, intrauterine fetal death, preterm birth, and preeclampsia, with concentrations of 0.040±0.002, 0.037±0.002, 0.034±0.004 and 0.034±0.003 mg/l, respectively. In addition, SOD activity was significantly increased in women with pregnancy complications, whereas CAT and GPx activities were decreased compared to women with normal pregnancies. Moreover, there was a strong correlation between plasma fluoride levels, antioxidant activities, and pregnancy complications. The presence of high plasma fluoride levels could lead to an increase in the prevalence of abortion, intrauterine fetal death, preterm birth, and preeclampsia, via the oxidative stress pathway in pregnant women living in Settat province, Morocco.

Keywords: Fluoride, normal pregnancy, oxidative stress, pregnancy complications, women.

Introduction

Pregnancy is a physiological period of transition with important physical and hormonal changes[1]. During pregnancy, significant anatomical and physiological changes occur in order to support and accommodate the growing fetus[2]. These changes require increased production of ATP, which in turn requires high consumption of oxygen. This process could lead to the accumulation of free radical species

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(ROS)[3]. However, there are several factors that further increase the generation of ROS levels in pregnant women, leading to oxidative stress, including malnutrition, infection, and environmental pollutants. Excessive production of ROS stimulates oxidative damage to lipids, proteins, and DNA[4]. This oxidative stress may cause many reproductive complications such as miscarriage, preeclampsia, fetal growth restriction, and preterm birth[5]. For instance, studies showed that spontaneous abortion is potentially related to extensive placental injury caused by widespread oxidative stress[6]. Moreover, high levels of peroxidation markers were observed in the plasma of pregnant women with preeclampsia[7].

Fluoride is a pollutant that is widely distributed in the environment. Chronic exposure to this halogen can lead to several toxic effects in the form of dental, skeletal, and non-skeletal fluorosis via oxidative stress pathways[8]. Fluorosis is a public health problem, and is endemic in several countries of the world. The association between this pollutant and pregnancy complications is well established in women living in several endemic fluorosis areas[9,10]. However, to our knowledge, all these studies are focused on the relationship between the prevalence of pregnancy complications and plasma or urinary fluoride levels. Considering all previous data, the assumption advanced in this study was that fluoride could cause oxidative stress, which would influence the course of pregnancy in women living in Settat Province, Morocco, where fluorosis is endemic[11]. In this context, the current study aimed to investigate the relationship between high plasma fluoride levels, oxidative stress, and pregnancy complications (abortion, intrauterine fetal death, preterm birth, and preeclampsia) in women living in Settat province, Morocco.

Materials and Methods

Study area and participants

This study was conducted among pregnant women living in Settat province, Morocco, who visited the provincial public hospital Hassan II of Settat, Morocco, between the period 2018 to 2019. A total of 130 participants aged 25 to 35 were enrolled. Sixty of them were presented with a normal gestation, while the remaining 70 had pregnancy complications such as abortion (n=20), intrauterine fetal death (n=10), premature delivery (n=20), and preeclampsia (n=20). Exclusion criteria were any other high-risk pregnancy.

Blood samples

Samples were collected from venous blood using heparin and EDTA tubes, for the measurement of plasma fluoride levels and erythrocyte enzymatic activities respectively. In order to separate plasma and erythrocytes, samples were centrifuged at 3000 x g for 15 minutes[12].

Determination of plasma fluoride levels

To determine the plasma fluoride levels, one volume of total ionic strength adjustment buffer (TISAB) was added to the same volume of sample, and plasma fluoride levels were then measured using a fluoride electrode (Thermo Scientific Orion 96-09, Orion Research, Cambridge, MA, USA) coupled to an analyzer ion (Star A214, Thermo Scientific Orion). The electrode was calibrated with standard fluoride solutions at concentrations of 0.01, 0.025, 0.05, 0.075, and 0.1 mg/l, and prepared with the same reagent used for the samples.

Determination of protein content

The protein content in erythrocytes was estimated according to the procedure described by Lowry et al.[13] using bovine serum albumin as a standard.

Determination of superoxide dismutase activity (SOD)

SOD activity was assayed as described by Beyer and Fridovich[14]. The reaction mixture contained 50 mM phosphate buffer, 0.025% Triton X-100, 0.1 mM EDTA (pH 8), 12 mM L-methionine, 75 mM NBT, aliquot and 2 µM riboflavin. The tubes were shaken and placed 30 cm below a light bank consisting of a 15 W fluorescent lamp for 10 min. The reaction was stopped by switching off the light and the absorbance was measured spectrophotometrically at 560 nm. Given the large number of samples, and the high cost of the reagents used, a microplate assay was therefore conducted as

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described by Babitha et al.[15], this being a simple, rapid, and cost-effective means for screening many samples at a time. The absorbance was read at 560 nm by a Tecan Microplate Reader Infinite 200 Pro.

Determination of catalase activity (CAT)

CAT activity was assayed as described by Ni et al.[16]. The 200 µl reaction mixture containing 10 µl of the aliquot was mixed with 30 µl of a 7.3 mM H_2O_2 solution. After 3 min of incubation, the reaction was stopped by adding 20 µl of H_2SO_4 at 6N and then 140 µl of $KmNO_4$ at 2 mM. The absorbance was read at 480 nm by a Tecan Microplate Reader Infinite 200 Pro. The specific activity of CAT was expressed as micromoles per minute per milligram of protein.

Determination of glutathione peroxidase Activity (GPx)

Glutathione peroxidase activity was measured following the method of Flohé and Günzler[17]. Briefly, the sample (60 µl) was incubated for 15 min at 37 °C in a reaction mixture containing 60 µl of potassium phosphate buffer (0.1 M, pH 7.0), 40 µl GSH (reduced glutathione, 2 mM), 20 µl H_2O_2 (1 mM) and 20 µl sodium azide (1 mM). Then, 100 µl of TCA (5%) was added to stop the reaction. After centrifugation for 5 min at 1500 × g, 20 µl of the supernatant was collected and added to 40 µl of phosphate buffer (50 mM, pH 7.0) and 140 µl of 5,5-dithiobis (2-nitrobenzoic acid) (DTNB) buffer (0.4 mg/ml). The absorbance was read at 420 nm by a Tecan Microplate Reader Infinite 200 Pro. The specific activity of GPx was expressed as micromoles of GSH per minute per milligram of protein.

Statistical analysis

Data were analyzed using IBM® SPSS® Statistics 21. The results were expressed as mean ± SD (standard deviation). A comparison of the two groups was performed with a Mann–Whitney U test; a P-value of 0.001 or less was deemed to be statistically significant. The Spearman coefficient was used to determine the correlation between complications and fluoride levels; $P<0.01$ was considered significant.

Results and discussion

Previous studies reported that chronic excessive fluoride intake is associated with several pregnancy complications[18,19]. On the other hand, it was reported that pregnancy showed behavioral, anatomical, physiological, and metabolic changes leading to dramatic variations in the concentration of several biochemical constituents of blood such as the antioxidant system, and certain minerals, mainly calcium[1,2,20]. These normal physiological changes are important for normal embryonic, placental, and fetal development[21]. However, under pathological conditions these changes could promote the production of oxygen radical species; these reactive forms produced in the body of the mother and the fetus could lead to oxidative stress, which affects the replication, differentiation, and maturation of cells in development, and thus lead to several complications during pregnancy. The aggravation of oxidative stress during pregnancy by chronic ingestion of fluoride has been well established in many animal species[22,23]. However, studies performed on women have focused only on the correlation between plasma or urinary fluoride and pregnancy complications. Therefore, the investigation of other biomarkers is necessary to gain a better understanding of the potential mechanisms by which fluoride could cause women pregnancy complications[9,10]. To our knowledge, this study is the first to investigate the relationship between plasma fluoride levels, oxidative stress, and pregnancy complications in women living in endemic fluorosis areas.

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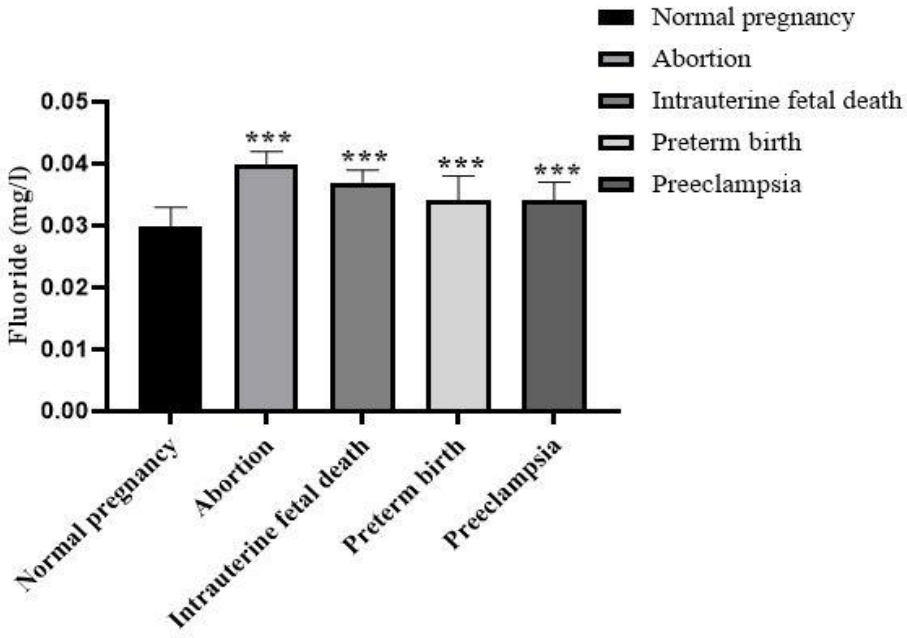

Figure 1. Plasma fluoride levels in women with normal gestation and women with a risk of abortion, intrauterine fetal death, preterm birth, and preeclampsia.

SD: Standard deviation;

***: indicates the significant difference between each pregnancy complication and normal pregnancy.

The data summarized in Fig. 1 revealed that plasma fluoride levels were significantly ($P<0.001$) lower in women presenting with normal pregnancy, with a concentration of 0.030±0.003 mg/l, compared to women presenting with abortion, intrauterine fetal death, preterm birth, and preeclampsia, with concentrations of 0.040±0.002, 0.037±0.002, 0.034±0.004 and 0.034±0.003 mg/l, respectively. Moreover, whether in women with normal gestation or pregnancy complications, the values of plasma fluoride obtained were similar to those of pregnant women exposed to fluoride or living in endemic fluorosis areas[18,19]. The high plasma fluoride values recorded could be explained by the high levels of fluoride in the water consumed by the population in the province of Settat, Morocco[24]. In this context, it has been reported that drinking water is the main contributor to the toxic effects of fluoride[8], and is positively correlated with plasma fluoride levels in pregnant women[25]. Additionally, our findings are consistent with several studies that found that fluoride was associated with anemia[26], abortion, low birth weight, preterm birth, and poor APGAR score[9,10,27].

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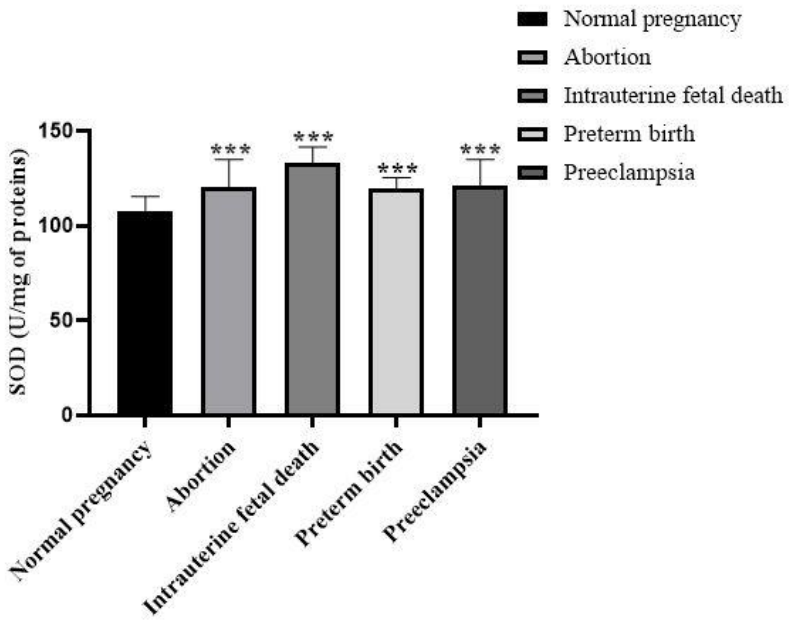

Figure 2. Erythrocyte superoxide dismutase activity in women with normal gestation and women with a risk of abortion, intrauterine fetal death, preterm birth, and preeclampsia.

SD: Standard deviation.

*: indicates a significant difference between each pregnancy complication and normal pregnancy.

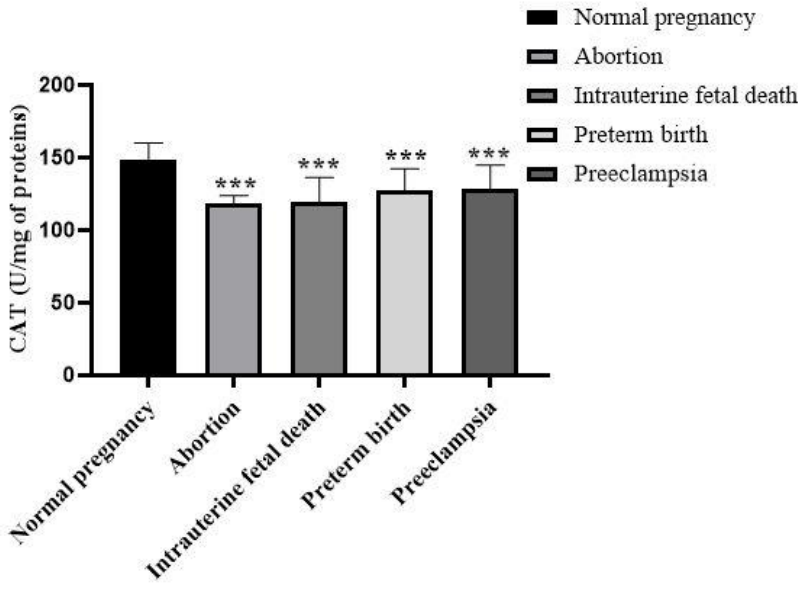

Figure 3. Erythrocyte catalase activity in women with normal gestation and women with a risk of abortion, intrauterine fetal death, preterm birth, and preeclampsia.

SD: Standard deviation.

*: indicates a significant difference between each pregnancy complication and normal pregnancy.

To determine the relationship between oxidative stress and pregnancy complications, the catalytic activities of antioxidant enzymes (SOD, CAT and GPx) were assessed in erythrocyte cells. As shown in Fig 2, SOD activity was significantly ($P<0.001$) lower in women presenting with normal pregnancy, with 107.88±07.49 U/mg of proteins, compared to those presenting with abortion,

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intrauterine fetal death, preterm birth, and preeclampsia, with 120.62±14.26, 132.82±08.67, 119.68±05.57, and 121.28±13.60 U/mg of proteins, respectively. Concerning CAT and GPx activities, the results presented in Figs 3 and 4 showed that the activities of these two enzymes were significantly (P<0.001) lower in pregnant women with abortion, intrauterine fetal death, preterm birth, and preeclampsia when compared to those with normal pregnancy. These results are similar to several previous studies[28,29]. For instance, Bharadwaj et al.[30] reported that total antioxidant status was lower in a preeclampsia group than a normal group of women living in South India. Another study reported that CAT activity was inversely associated with the severity of preeclampsia and suggested a correlation between oxidative stress and the progression of this complication[31]. Furthermore, oxidative stress is strongly associated with other complications such as preterm birth, endometriosis, miscarriages, gestational diabetes, and fetal growth restriction [32].

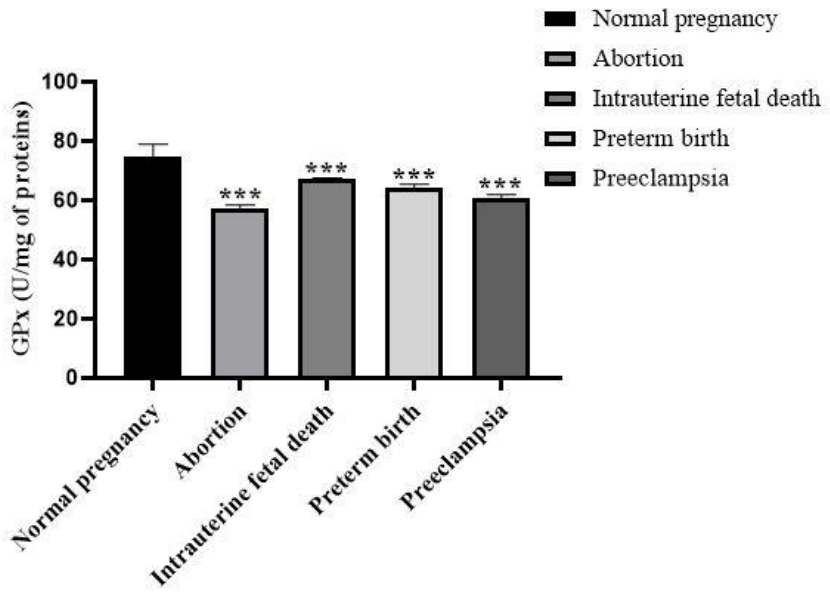

Figure 4. Erythrocyte glutathione peroxidase activity in women with normal gestation and women at risk of abortion, intrauterine fetal death, preterm birth, and preeclampsia.

SD: Standard deviation.

*: indicates a significant difference between each pregnancy complication and normal pregnancy.

More importantly, according to the Rho Spearman test presented in Table 1, the results revealed that pregnancy complications were positively correlated with plasma fluoride levels (r=0.72; P<0.01) and SOD activity (r=0.57; P<0.01), while negative correlations were observed between pregnancy complications and CAT (r=-0.72; P<0.01) and between pregnancy complications and GPx (r=-0.86; P<0.01). It also showed a positive correlation between plasma fluoride levels and SOD activity (r=0.59; P<0.01). Furthermore, plasma fluoride levels were negatively correlated with CAT activity (r=-0.96; P<0.01) and GPx activity (r=-0.81; P<0.01). Fluoride is a chemical halogen recognized for its high electronegativity. After its absorption, this element is acidified and oxidized, and consequently, it can readily bind to several biological molecules such as cations, proteins, and enzymes to form stable and strong bonds[33]. Additionally, due to its high affinity towards calcium, fluoride reduces calcium absorption, leading to hypocalcemia[34]. Interestingly, another study documented that hypocalcemia is associated with hypertensive disorders and can increase the risk of numerous problems such as preeclampsia[35]. On the other hand, other studies reported that fluoride can disrupt the antioxidant system via the inhibition of enzymes that have an electropositive cofactor[33]. In this study, the negative correlation between plasma fluoride levels and GPx enzymatic activity in women with

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pregnancy complications could be due to the binding between fluoride and selenium, which is the key cofactor of GPx. Therefore, the use of selenium supplementation as a chelator and contributor to the antioxidant system to reduce the toxic effects of fluoride has been investigated previously, and encouraging degrees of success have been achieved[36,37]. Hence, studies focused on the supplementation of pregnant women with selenium in endemic fluorosis areas could be beneficial, especially in several Moroccan endemic fluorosis areas including Settat province, where selenium deficiency has been reported[38].

Table 1. Correlation between pregnancy complications, fluoride levels, and enzymatic activities

Rho of Spearman	Complications	Fluoride	SOD	CAT	GPx
Complications	1.00	0.72**	0.57**	-0.727**	-0.86**
Fluoride	0.72**	1.00	0.59**	-0.96**	-0.88**
SOD	0.57**	0.59**	1.00	-0.61**	-0.50**
CAT	-0.72**	-0.96**	-0.61**	1.00	0.83**
GPx	-0.86**	-0.81**	-0.50**	0.83**	1.00

It is well known that SOD is the first line of defense against oxidative stress as it catalyzes the dismutation of superoxide anion free radical (O_2^-) into molecular oxygen and hydrogen peroxide (H_2O_2). Afterwards, CAT and GPx transform H_2O_2 into H_2O. However, inhibition of these two enzymes by fluoride can increase the accumulation of ROS[8]. These radicals generate oxidative stress, which might result in aberrant spiral artery formation, increased placental vascular resistance, and decreased uterine perfusion[39]. The ROS can also damage DNA, lipids, and proteins, shorten telomeres, accelerate the aging of fetal membranes, and induce the "aging" of placental structures, leading to placental failure and the development of pregnancy complications such as early pregnancy loss, recurrent miscarriages, preeclampsia, intrauterine growth restriction, and preterm birth[40].

Conclusion

In conclusion, high levels of fluoride were observed in the plasma of pregnant women enrolled in the present study. Moreover, excessive intake of this element could lead to an increase in the prevalence of abortion, intrauterine fetal death, preterm birth, and preeclampsia, via oxidative stress. Further studies are needed on the supplementation of pregnant women with minerals (mainly calcium and selenium) as fluoride chelators, and antioxidants as free radical scavengers, to reduce the prevalence of pregnancy complications in endemic fluorosis areas. On the other hand, raising awareness among women living in endemic areas of the importance of the nutritional aspect in protecting against the risks of fluoride during pregnancy is necessary. Precisely, they must be encouraged to consume foods rich in natural biomolecules, especially red, orange and purple-colored fruits and vegetables which are rich in bivalent minerals capable of chelating fluoride in the body, and antioxidants that can compensate for the oxidative stress generated by fluoride excess.

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Author's Declaration

- Conflicts of Interest: None.
- We hereby confirm that all the Figures and Tables in the manuscript are ours. Furthermore, any Figures and images, that are not ours, have been included with the necessary permission for re-publication, which is attached to the manuscript.

- Ethical Clearance: The project was approved by the local ethical committee in the Direction of Epidemiology and Diseases Control of the Ministry of Health of Morocco.
- Authors sign on ethical consideration's approval. The work approved by Health Ministry under number 198/25 was obtained from the Direction of Epidemiology and Disease Control of the Ministry of Health of Morocco.

Author's contribution

K.M. L.A., B.H, and R.A: performed the experiments, analyzed the data, and wrote the paper; E.K.R, E.A: analyzed and discussed the data, and reviewed the paper. All authors have read and agreed to this manuscript.

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العلاقة بين سمية الفلوريد والإجهاد التأكسدي ومضاعفات الحمل لدى النساء اللواتي يعشن في مناطق التسمم بالفلور

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الخلاصة

كان الهدف من هذه الدراسة هو التحقيق من العلاقة بين مستويات فلوريد البلازما المرتفعة، والإجهاد التأكسدي، ومضاعفات الحمل (الإجهاض، وموت الجنين داخل الرحم، والولادة المبكرة، وتسمم الحمل) لدى النساء اللواتي يعشن في إقليم سطات بالمغرب. تم جمع عينات الدم من النساء الحوامل ذوات الحمل الطبيعي (عدد = 60)، والإجهاض (عدد = 20)، وموت الجنين داخل الرحم (عدد = 10)، والولادة المبكرة (عدد = 20)، وتسمم الحمل (عدد = 20). بعد ذلك، تم تحديد مستويات فلوريد البلازما والأنشطة الأنزيمية لخلايا الدم الحمراء من superoxide dismutase (SOD)، catalase (CAT)، glutathione peroxidase (GPx). أظهرت النتائج أن مستويات الفلوريد في البلازما أقل بشكل ملحوظ عند النساء ذوات الحمل الطبيعي بتركيز 0.030 ± 0.003 ملغم / لتر مقارنة بالنساء اللائي تعرضن للإجهاض وموت الجنين داخل الرحم والولادة المبكرة وتسمم الحمل، بتركيزات 0.040 ± 0.002، 0.037 ± 0.002، 0.034 ± 0.004 و0.034 ± 0.003 ملغم / لتر، على التوالي. بالإضافة إلى ذلك، زاد نشاط SOD بشكل ملحوظ عند النساء اللواتي يعانين من مضاعفات الحمل، بينما انخفضت أنشطة CAT وGPx مقارنة بالنساء ذوات الحمل الطبيعي. علاوة على ذلك، لوحظ وجود علاقة قوية بين مستويات فلوريد البلازما وأنشطة مضادات الأكسدة ومضاعفات الحمل. قد يؤدي وجود مستويات عالية من فلوريد البلازما إلى زيادة انتشار الإجهاض ووفاة الجنين داخل الرحم والولادة المبكرة وتسمم الحمل، عبر مسار الإجهاد التأكسدي لدى النساء الحوامل اللواتي يعشن في إقليم سطات بالمغرب.

الكلمات المفتاحية: الفلوريد، الحمل الطبيعي، الإجهاد التأكسدي، مضاعفات الحمل، النساء.