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IMPACT OF ENVIRONMENTAL TOXICS AND OF METEOROLOGICAL CONDITIONS ON REPRODUCTIVE LOSS AND STILLBIRTH

UTJECAJ TOKSIČKIH TVARI OKOLIŠA I METEOROLOŠKIH OKOLNOSTI NA REPRODUKTIVNI GUBITAK I NA MRTVOROĐENOST

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Original paper

Key words: oxidative stress, methemoglobinemia, meteorological conditions, fossil fuels, stillbirth, fetal preeclampsia

SUMMARY. ***Background.*** The aim of this review is to point out the excessive maternal exposure to environmental oxidants. We have reviewed the correlation between environmental toxics and local meteorological conditions as a contribution to the explanation of pregnancy loss and unexplained stillbirth. ***Methods.*** The pregnant women living near coal-powered thermoelectric power plant Plomin 1, in Labin, Croatia were investigated. The data were processed by using the Chi-Square analysis and linear correlation tests. ***Results.*** The frequency of reproductive loss was significantly different (p=0.0369) between the »control« (N=4) and »exposure« periods (N= 10) as well as the frequency of stilbirth caused by increased amount of methemoglobin (>1,5 g/L) in the exposure period. (p=0.0336). It was also observed that stillbirth significantly occurred only in the second half of pregnancy. ***Conclusions.*** Continuous methemoglobin monitoring in cases of stillbirth can indirectly explain the causes of fetal death when the level of fetal methemoglobin is increased. Meteorological conditions may support the explanation for the acute failure of fetal vital organs (first time expressed as »fetal preeclampsia«) and stillbirth. This assumption requires further investigations which may confirm the relation between fetal methemoglobin and reproductive loss and death, frequently referred to as unexplained.

Izvorni članak

Ključne riječi: oksidativni stres, methemoglobinemija, meteorološki uvjeti, fosilna goriva, mrtvorođenost, fetalna preeklampsija

SAŽETAK. ***Cilj*** ovog epidemiološkog rada je ukazati na prekomjernost i štetnost izloženosti trudnica oksidantima iz čovjekova okoliša koji uzrokuju porast razine methemoglobina, a kojima je i fetus ugrožen. Razina koncentracijje methemoglobina koji ima svojstvo oksidanta. kao produkt nepovoljnog utjecaja sagorjevanja ugljena kao i utjecaja meteoroloških prilika u mikroregionalnim uvjetima, doprinos su objašnjenju iznenadne intrauterine smrti fetusa, koja su i nakon poroda u trećini slučajeva neobjašnjiva. ***Metode.*** Da bi se utvrdila incidencija reproduktivnog gubitka u krugu djelovanja TE Plomin1 (Labin) obrađena je populacija trudnica u razdoblju »izloženosti« (N=122) i u »kontrolnom« razdoblju (N=138).Podaci su obrađeni χ^2 analizom i linearnim korelacijskim testovima. ***Rezultati.*** Dobiveni rezultati pokazuju da je reproduktivni gubitak u trudnoći statistički značajno veći (p=0.0369) u razdoblju »izloženosti« (N=10), nego u »kontrolnom« razdoblju (N=4), te da je u razdoblju izloženosti učestalost mrtvorođenosti s povećanom koncentracijom methemoglobina u krvi također statistički značajnija, nego u »kontrolnom« razdoblju (p=0.0336). Uočeno je, također, da je u razdoblju »izloženosti« prizemna koncentracija SO_2 bila viša u »sunčanim i dominantno sunčanim danima«. ***Zaključak.*** Ciljani, kontinuirani i preporučeni monotoring razine majčina methemoglobina može neizravno ukazati na neprepoznatu, prekomjernu fetalnu razinu methemoglobina te objasniti akutno zatajenje vitalnih organa (prvi puta izraženo kao »fetalna preeklampsija«) i iznenadnu intrauterinu smrt fetusa. Ova pretpostavka zahtijeva daljnja istraživanja koja mogu voditi do potvrde uloge fetalnog methemoglbina kao potencijalnog uzroka iznenadne intrauterine smrti, često klasificirane kao »neobjašnjive«.

Background

According to International Stillbirth Alliance (ISA) the sudden intrauterine unexplained death is defined as the death which occurs ante partum and results in stillbirth for which there is no explanation in spite of postmortem examinations. Our epidemiological research is directed toward the development of better predictive tests in order to identify women at high risk for fetal loss and to evaluate the role of environmental toxic factors as potential cause of stillbirth and/or neonatal death.

Our data suggest that methemoglobinemia can cause the deterioration of maternal and fetal hypoxia, which can indirectly explain how unrecognized level of fetal methemoglobin can cause sudden fetal death and stillbirth which is frequently referred to as »unexplained«. The aim of the study is to point out the correlation between the outdoor – indoor air pollution and local meteorological conditions as a possible causative factor of miscarriage and unexplained stillbirth.

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Causal mechanism

The concentration of fetal hemoglobin is relatively high in the early months of life, and forms oxihemoglobin more readily than adult hemoglobin does. This by analogy means that it may be susceptible to the oxidation to methemoglobin. The level of methemoglobin in erythrocytes under normal conditions is less than 1% of the total hemoglobin.[1] Ante partum stillbirth is associated with fetal abnormality, congenital infection, rhesus isoimmunisation, maternal medical conditions and complications of pregnancy, such as preeclampsia and placental abruption. However the majority of stillbirth can not be connected with direct obstetrical causes and are referred to as unexplained.[2,3]

From the conception and under the influence of oxidants and oxidative stress, according to my own hypothesis, the mother from early pregnancy transits three stages of complication to eclampsia and/or death as the final form of »mother preeclampsia«.[4]

As the blood level of methemoglobin rises, the adults show signs of hypoxia, this may lead to coma and death if blood methemoglobin reaches the concentration of 70%. Methemoglobinemia during pregnancy is often unrecognized and under-emphasized by obstetricians. The symptoms of the increased methemoglobin in mother include headache, dyspnea, pallor, cyanosis, palpitations, chest pain, and confusion, delirium to the tonic-clonic convulsions, coma and death. The author has personally observed that these symptoms are also common in severe anemia, preeclampsia and eclampsia, suggesting that methemoglobinemia may also be a precursor for these conditions. When the high level of methemoglobin as an oxidant becomes irreversible, the deficiency of antioxidants persists and oxidative stress continues, attacking the vascular endothelium of kidneys, brain and other vital organs and tissues of the mother. This can result in eclampsia and/or death as the final form of »maternal preeclampsia«. As the oxidants have the capacity to cross the damaged fetomaternal placental barrier, »fetal preeclampsia« is qualified to be the expected manifestation. Under these adverse conditions, the level of methemoglobin in the fetus increases, also resulting in preterm birth, stillbirth or early neonatal death. We the first time use the term »fetal preeclampsia« since along with the excessive maternal exposure to environmental oxidants, the fetus, in its more susceptible pathophysiological phase, is also involved. The development of eclampsia is associated with the increased risk of an adverse outcome for both the mother and the fetus, particularly in developing countries.[5]

This hypothesis is based on our findings that the level of maternal methemoglobin, the incidence of methemoglobinemia and stillbirth in the »exposure period« are statistically significant. The impact of seasonal variations in the ambient air pollution with some compounds (PM, SO_2, CO, NO_2) on stillbirth was studied and changes in concentration were found to affect stillbirth[6] and the occurrence of abortion.[7]

Methods

When estimating the health risk from the exposure to air pollution, it is essemtial to have a good measure of exposure. In this study, indirect substituted measures of exposure were used. Because of lack of evidence of fetal methemoglobin, we have used the findings of proper former studies of maternal methemoglobinemia in human pregnancy, where during the »control« and »exposure period« the blood samples were taken and tested three times one month apart. The blood concentrations of methemoglobin were correlated to air pollution parameters.[8] To confirm the incidence of reproductive loss and the association with adverse effects of environmental inhaled toxic, the population of pregnant women living near thermoelectric plant Plomin 1, was investigated. Coal-powered thermoelectric plant in the district of Labin (about 25.500 residents), Istra, Croatia is a single major air polluter. During each hour of operation, the plant emits 8.5 tons (18,080 mg/ m^3, or 6,900.8 ppm) of sulfur dioxide in addition with nitrogen oxides, carbon dioxide, carbon monoxide, total suspended particles, and other coal combustion products. The coal from this area has a high sulfur content (9–11 %) and a high level of radioactivity. Since the plant was closed from February 19, 1989 to September 6, 1989, it was possible to carry out the frequency of reproductive loss (spontaneous abortions, prematurity and stillbirths rates) in two periods: the »control« period from April to July 1989 and the »exposure« period from December 1989 to March 1990.

In the »exposure period« the daily discharge of SO_2 was monitored in three areas of Labin municipality and the daily meteorological situation (daily maximum and minimum air temperature, rainfall amount, wind direction, cloudiness) was monitored in Labin's meteorological station. For the analysis of reproductive loss data we used the Chi-square test and the statistical linear correlation tests. Data were obtained from the medical records of the Women's Health Care Centre in Labin, from admissions of pregnant women from Labin district to Rijeka's University Clinic of Obstetrics and Gynecology, Obstetric Hospital in Pula, to Department of preterm and low birth-weight babies in Pula and Rijeka. Data were collected from the Central Bureau of Statistics in Zagreb, too.

Results

The aim of the prospective study was to determine whether the level of methemoglobin concentration in the bloodstream of pregnant women was correlated with the inhallation of the substances generated from coal combustion (SO_2, NOx, NO, NO_2 and other). The spectrophotometric level of methemoglobin in the bloodstream was laboratorically determined from these samples three times, with a one-month pause between each test, for each pregnant woman (N=122) in the exposure period of power plant operation as well as for each preg-

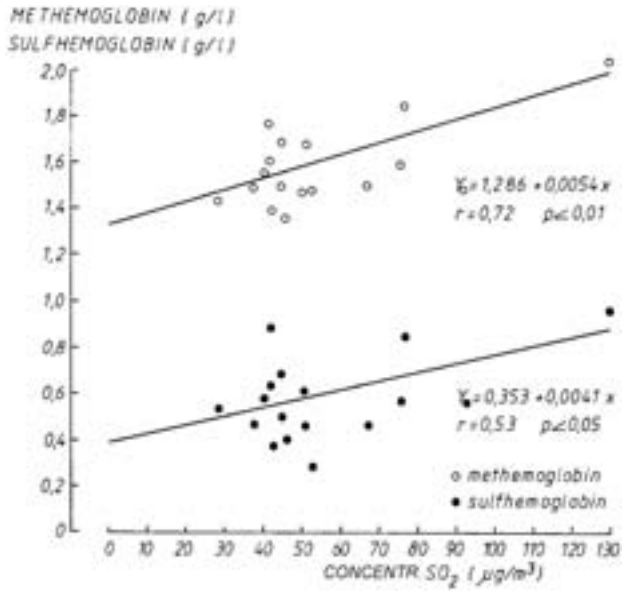

Figure 1. The correlation between the level of methemoglobin and sulfhemoglobin of pregnant women, as product of inhaled nitrogen and sulfur compounds of coal combustion to the daily ground level concentration of SO_2 in the exposure period (December 20,1989.to 20.03.1990.).

Slika 1. Korelacija razine methemoglobina i sulfhemoglobina, kao produkta udahnutih dušikovih i sumpornih spojeva u trudnica pri izgaranju ugljena i dnevne prizemne koncentracije sumpornog dioxida u razdoblju izlaganja (20. prosinca 1989. do 20. ožujka 1990.)

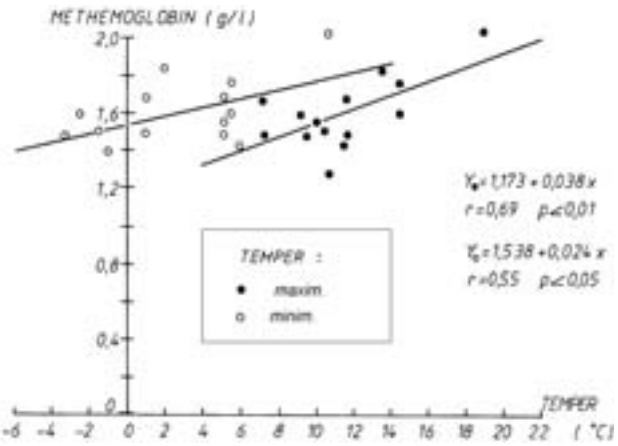

Figure 2. The correlation between the level of methemoglobin of pregnant women and the daily maximum and minimum air temperature in the exposure period (December 20, 1989.to March 20, 1990.).

Slika 2. Korelacija razine methemoglobina u trudnica i dnevne najviše i najniže temperature u razdoblju izlaganja (20. prosinca 1989. do 20. ožujka 1990.).

nant woman in the control period when the power plant was closed (N=138). The examination has demonstrated the significant positive correlation of the level of methemoglobin (as product of inhaled nitrogen compounds of coal combustion) and sulfhemoglobin in the blood of pregnant women to the daily ground level concentration of SO_2 ($r=0.72$, $p<0.01$) from coal combustion. (*Figure 1*) The nitrogen compounds are strong oxidants, which, by oxidation of oxyhemoglobin (Fe II), turn it into a reversible pathological form of methemoglobin (FeIII) which has no ability of linking the oxygen, thus contributing to the decline of tissue oxigenation. With the aim to verify whether these obtained results may contribute to the explanation of an adverse pregnancy course, we have performed a research on reproductive losses in the exposure and control periods. The Chi-square test showed that the rate of reproductive loss were significantly different ($p=0.0369$) between the »control« (N= 4:138) and »exposure« periods (N=10:122) and that the frequency of stillbirth with the increased amount of methemoglobin (>1,5 g/L) in the exposure period was also statistically significant (3:10 versus 0:4; $p=0.0336$).

The level of methemoglobin rises in correlation with an increase of the daily air temperature; it means that as the daily maximum and minimum temperature rise, the level of methemoglobin in the blood of pregnant women rises too ($r=0.69$,$p<0.01$ for maximal temperature, $r= 0.55$, $p<0.05$ for minimal temperature; *Figure 2*).

The monitoring of meteorological situation in the »exposure period« (December 1989 to March 1990) has shown that the ground level concentration of SO_2 was lower when the weather was »predominantly cloudy with rain«, influenced by humid southeast winds (25, 3% days), while when there were »sunny and predominantly sunny days« (65, 0% days) the ground level concentration of SO_2 was higher. (*Figure 3*)

Discussion

We have established a significant correlation between the upward trend of the level of maternal methemoglobin and the ground level concentration of SO_2. The fact that we have also found the increase of the daily air temperature followed by »sunny and predominantly sunny days«, confirms our hypothesis that reproductive loss and stillbirth in the »exposure period« are very likely the results of fetal methemoglobinemia and »fetal preeclampsia« caused by oxidants inhaled through coal combustion. Our hypothesis points out that the exposure to environmental toxic substances originating from coal burning is the most decisive for the impacts of metabolic synergism of nitrogen oxides as oxidants that cause hemoglobin oxidation to methemoglobin, and sulfur dioxide metabolites as inhibitors of antioxidants, during the entire pregnancy period.

Lone et al.[9] found the relationship between maternal anemia (< 111 g/L) and perinatal morbidity and mortality. Allessandri et al.[10] suggest that unexplained ante partum stillbirths are not merely the results of an inadequate obstetrical management but consist of a series of fetal disease states which are not currently practicable to detection. Observational studies have demonstrated various correlations between hypertensive disorders of pregnancy and different weather parameters. The incidence of eclampsia is significantly higher when the weather is cooler and humid with a lower barometric pressure.[11] The important result is that the winter increase in preterm births is negatively correlated with mean winter temperature ($r=–0.424$, $p=0.003$) and on

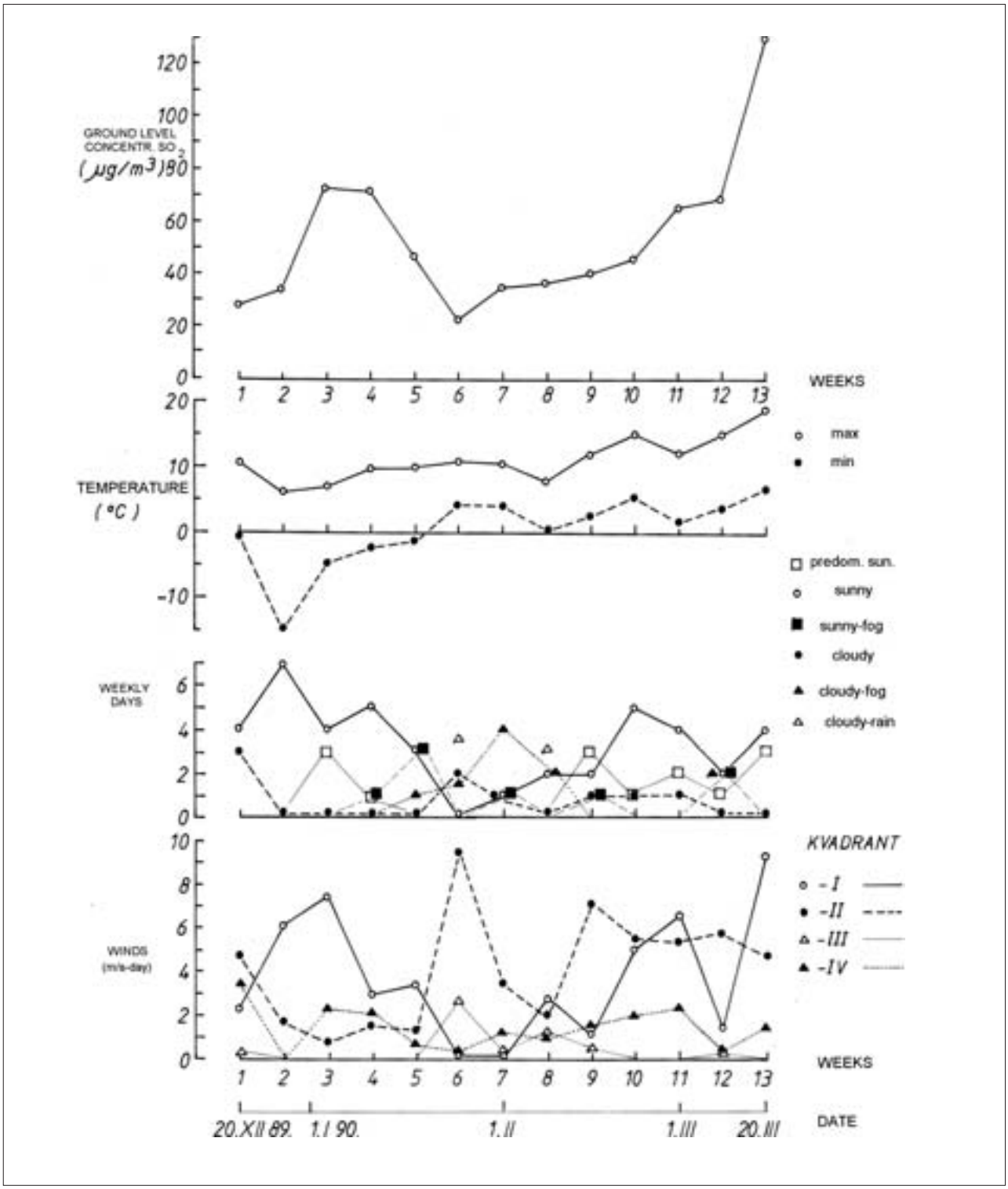

Figure 3. The trend of weekly ground level of concentration of SO_2 μg/m^3, the trend of weekly maximal and minimal temperature C°, weather and winds in the exposure period (December 20,1989.to March 20, 1990.).

Slika 3. Trend tjedne prizemne koncentracije SO_2 μg/m^3, trend tjedne najviše i najniže temperature C°, vremena i vjetra u razdoblju izlaganja (20. prosinca 1989. do 20. ožujka 1990.).

the contrary the summer increase in preterm birth is positively correlated with the average summer temperature (r= 0.549, p< 0.001).[12] Simpson[13] states that about 10% of fetal deaths are related to maternal medical illnesses as hypertension, diabetes, obesity, systemic lupus erythematosus, chronic renal disease, thyroid disorders and cholestasis of pregnancy. More than a thousand of infants have been etiologically investigated and the major-

ity of the established causes of intrauterine death are those of fetal etiology.[14] Unexplained stillbirth makes a quarter of all perinatal deaths and is the highest among preterm deliveries.[15]. Tabacova et al.[16,17] confirmed that methemoglobinemia is linked with complications during pregnancy and that the measured methemoglobin is a valuable biomarker of individual exposure. They also found that maternal methemoglobin was strongly associated with cord methemoglobin (P<0.0001). Maternal and cord methemoglobin levels were higher in cases of abnormal birth outcomes. The mean maternal methemoglobin values were approximately twofold higher in mothers of infants born prematurely and in fetal distress than in mothers who gave birth to normal babies. Ten out of 14 analyzed maternal blood samples in cases of poor birth outcomes had methemoglobin levels above the physiological limit. Cord blood methemoglobin levels were excessively high in preterm births and these levels were also elevated in low birth-weight births, although less markedly than in preterm births.[16,17]

Lyall et al.[18] demonstrated that total nitrites were significantly increased in fetoplacental circulation in preeclampsia ($p< 0.01$).[18] Kato et al.[19] have found that fetal oxidative stress occurs in preeclampsia before the onset of labor.[19] Hjelt et al.[20] measured the level of newborn fetal methemoglobin. Out of 415 neonates, 33 cases (8%) were methemoglobin-positive (metHb ≥6%), the mean methemoglobin value was 19% (range 6.5–45.5%). They found that about 40% of neonates born at 25–30 weeks and 60% with a birth weight <1000 grams were methemoglobin-positive. There was also a negative correlation between the highness of a methemoglobin-positive concentration and gestational age ($r=0.38$, $p=0.02$). These data confirm the assumption of early adverse effects of oxidative stress on fetus.

Conclusion

The continuous methemoglobin monitoring for the risk of pregnancy complications could indirectly explain the unrecognized excess of the level of fetal methemoglobin. Under the conditions of the daily temperature increase and other meteorological situations, the subsequent acute fail of fetal vital organs influenced by environmental toxics has an impact on reproductive loss, sudden intrauterine fetal death and stillbirth. This epidemiologic retrospective study requires further investigations that may lead to the confirmation that the level of fetal methemoglobin is related to the reproductive loss and death, frequently referred to as unexplained.

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