Risk of preeclampsia among women exposed to H2S emission due to sargassum stranding in Martinique, a French Caribbean Island

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Abstract

Objective: Our objective was to determine whether chronic exposure to ambient H2S due to sargassum strandings is associated to increased occurrence of preeclampsia in Martinique, a French Caribbean Island. Design: Observational case control study Settings and population: Data for this study derive from 25/01/2016 to 31/07/2020 births database of the University Hospital of Martinique. Methods: Women were considered exposed to H2S if living and/or working in cities along the Atlantic coast of Martinique known to be impacted by sargassum strandings. Main Outcome Measures: Primary endpoint was occurrence of preeclampsia as defined by the International Society for the Study of Hypertension in Pregnancy in 2018. Secondary endpoint was preeclampsia free survival time, which was defined by the number of months free of preeclampsia between the 20th and 37th week of amenorrhea. Results: In the exposed population, median H2S concentration, averaged across pregnancy length, was 300 ppb (IQR H-spread 197). There were no differences (p=0.20) in preeclampsia incidence rate between H2S exposed (n=623) and non-exposed (n=2367) pregnant women during the follow-up period (7.5% versus 6.1%, respectively). Time to preeclampsia between the 20th and 37th week of amenorrhea was shorter (p=0.02) in H2S exposed compared with non-exposed pregnant women (median=30.9 months - IQR 8.6 versus 32.9 months - IQR 6.0, respectively) Conclusions: We found that onset of preeclampsia was earlier in women living and/or working in areas impacted by sargassum seaweed strandings compared with non-exposed pregnant women. Funding: None

INTRODUCTION

Pre-eclampsia is defined as hypertension developing after 20 weeks' gestation with one or more of the following: proteinuria, maternal organ dysfunction (including renal, hepatic, hematological, or neurological complications), or fetal growth restriction [1-3]. The mechanisms involved in the onset of pre-eclampsia are still unclear, but may involve an abnormal placentation with subsequent release of antiangiogenic biomarkers, mediated primarily by soluble fms-like tyrosine kinase-1 (sFlt-1) and soluble endoglin (sEng)[4,5]. Soluble sFlt-1 is an anti-angiogenic protein that binds to the functional receptor binding domain of vascular endothelial growth factor (VEGF), neutralizing the ability of VEGF to signal to endothelial cells lining arteriolar blood vessels to maintain vasorelaxation [4,5]. These events are combined with suppression of the release of pro-angiogenic placental growth factor (PlGF), which further limits the promotion of development and maturation of the placental vascular system [1,4]. Beside their anti-angiogenic effects, high levels of sFlt-1 and sEng combined to the suppression of PlGF, also result in endothelial dysfunction, vasoconstriction, and immune dysregulation, which can negatively impact every maternal organ system and the fetus [1-6].

Gaseous molecules such as nitric oxide (NO), carbon monoxide (CO) and hydrogen sulfide (H_2S) have the potential to regulate placental blood through their roles in angiogenesis, cytoprotection and regulation of vascular tone [6-10]. Abnormal vascular tone and endothelial dysfunction in pre-eclampsia are attributed to the reduction of NO and H_2S bioavailability, which are key vasodilator regulators in placenta [5-7]. Researchers have showed that activation of heme oxygenase-1 (HO-1)/carbon monoxide (CO) as well as H_2S/cystathionine-γ-lyase system can suppress sFlt-1 and sEng release and prevent placental stress in experimental models [7]. Placental production of H_2S, expression of H_2S-producing enzymes (i.e., cystathionine beta-synthase and cystathionine-γ-lyase), and plasma H_2S concentrations are all reduced in human pregnancies complicated by preeclampsia [5-7]. Interestingly, the potential of H_2S as a mechanism-based therapy for preeclampsia has been successfully tested with several H_2S donors in preclinical studies [11].

Since 2016, repetitive and massive strandings of sargassum seaweed have occurred along Caribbean coasts resulting in H_2S emission, which comes from the natural decomposition of sargassum in the absence of oxygen [12-14]. Depending on H_2S levels, clinical characteristics of H_2S exposure range from mucosal irritation (10-50 ppm) to pulmonary edema, coma and cardiopulmonary arrest ($>$ 500 ppm) [15-18]. While the effects elicited by acute exposure are reasonably well documented, less is known about the deleterious effects of H_2S exposure over longer periods[19]. Long-term exposure to H_2S levels in industrial and geothermal areas have previously shown increased morbidity for respiratory diseases and disorders of the central nervous system, whereas others studies found no evidence of an association[20-29]. In the specific context of sargassum strandings, we have previously reported associations between day-to-day variations in H_2S levels and disorders of the central nervous, respiratory system, and small intestine in subjects living in the most intensely impacted coastlines with the highest ambient H_2S levels [13].

Regarding the cardiovascular impact of chronic H_2S exposure, the few epidemiological studies carried out evaluating the relationship between H_2S and cardiovascular diseases are inconclusive [20,26,27]. Evidence of both protective role and deleterious effects of H_2S in cardiovascular diseases, including hypertension, has been demonstrated[30-32]. Whether increased ambient H_2S levels due to sargassum strandings may alter the incidence of preeclampsia in pregnant women is unknown. The main objective of the present study was to determine whether H_2S exposure due to anaerobic decomposition of sargassum strandings was associated to occurrence of preeclampsia in Martinique, a French Oversea Caribbean Island.

METHODS

Population and data collection

In this epidemiologic, monocentric, observational, longitudinal and retrospective study, data derive from the administrative and medical databases of the University Hospital of Martinique, which is the main obstetric center in Martinique dealing with an average of 3050 births per year, over an average of 3600 births per year out of a population of approximately 380 000 inhabitants. Pregnant women residing in Martinique, a French Caribbean oversea Island were recruited from the Mother and Child Centre of the University Hospital of Martinique. Mean age, body mass index (BMI), tobacco use, medical and surgical information as well as specific information regarding the pregnancy and obstetrical history and complications of the ongoing pregnancy were recorded. We restricted the study to those with pregnancy (determined by ultrasound dating scan before 12 weeks and date of delivery) during the period from 25/01/2016 to 31/07/2020. To be included in the present study, the women had to have at least 18 years old, a gestational age of 20 weeks or more, and be registered and followed-up at the CHUM Mother and Child Centre. From the eligible population, we excluded the women who were unable or refuse to consent and having pregnancy with more than two baby at a time. We also excluded those women with moving geographical location during the pregnancy period, making difficult to determine the actual exposure to air H_2S pollution.

Ethical consideration

The study was conducted in accordance with the amended Declaration of Helsinki (http://www.wma.net/en/30publications/10policies/b3/). Written informed consent was obtained from all patients. The protocol was approved by the CPP (Comité de Protection des Personnes, French equivalent of the Research Ethics Committee). A notice of adequacy to statistical quality standards from the CNIL (Commission Nationale de l'Informatique et des Libertés, the French independent administrative authority responsible for data protection) for the study database creation. The local Institutional Review Board IRB of the University Hospital of Martinique approved this study (reference number 2019/028).

Definition of maternal H_2S exposure

Women were considered exposed to H_2S if they were living and/or workplace in cities along the Atlantic coast of Martinique, which are known to witness sargassum strandings since 2016. Air pollution by H_2S were previously identified by a network of ground sensors deployed at these regularly impacted areas along the north central and south Atlantic coast of Martinique. Only women located at a maximum distance of 2000 meters from the closest monitoring site were selected. In this way, all cases that occurred too far from the monitoring sites were excluded, because H_2S levels cannot be representative of individual exposure at such distances. All women living and/or workplace in cities outside of the Atlantic coast were assumed to be not exposed to H_2S.

Definition of preeclampsia and endpoints

Primary endpoint was occurrence of preeclampsia as defined by the International Society for the Study of Hypertension in Pregnancy in 2018[3]. In brief, the diagnosis of preeclampsia was persistent de novo gestational hypertension that develops at or after 20 weeks' gestation accompanied by one or more of the following new-onset conditions: 1) proteinuria (>30 mg/dL); 2) other maternal organ dysfunction, including: acute kidney injury, liver involvement, neurological complications, hematological complications; 3) uteroplacental dysfunction (such as fetal growth restriction, abnormal umbilical artery Doppler wave form analysis, or stillbirth). Eclampsia was defined by new-onset of tonic-clonic, focal or multifocal seizures in the absence of other causative conditions such as epilepsy, cerebral arterial ischemia and infarction, intracranial hemorrhage, or drug use. Secondary endpoint was time to preeclampsia free survival, which was defined by the number of months free of preeclampsia between the 20th and 37th week of amenorrhea. Patients were censored after the 37th week of amenorrhea.

Statistical analysis

In absence of previous pilot study to calculate the sample size for the prevalence of preeclampsia in women exposed to H_2S pollution, we have considered that incidence of preeclampsia of women in non-exposed areas was 6%. Assuming alpha=0.05 and power of 85% with a non-exposed/exposed ratio of 4, a sample of 3020 women was planned to be able demonstrate a 3-point difference between non-exposed/exposed women. For all descriptive analyzes, assumption of normal distribution of the data was analyzed. Mean and standard deviation, or median and interquartile range were reported when appropriate. Categorical variables were presented as absolute values and percentages. The following tests were used for group comparisons depending of the conditions of application: Student t-test, Mann-Whitney test, Chi-square test or Fisher's exact test. Kaplan-Meier analysis was conducted to describe preeclampsia free survival time and compared using the log-rank test. The level of statistical significance was set at $p<0.05$. All statistical analyses were conducted using SAS software 9.4 for Windows (SAS Institute, Cary North Carolina, USA).

RESULTS

Three thousand and twenty pregnant women have been included in our study. The mean age of the study participants was 29 (±5) years. Initial body mass index of participants was 26 (±7) kg/m^{2}. Among those 3020 women, 623 (21,6%) were living and/or working in H_2S exposed areas and 194 (6,4%) met the primary endpoint, i.e., preeclampsia, during the follow-up period. In the exposed population, median H_2S concentration, averaged across pregnancy length, was 300 ppb (IQR H-spread 197). Main characteristics of H_2S exposed and non-exposed pregnant women are presented Table 1. There were no differences (p=0.20) in preeclampsia incidence rate between H_2S exposed and non-exposed pregnant women during the follow-up period (7.5% versus 6.1%, respectively). In sharp contrast, time to preeclampsia between the 20th and 37th week of amenorrhea was shorter (p=0.02) in H_2S exposed compared with non-exposed pregnant women (median=30.9 months - IQR 8.6 versus 32.9 months - IQR 6.0, respectively) (Figure1).

DISCUSSION

Main findings

In this monocentric, observational, longitudinal and retrospective study, H_2S exposure during pregnancy was associated with accelerated onset of preeclampsia between the 20^{th} and 37^{th} week of amenorrhea in women living and/or working in the Atlantic coastlines of Martinique. This finding is consistent with previous studies in industrial and geothermic areas which have reported associations between H_2S exposure and cardiovascular diseases, but conflict the great number of studies suggesting cardioprotective action of H_2S.

Interpretation

Martinique is an insular region of France located in the Lesser Antilles of the West Indies in the eastern Caribbean Sea. Coastlines of Martinique have witnessed successive and massive waves of sargassum seaweed invasions over the last two decades [12-14]. Ecological prediction models indicate that these massive strandings are likely to repeat leading to economic, social and public health concerns[34]. Due to marine currents and maritime trade winds, strandings of sargassum seaweed only impacted the Atlantic coastlines of Martinique. Specific areas are particularly impacted by sargassum strandings, which motivated the installation of ground gas sensors to monitor H_2S released from anaerobic degradation of sargassum strandings. Since 2016, this network has allowed to evaluate exposure of the population, to inform the local population and authorities about air quality on a daily basis, as well as to launch population evacuation warnings when required. In our study, we used the living place and/or workplace by define H_2S exposure[13]. We observed that less than a half of pregnant women had a job, which was located in the borough of residency in more than ninety percent of cases (data no shown). Overall, qualitative classification of H_2S exposure of pregnant women was reasonable well defined.

The increased risk of preeclampsia that we found in H_2S exposure pregnant women seem to conflict the large body of literature showing protective action of H_2S in cardiovascular pathologies such as hypertension, atherosclerosis and pulmonary hypertension [30-32]. Proposed mechanisms of H_2S-induced vascular beneficial effects include anti-oxidative action, preservation of mitochondrial function, reduction of apoptosis, anti-inflammatory responses, angiogenic action, regulation of ion channel, and increasing the production of NO[9,10, 30-32]. In line, few epidemiological studies have previously suggested a protective role of H_2S in atherosclerosis onset and development [20,23,24,27]. As a different paradigm, H_2S have several mechanisms of toxicity, including inhibition of cytochrome c oxidase activity, protein kinases (JNK and Erk) activation and cellular damage from reactive oxygen species, which participate to vascular structure and function impairment [30-32]. Although the primary action of H_2S on the vasculature is relaxation, H_2S can exert vasoconstriction under some conditions[9]. Indeed, H_2S exerts biphasic effect on vascular tissue and produces vasoconstriction at low concentrations, while inducing vasorelaxation at higher concentrations. H_2S-induced vasoconstriction has been attributed to NO quenching or inactivation, inhibition of endothelial cell NO synthase, and NO-independent mechanisms which include lowering cyclic adenosine monophosphate (cAMP) levels in vascular smooth muscle cells[9,11,31,33]. Such impact of H_2S on the vasculature may explain the deleterious cardiovascular effects of H_2S exposure observed in geothermal areas and industrial regions. For example, a significant increase of incidence for diseases of circulatory system and of mortality for hypertensive disease was observed in the geothermal area and industrial regions[20,26,27]. Overall, increased risk of preeclampsia that we found in H_2S-exposed pregnant women is consistent with these previous studies.

Strengths and limitations

While H_2S levels was measured by ground sensors to qualitatively witness gas exposure, the main study limitation is related to the definition of exposed pregnant women, which was based on residence's location, but not individual portative H_2S sensors. Portable gas detectors would represent the best way to compute actual matrix of H_2S exposure. Detection of gases emitted by decomposing sargassum seaweed was also limited to H_2S, which may not be the unique pollutant emitted by decomposing sargassum seaweed. Increased risk of preeclampsia that we found in exposed pregnant women may be due to volatile and non-volatile compounds which are produced during the process of sargassum seaweed decomposition. It should be wise to compute a proxy indicator, integrating parameters such as multiple gas sensor data, distance between sensors and inhabited zones, as well as pertinent climatic parameters. Air pollutants such as O_3, NO_x, NO_2, SO_2 and ambient particulate matters should have been monitored during the study period as they are known risk factors for preeclampsia.

CONCLUSION

Maternal H_2S exposure elicited by decomposition of sargassum seaweed was associated with accelerated onset of preeclampsia between the 20th and 37th week of amenorrhea in women living and/or working in the Atlantic coastlines of Martinique. The findings have major implications for local population and health authorities to improve pregnancy management in H_2S exposed areas, worldwide.

Declaration

Ethics approval and consent to participate

Our manuscript includes a statement on ethics approval and consent and the name of the ethics committee that approved the study and the committee's reference number.

Availability of data and materials

The data that support the findings of this study are available from NEVIERE Remi but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are, however, available from the authors upon reasonable request and with permission of NEVIERE Remi.

Competing interests

The authors declare that they have no competing interests

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None

Authors' contributions

DB, AM and MJL collected patient data. RN, DR and MD analyzed and interpreted the patient data. RN and MD wrote the manuscript. All authors read and approved the final manuscript

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Table 1 : Main characteristics of H_2S exposed and non-exposed pregnant women.

	Exposed N= 653	Exposed N= 653	Non-exposed N= 2367	Non-exposed N= 2367	p
	n	%	n	%	
Age [?] 30 years	326	49.9	1125	47.5	0.28

	Exposed N= 653	Exposed N= 653	Non-exposed N= 2367	Non-exposed N= 2367	p
BMI [?] 25 kg/m²	328	51.3	1186	52.6	0.55
Nulliparity	320	49.0	1110	46.9	0.34
Primi-paternity	371	82.3	1304	81.6	0.78
Twin pregnancy	12	1.8	59	2.5	0.33
Active tobacco use	39	6.0	157	6.6	0.54
Medical history					
Endometriosis	18	2.8	42	1.8	0.11
Hypertension	41	6.3	120	5.1	0.22
Chronic hypertension	20	3.1	53	2.2	0.22
Gestational hypertension	21	3.2	67	2.8	0.60
Diabetes	24	3.7	66	2.8	0.24
Auto-immune, multi organ disease	4	0.6	26	1.1	0.37
Chronic kidney diseases	1	0.2	0	0.0	0.22
Sickle cell disease	2	0.3	8	0.3	0.90
Thyroid disease	13	2.0	42	1.8	0.71
Polycystic ovary syndrome	8	1.2	41	1.7	0.36
Personal preeclampsia	16	2.4	40	1.7	0.20
Family history of preeclampsia	1	0.2	4	0.2	1.00
Pregnancy complica-tion					
Preeclampsia	49	7.5	145	6.1	0.20
Gestational diabetes	50	8.0	201	9.1	0.41
Gestational hypertension	85	13.0	304	12.8	0.91
Postpartum hypertension	15	3.9	112	6.2	0.09
HELLP syndrome	11	1.7	15	0.6	0.02

	Exposed N= 653	Exposed N= 653	Non-exposed N= 2367	Non-exposed N= 2367	p
Threat of premature labor	150	23.0	540	22.8	0.93
Obstetrical hemorrhage	28	4.3	99	4.2	0.91
Aspirin use	17	2.6	35	1.5	0.05
Neonatal death	12	1.8	51	2.2	0.62
Type of delivery					
Vaginal birth	534	81.8	2013	85.0	0.04
Spatula and forceps births	59	9.0	216	9.1	0.94
Cesarians	119	18.2	354	15.0	0.04

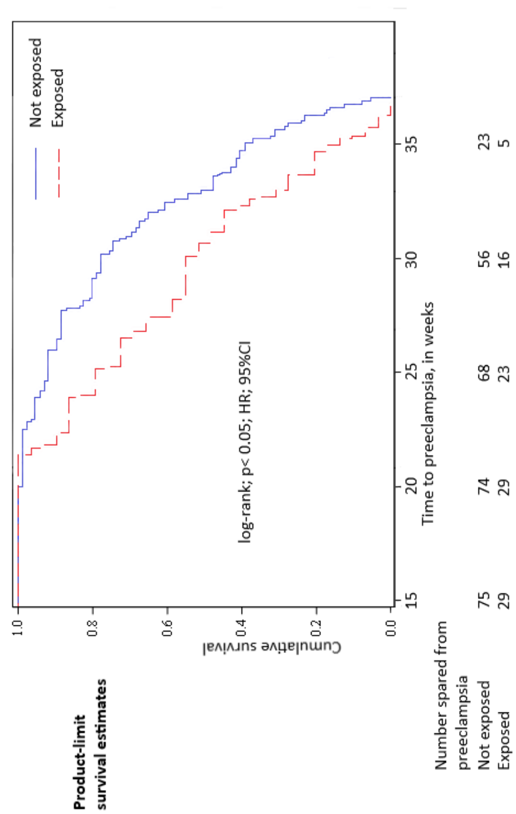
Categorical variables were presented as absolute values and percentages. The following tests were used for group comparisons depending of the conditions of application: Chi-square test or Fisher's exact test.

Abbreviations: BMI, Body Mass Index; HELLP, Hemolysis Elevated Liver Enzymes Low Platelet count. Results are presented as number (n) and percent (%).

Data are missing for primi-paternity, i.e., first pregnancy with a new partner (n=970), tobacco use (n=5), history of chronic hypertension (n=3), gestational hypertension (n=3), gestational diabetes (n=178), obstetrical hemorrhage (n=5), post-partum hypertension (n=818).

Figure legend

Figure 1 : Time to preeclampsia defined as the number of months free of preeclampsia between the 20^{th} and 37^{th} week of amenorrhea.


Product-limit
survival estimates
Not exposed
Exposed
log-rank; p< 0.05; HR; 95%CI
Cumulative survival
1.0
0.8
0.6
0.4
0.2
0.0
15
20
25
30
35
Time to preeclampsia, in weeks
Number spared from
preeclampsia
Not exposed
Exposed
75
29
74
29
68
23
56
16
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5