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Oxidative stress in newborns by different modes of delivery

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Abstract

OBJECTIVES: The aim of our study is to investigate the impact of the type of delivery – vaginal vs. cesarean section on oxidative damage determined as the lipid peroxidation (15-F2t-isoprostane (15-F2t-IsoP) in the cord blood of newborns and venous blood from mothers in two localities with different levels of air pollution: Ceske Budejovice (CB), a locality with a clean air, and Karvina, a locality with high air pollution.

RESUTLS: In Karvina, the concentration of PM2.5 was higher than in CB in the summer 2013 (mean±SD: 20.41±6.28 vs. 9.45±3.62 μg/m3, $p<0.001$) and in the winter 2014 (mean±SD: 53.67±19.76 vs. 27.96±12.34 μg/m3, $p<0.001$). Similarly, the concentration of B[a]P was higher in Karvina than in CB in the summer 2013 (mean±SD: 1.16±0.91 vs. 0.16±0.26 ng/m3, $p<0.001$) and in the winter 2014 (5.36±3.64 vs. 1.45±1.19 ng/m3, $p<0.001$). Delivery procedures differed by the type of anesthesia; at the Cesarean section in CB was used general anesthesia in 73.8% vs. 20.8% in Karvina ($p<0.001$), epidural anesthesia in CB in 26.2% vs. 77.1% in Karvina ($p<0.001$), at vaginal delivery was local anesthesia used in CB in 58.9% vs. 14.1% in Karvina ($p<0.001$). In CB was oxidative stress higher after vaginal delivery (101.7±31.0 pg 15-F2t-isoP/ml plasma) vs. Cesarean section (83.9±26.9 pg 15-F2t-isoP/ml plasma, $p<0.001$), no difference between the type of delivery was observed in Karvina.

CONCLUSION: No difference between the types of delivery was observed in mothers in CB as well as in Karvina. Oxidative stress in newborns in Karvina was significantly affected by the concentrations of PM2.5 and B[a]P in the polluted air.

Abbreviations:

CB	- Ceske Budejovice	LP	- lipid peroxidation
CS	- Cesarean section	PM2.5	- particulate matter of aerodynamic diameter <2.5 μm
15-F2t-IsoP	- 15-F2t-isoprostane	PAHs	- polycyclic aromatic hydrocarbons
B[a]P	- benzo[a]pyrene	ROS	- reactive oxygen species
EP	- environmental pollution	VD	- vaginal delivery

ORIGINAL ARTICLE

INTRODUCTION

Oxidative stress results from an imbalance between the formation of reactive oxygen species (ROS) and the ability of the organism to readily detoxify the reactive intermediates or to repair the resulting damage (Mazzoli-Rocha *et al.* 2010). Oxidative damage to cellular macromolecules (nucleic acid, lipids and proteins) is associated with the development of cancer, respiratory tract and cardiovascular diseases (Yang and Omaye 2009), neurodegenerative diseases (Andersen 2004) as well as ageing (Evans *et al.* 2004). Lipid peroxidation (LP) is caused by the attack of ROS on lipid molecules, primarily those in plasma membranes (Montuschi *et al.* 2004). Their peroxidation modifies cell membranes properties, thus disrupting regular cellular functions (Niki 2009). Isoprostanes are considered to be the most reliable markers of lipid peroxidation. They include several groups, but F2-isoprostanes (F2-IsoPs), particularly 15-F_{2t}-isoprostane (15-F2t-IsoP), are the most often studied compounds (Cracowski *et al.* 2002; Rossner *et al.* 2008). F2-IsoPs are derived from arachidonic acid in membranes via a free radical-catalyzed mechanism (Morrow *et al.* 1990). F2-IsoPs are cleaved from the sites of their origin and then either circulate in plasma or are excreted in urine (Morrow *et al.* 1992). Measurement of 15-F2t-IsoP in urine or plasma has been shown to reflect the oxidative stress in a number of human diseases (Wu *et al.* 2008).

Oxidative stress in newborns may be induced by abnormal placentation and adverse pregnancy outcomes, air pollution (PM2.5, polycyclic aromatic hydrocarbons – PAHs), social environment as maternal diet, smoking, chronic stress (Erikson and Arbour 2014).

From this point is raised an important question, on "which type of delivery represents a higher risk of oxidative damage for the newborns". Literature review about this topic brings controversial results similarly as the opinion of obstetricians about spontaneous vaginal delivery (VD) and Cesarean section (CS) may be contradictory.

The level of lipid peroxidation was studied by different methods. Hracsko *et al.* (2007) determined malonyl dialdehyde (MDA) using thiobarbituric acid (TBA) method in red blood cells (RBC) in cord blood. MDA levels were significantly higher in the CS group. Similarly Noh *et al.* (2014) observed higher MDA levels in umbilical venous blood by planned CS than VD. But when MDA was determined in plasma, LP was higher in newborns delivered through VD (Inanc *et al.* 2005, Vakilian *et al.* 2009, Gulbayzar *et al.* 2011, Adenkanle *et al.* 2013). The same conclusion was reached by Greco *et al.* (2007) measuring LP by 15-F2t-IsoP in plasma, levels were higher in infants born after vaginal delivery.

All these studies indicate that oxidative damage determined in newborns in their cord blood plasma by MDA or 15-F2t-IsoP may be higher after vaginal delivery.

In our previous study (Ambroz *et al.* 2016) we observed that PM2.5 (particulate matter < 2.5 mm) and benzo[a]pyrene (B[a]P) concentrations in polluted air are significant predictor for 15-F2t-IsoP (15-F2t-isoprostane) levels. The aim of our study is to analyze, what is the effect of the type of delivery (vaginal vs. Cesarean section) to the oxidative damage in newborns and mothers in regions with a different level of air pollution.

MATERIALS AND METHODS

Subjects

The samples were collected in the Ceske Budejovice Hospital, Department of Obstetrics and Department of Neonatology (CB), and in the Karvina Hospital, Department of Obstetrics and Department of Neonatology. The study was approved by the Ethics Committee of both hospitals and the Institute of Experimental Medicine AS CR in Prague. The samples were collected from normal deliveries (38–41 week+) of nonsmoking mothers and their newborns in the summer and winter season to account for differences in air pollution. The samples included venous blood and urine from 99 mothers (summer) and 100 mothers (winter) at Ceske Budejovice, a locality with relatively clean air, and 70 mothers (summer) and 73 mothers (winter) at Karvina, a locality with high air pollution, and cord blood and urine from 99 newborns (summer) and 100 newborns (winter) at Ceske Budejovice and 71 newborns (summer) and 74 newborns (winter) at Karvina. The basic characteristics of the groups studied are shown in Table 1. Blood was collected in EDTA tubes to isolate DNA and plasma. Urine samples were collected into 50 mL tubes (Greiner Bio-one) and stored at –20 °C until transported to the Institute of Experimental Medicine. Aliquots (1–2 mL) of urine were frozen at –80 °C until analysis.

For each mother was fulfilled the medical questionnaire by her doctor: clinical risk factors, type of delivery – vaginal, Cesarean section, forceps, VEX; anesthesia – general, epidural, local, none; length of delivery; medication; delivery complications, pregnancy outcomes: date, time, gender, birth weight g, birth length cm, Apgar 5', head circumference cm, placenta weight g; newborn abnormal signs; name of child; ethnicity; birth defects. Each mother fulfilled maternal questionnaire: name; address; height cm; weight before pregnancy kg; weight before delivery kg; menses; education; marital status; employment; occupational risk factors; information about partner – employment, smoking, alcohol; health status – chronic diseases, short-term diseases, time of diagnosed pregnancy, during this pregnancy – vitamins, smoking, active smoking, passive smoking, alcohol, drinking coffee and tea; previous pregnancies; food intake during this pregnancy.

Air sampling and analysis of selected air pollutants

Particulate matter ≤2.5 μm (PM2.5) was collected by a High Volume (HiVol) 3000 Air Sampler (model

ECO-HVS3000, Ecotech, Australia) on Pallflex membrane filters (EMFAB, TX40HI20-WW) in both study localities. The sampling was conducted as previously described (Topinka *et al.* 2011). Detailed information on air sampling, extraction of organic complex mixtures (EOM) from the filters and chemical analysis of B[a]P is given in Topinka *et al.* (2011). Concentrations of air pollutants was expressed in μg/m^3 (PM2.5) and ng/m^3 (B[a]P).

15-F_{2t}-isoprostane immunoassay

Blood plasma 15-F2t-isoprostane levels (15-F_{2t}-IsoP) were analyzed using immunoassay kits from Cayman Chemical Company (Ann Arbor, MI, USA) according to the manufacturer's protocol. Each sample was analyzed in duplicate. The 15-F2t-IsoP concentrations were expressed as pg 15-F2t-IsoP/ml plasma (Rossner *et al.* 2008).

Cotinine level

Urinary cotinine levels as a marker of active and passive smoking were analyzed by radioimmunoassay (Langone and Van Vunakis 1982) to check the tobacco smoke exposure reported in the lifestyle questionnaires.

Statistical analysis

For the statistical analysis of oxidative DNA damage and lipid peroxidation, we used Statistica software (version 7.0, StatSoft, Dell, Tulsa, USA) and SAS software (version 9.3, SAS Institute Inc., Cary, NC, USA).

In order to compare the data not following normal distribution, nonparametric methods were used: Mann-Whitney Rank Sum U-test to compare continuous values of two groups, regions or sample periods. Logistic regressions were used either for comparison of frequency in groups or for multivariate estimates, where continuous parameters were transformed into a binary 1/0 value using the median of distribution to the above/ below median value scale.

Multivariate linear regressions were used for estimation of multivariate impact models using available values of environment pollution (EP) and other continuous or discrete factors. To estimate the effects of EP on oxidative stress markers, we used the average concentrations of PM 2.5 or B[a]P measured 7 days before delivery.

Tab. 1. Characteristics of mothers.

	Vaginal delivery		*p*-value	Cesarean section		*p*-value	*p*-value
	CB	Karvina		CB	Karvina		CB vs. Karvina
Maternal age	32.1 ±4.2	29.2±4.7	<0.001	32.7±4.2	30.9±4.8		<0.05 K
Maternal BMI	23.8±4.0	23.7±4.2		23.7±5.3	24.5±4.6		
Maternal height	169.2±5.6	167.1 ±6.1	<0.05	166.4±7.4	165.5±7.8		<0.01 CB
Mat weight pre-pieg	68.2±12.7	66.4±14.0		65.6±14.3	67.1 ±13.8		
Mat weight pre-çieJjy	81.2±12.9	80.5±14.2		79.0±14.4	81.3±13.6		
Menses reg.	84.5%	77.6%		80.0%	66.7%	<0.01	
Gestation age	39.6	40.4	<0.001	39.0	39.9	<0.01	<0.001 CB
Maternal education							
Higher second.	50.4%	40.0%		50.8%	39.6%		
University	38.0%	35.3%		36.9%	31.3%		
Married	65.1%	54.1%		58.5%	54.2%		
Maternal smoking							
Before pregnancy	31.8	35.3		29.2	22.9		
Passive smoking	2.1 cig.	4.2 cig.		2.2 cig.	4.7 cig.		
Beverages before pregnancy							
Cola	0.4	1.0	<0.01	0.4	0.5		
Fruit tea	0.9	1.5	<0.01	1.3	1.9		<0.01
Beverages during pregnancy							
Coffee	0.6	0.6		0.8	0.7		< 0.01 CB
Cola	0.4	0.6	<0.01	0.3	0.6		
Fruit tea	1.1	1.9	<0.001	1.2	2.1		<0.05

RESULTS

Characteristics of mothers

The basic characteristics of mothers related to vaginal delivery vs. Cesarean section include (Table 1): maternal age, maternal BMI, maternal height, maternal pre-pregnancy weight, maternal pre-delivery weight, regularity of menses, gestation age, maternal education, maternal smoking before pregnancy, passive smoking, beverages before pregnancy, beverages during pregnancy. There were age differences between mothers with VD between CB and Karvina ($p<0.001$), in Karvina were younger mothers with VD than CS ($p<0.05$). Maternal height in mothers with VD was shorter in Karvina ($p<0.05$), in Karvina were shorter mothers with CS ($p<0.01$). Irregular menses were more often in mothers with CS in Karvina ($p<0.01$). Gestation age was shorter in CB vs. Karvina in mothers with VD ($p<0.001$) as well as with CS ($p<0.01$), and in CB in mothers with CS than with VD ($p<0.01$). Other differences (Table 1) were seen in using beverages: before pregnancy more Cola in mothers with VD in Karvina ($p<0.01$) and fruit tea in Karvina in mothers with VD ($p<0.01$) as well as CS ($p<0.01$). During pregnancy was more often consumed coffee in CB in mothers with CS, Cola in Karvina in mothers with VD, fruit tea in Karvina in mothers with VD ($p<0.001$) as well as with CS ($p<0.05$).

Concentration of air pollutants

In Karvina, the concentration of PM2.5 was higher than in CB in the summer 2013 (mean±SD: 20.41±6.28 vs. 9.45±3.62 μg/m^3, $p<0.001$) and in the winter 2014 (mean±SD: 53.67±19.76 vs. 27.96±12.34 μg/m^3, $p<0.001$). Similarly, the concentration of B[a]P was higher in Karvina than in CB in the summer 2013 (mean±SD: 1.16±0.91 vs. 0.16±0.26 ng/m^3, $p<0.001$) and in the winter 2014 (5.36±3.64 vs. 1.45±1.19 ng/m^3, $p<0.001$). The concentrations of air pollutants were higher in the winter season in comparison with the summer season for both locations.

Type of anesthesia and delivery procedures

Significant differences between CB and Karvina were observed in the type of anesthesia and delivery procedures (Table 2).

Local anesthesia during VD was more often in CB (58.9% vs. 14.1%, $p<0.001$), none anesthesia in Karvina (69.4% vs. 29.5%, $p<0.001$). During CS was general anesthesia more often in CB (73.8% vs. 20.8%, $p<0.001$), spinal anesthesia in Karvina (77.1% vs. 23.1%, $p<0.001$).

Both locations also differed in the blood loss during CS, which was lower in Karvina (<300 ml 20.8% vs. 3.1%, $p<0.01$, 300–500 ml 66.7% vs. 93.8%, $p<0.001$).

No medication or induced birth were used during VD in Karvina (69.4% vs. 55.0%, $p<0.05$).

Impact of delivery to oxidative stress

We found no significant differences to oxidative stress in mothers in both localities, either between VD and CS delivery, or between VD and CS delivery in each locality (Table 3).

In newborns in CB we observed significantly higher lipid peroxidation after vaginal delivery vs. Cesarean section (101.7±31.0 vs 83.9±26.9 pg/ml 15-F2t-IsoP, $p<0.001$). But no difference between the level of lipid peroxidation according to the type of delivery was observed in Karvina (Table 4).

When we used multivariate logistic models for 15-F_{2t}-IsoP in newborns, we observed different outcomes between Ceske Budejovice and Karvina. In CB the oxidative stress was lower after CS than VD (OR=0.40; 0.21–0.77; $p<0.01$). When B[a]P was added to the model, there was only the effect of local anesthesia (OR=2.47; 1.12–5.43; $p<0.05$), no effect of the B[a]P concentration or the type of delivery was observed When PM2.5 was added to the model, the

Tab. 2. Type of anesthesia and delivery procedures.

	Vaginal delivery		*p*-value	Cesarean section		*p*-value	*p*-value
	CB	Karvina		CB	Karvina		CB vs. Karvina
Anesthesia type							
General	3.1%	2.4%		73.8%	20.8%	<0.001	
Epidural	7.8%	13.0%		26.2%	77.1%	<0.001	
Local	58.9%	14.1%	<0.001	0%	0%		
None	29.5%	69.4%	<0.001	0%	0%		
Delivery procedures							
None	55.0%	69.4%	<0.5	38.5%	47.9%		
Medication	16.3%	12.8%		3.1%	14.9%		
Induced birth	24.0%	11.6%		10.8%	14.3%		

effect of local anesthesia was seen, too (OR=2.67; 1.15–6.20; $p<0.05$), but no effect of PM2.5 concentration or the type of delivery. In Karvina the oxidative stress was higher after CS than VD (OR=3.67; 1.15–11.77; $p<0.05$). This effect was decreased by passive smoking during pregnancy (OR=0.39; 0.19–0.79; $p<0.01$). When B[a]P was added to the model, the concentration of B[a]P significantly increased oxidative stress (OR=1.27; 1.04–1.54; $p<0.05$), there was no effect by the type of delivery, but decreased by passive smoking during pregnancy (OR=0.40; 0.18–0.86; $p<0.05$) and spinal anesthesia (OR=0.06; 0.00–1.06; $p=0.0546$). When PM2.5 was added to the model, the concentration of PM2.5 significantly increased oxidative stress (OR=6.75; 2.00–22.85; $p<0.01$), but similarly there was no effect by the type of delivery. But oxidative stress was decreased by passive smoking during pregnancy (OR=0.37; 0.16–0.83; $p<0.05$) and spinal anesthesia (OR=0.06; 0.01–0.65; $p<0.05$). Further we used multivariate regression models for isoprostanes in newborns. In Ceske Budejovice was oxidative stress lower after CS than VD (Beta = –0.273±0.070, $p<0.001$). Oxidative stress was increased by drinking green tea during pregnancy (Beta = 0.143±0.070, $p<0.05$). When was added to the model B[a]P or PM2.5, they had no effect on oxidative stress., In Karvina the oxidative stress was higher after CS than VD (Beta = 0.169±0.085; $p<0.05$) using bivariate model. From other factors the oxidative stress was decreased using medication (Beta= –0.179±0.090, $p<0.05$) and by shorter gestation age (Beta=–0.207±0.088, $p<0.05$). With the full model the oxidative stress in newborns was increased by daily maternal alcohol intake (Beta=0.282±0.141, $p<0.05$). When was added to the model B[a]P or PM2.5, B[a]P concentrations (Beta = 0.242±0.0.084, $p<0.01$) as well as PM2.5 (Beta = 0.388±0.079, $p<0.001$) significantly increased the level of 15-F_{2t}-IsoP in newborns. In both cases with B[a]P and PM2.5 the oxidative stress was higher after CS than VD (Beta=0.217±0.109, $p<0.05$, and Beta=0.196±0.078, $p<0.05$), respectively. In the model with B[a]P was the oxidative stress increased by maternal alcohol intake (Beta=0.191±0.084, $p<0.05$) and decreased by gestation age (Beta=–0.220±0.105, $p<0.05$). In the model with PM2.5 was the oxidative stress decreased by induced birth (Beta=–0.186±0.078, $p<0.05$).

Further we used multivariate logistic models for isoprostanes in newborns (Table 5). In Ceske Budejovice was the oxidative stress significantly lower after CS than VD (OddR = 0.40; 0.21–0.77; $p<0.01$). When was B[a]P added to the model, the oxidative stress was increased by the local anesthesia (OddR = 2.47; 1.12/5.43; $p<0.05$). When PM2.5 was added to the model, the oxidative stress was similarly increased by the local anesthesia (OddR = 2.67; 1.15–6.20; $p<0.05$). In Karvina was the oxidative stress increased after CS

Tab. 3. Impact of delivery to oxidative stress in mothers (level of 15-F2t-isoprostane, pg/ml plasma).

Type of delivery	N	CB	N	Karvina
Vaginal	129	61.69±26.0	86	62.08±26.03
Cesarean	64	60.41±9.21	49	61.64±20.84

Tab. 4. Impact of delivery to oxidative stress in newborns (level of 15-F2t-isoprostane, pg/ml plasma).

Type of delivery	N	CB	N	Karvina
Vaginal	129	101.7±31.0	86	78.3±34.5
Cesarean	64	83.9±26.9***	49	91.7±42.6

*** $p<0.001$

Tab. 5. Multivariate logistic models to 15-F2t-isoprostane in newborns.

Models	CB		Karvina	
		OddR (L-U, p-value)		OddR (L-U, p-value)
Stepwise without EP	CS vs. vaginal	0.40 (0.21–0.77; $p<0.01$)	CS vs. vaginal	3.67 (1.15–11.77; $p<0.5$)
			Passive smoking	0.39 (0.19–0.79; $p<0.01$)
Stepwise B[a]P	B[a]P	0.83 (0.62–1.13; $p=0.23$)	B[a]P	1.22 (1.02–1.46; $p<0.05$)
	CS vs. vaginal	0.73 (0.33–1.64; $p=0.45$)	CS vs. vaginal	3.00 (0.89–10.14; $p=0.076$)
	Anesthesia – local	2.47 (1.12–5.43; $p<0.05$)	Passive smoking	0.43 (0.21–0.91; $p<0.05$)
Stepwise PM2.5	PM2.5	1.37 (0.68–2.75; $p=0.38$)	PM2.5	5.21 (1.61–16.85; $p<0.01$)
	CS vs. vaginal	0.71 (0.29–1.76; $p=0.46$)	CS vs. vaginal	5.40 (1.33–21.99; $p<0.05$)
	Maternal alcohol-rare	0.48 (0.22–1.06; $p=0.071$)	Passive smoking	0.44 (0.20–0.96, $p<0.05$)
	Anesthesia – local	2.67 (1.15–6.20; $p<0.05$)	Maternal – drinking tea	0.27 (0.07–1.04; $p=0.057$)
	Induced birth	2.54 (0.84–7.65; $p=0.097$)		

vs. VD (OddR = 3.67; 1.15–11.77; $p<0.05$), decreased by passive smoking (OddR = 0.39; 0.19–0.79; $p<0.01$). When was B[a]P added to the model, the oxidative stress was increased by B[a]P (Odd R = 1.22; 1.02–1.46; $p<0.05$, decreased by passive smoking (OddR = 0.43; 0.21/0.91; $p<0.05$]). When PM2.5 was added to the model, the oxidative stress was increased by PM2.5 (OddR = 5.21; 1.61–16.85; $p<0.01$), CS vs. VD (OddR = 5.40; 1.33–21.99; $p<0.05$), decreased by passive smoking (OddR = 0.44; 0.20–0.96; $p<0.05$).

Impact of cotinine to oxidative stress

Mothers lipid peroxidation was not affected by the cotinine level in urine: <=1 ng/ml 61.64±25.46 (N=318) vs. >1 ng/ml 58.20±20.77 pg/ml 15-F2t-IsoP (N=22). Similarly, no effect was observed in newborns: maternal cotinine <=1 ng/ml 91.90±34.88 (N=320) vs. >1 ng/ml 85.90±32.00 pg/ml 15-F2t-IsoP (N=22).

DISCUSSION

Our results seem to indicate that oxidative damage in newborns, measured in their plasma as lipid peroxidation by isoprostanes, is significantly affected by air pollutants as PM2.5 and B[a]P. This may be probably the main reason why types of delivery significantly differ between two locations with different levels of those two pollutants.

In the control district of Ceske Budejovice the oxidative stress was lower after CS than VD, and it was increased after drinking of green tea as well as local anesthesia.

In the polluted district of Karvina was observed an opposite outcome – oxidative stress was higher after CS than VD. From other factors were significant that only air pollutants PM2.5 and B[a]P, oxidative stress was increased by maternal alcohol intake, decreased by medication at delivery, induced birth, and shorter gestation age. When we have tried to speculate what may be the reason, we came to the assumption that oxidative stress was lower in CB after CS, and we see differences in anesthesia (Table 2). The most significant difference was in the level of air pollution, which significantly affected oxidative stress in newborns. Data from Ceske Budejovice correspond to previous results by Inanc *et al.* (2005), Greco *et al.* (2007), Vakilian *et al.* (2009), Gulbayzar *et al.* (2011), and Adenkanle *et al.* (2013). Data from Karvina differ especially by a significant air pollution. It seems to be the only reason, why oxidative damage in newborns differ according to different type of delivery.

Our study seems to be unique, in terms of studying oxidative damage in newborns in two locations, which are different by the significant air pollution. We may hypothesize that in the regions with a low concentrations of PM2.5 and B[a]P Cesarean section induce less oxidative damage in newborns than vaginal delivery, as was seen also by other authors, who determined lipid peroxidation in plasma. But this relationship does not apply to situation, when oxidative damage is induced by high concentrations of PM2.5 and B[a]P.

It seems to be pertinent to repeat our study on a larger cohorts together with monitoring air pollution by PM2.5 and B[a]P as well as follow children included to the study for their morbidity in a preschool age. It could indicate the impact of oxidative stress in newborns to a later morbidity as well as lo learn, if different modes of delivery may affect morbidity in children.

CONCLUSIONS

The oxidative stress in newborns measured in plasma is significantly affected by increased concentrations of air pollution as benzo[a]pyrene and fine particles (PM2.5). Differences in the oxidative stress induced by Cesarean section or vaginal delivery may be affected by the type of anesthesia, medication at delivery, induced birth, as well as by air pollution.

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Conflict of Interests. *None declared.*

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