Antenatal exposure to household air pollution and its association with increased risk of retinopathy

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ABSTRACT

Background: Household air pollution (HAP) has been implicated in endothelial dysfunction and systemic inflammation which are the underlying mechanisms for retinopathy of prematurity (ROP). **Objective:** The study aims to estimate the incidence of ROP and its risk factors, specifically exploring antenatal exposure to HAP due to the use of traditional stoves/chullah as a risk factor for ROP. **Methods:** This cross-sectional observational study was conducted at a neonatal intensive care unit (NICU) of tertiary care hospital in Nagpur, India. Screening for ROP was done in 196 hospitalized preterm neonates discharged from NICU for a period of 23 months in between December 2012 and October 2014. Mothers were considered as exposed to HAP if there was predominant use of chullah or open fire using wood, charcoal, crop waste, etc., for household cooking activities during her pregnancy and if cooking was done in the same room as the living room. **Results:** The incidence of any ROP in preterm neonates of mothers who were exposed to high polluting fuels (HPFs) antenatally was 51% as compared to 30% among those exposed to low polluting fuels. Those pregnant women who cooked outdoors or in a separate room had significantly lesser chances of developing ROP. Multivariate analysis showed that environmental factors such as smoking in the household and usage of HPFs while cooking in the living room of the house (odds ratio 10.15; 95% confidence interval [1.3, 79.43]) increased the risk of developing ROP, after adjusting for other risk factors. In our study population, exposure to smoking and HAP were associated with higher risks of developing ROP, independent of covariates. **Conclusion:** Effective interventions to a committed and determined intersectoral coordination toward the promotion of public health are the need of the hour.

Key words: *Central India, Chullah, Household air pollution, Retinopathy of prematurity, Smoking*

Retinopathy of prematurity (ROP) is a vasoproliferative disorder of the retina among preterm or premature infants. Its key pathologic change, retinal neovascularization, appears to be associated with preceding local ischemia and subsequent development of neovascularization [1]. It has been observed that ROP is usually associated with premature birth, but it is an interplay of several risk factors that lead to its occurrence. Gestational age (GA) ≤30 weeks and low birth weight (LBW) ≤1500 g are the predominant risk factors contributing to the development of ROP, but besides these, other factors such as poor weight gain, percentage saturation of oxygen in the inhaled air, and exposure to household air pollution (HAP) also demonstrate a significant association in the causation of ROP [2].

Out of the approximate 26 million annual live births in India, approximately 8.7% of newborns weighs <2000 g [3]. It implies that almost 2 million newborns are at risk for developing ROP which is emerging as one of the leading causes of preventable childhood blindness in India [4]. About 33.6 million or 17.5% Indian homes use liquefied petroleum gas (LPG) as their primary cooking fuel whereas 78% homes rely on biomass fuels [5] and another 3% on coal. HAP occurs from incomplete combustion of commonly used solid fuels in traditional cooking stoves or chullahs such as wood, coal, and crop residue. This exposes a pregnant woman who spends long hours cooking to pollutants such as carbon monoxide, oxides of sulfur, nitrogen, particulate matter, and polycyclic aromatic hydrocarbons (PAHs). Results from epidemiological and experimental studies show that fetuses and infants are especially susceptible to the toxic effects of pollutants such as suspended particles, PAH, and tobacco smoke [6-8].

Exposure to HAP leads to chronic fetal hypoxia and adverse pregnancy outcomes such as preterm deliveries, stillbirths, and increased risk of neonatal mortality [9]. Exposure to HAP in utero leads to the development of chronic hypoxemia, which per se is a risk factor for ROP. When these preterm infants are born to such mothers and administered 100% oxygen after birth, it could possibly result in higher rates of ROP [10,11]. Although HAP is a biologically plausible risk factor for ROP, it has never been

evaluated previously and could possibly contribute to the large burden of blindness in developing countries and the global burden of disease due to HAP.

The question that remains unanswered is, do preterm neonates born before 35 weeks of GA showing signs of ROP, develops it as a result of maternal exposure to HAP during the antenatal period. No study has investigated HAP as an independent risk factor for ROP. This hospital-based study was conducted to evaluate the incidence of ROP in preterm neonates admitted to our hospital and its risk factors with a particular interest in examining if exposure of the mother to HAP during pregnancy increases the risk of ROP.

METHODS

This was an observational study, conducted for a period of 23 months (December 2012–October 2014) in preterm neonates admitted to the neonatal intensive care unit (NICU) of a tertiary care hospital in Nagpur, India. The study included a cohort of 196 preterm neonates with GA <35 weeks who were assessed by LMP and also verified by physical characteristics at birth by a neonatologist. They were screened for ROP for inclusion in the study. Infants with GA more than 35 weeks, all term infants, and all post-term infants were not included. Prior written informed consent was obtained from the parent of each neonate. Approval of Institutional Ethics Committee was also obtained. Confidentiality of data was ensured.

The data on the sociodemographic characteristics and clinical correlates were collected from the hospital records. Whereas, data related to HAP exposure factors were taken from the participant using a structured close-ended questionnaire. The data on neonatal factors such as age, sex, GA at birth, weight, mode of delivery, resuscitation required, requirement of oxygen, respiratory distress, apnea, seizures, jaundice, cyanosis, sepsis, anemia, history of blood transfusion, received phototherapy, hypoxic-ischemic encephalopathy, shock (any time during NICU stay), the length of stay in NICU, and length of time for which oxygen was administered were collected.

In addition, data on maternal factors such as age, occupation, religion, economic status, receiving blood transfusion, steroid use in pregnancy, maternal complications and exposure to HAP was also collected. All antenatal mothers, who predominantly used chullah or open fire using wood, charcoal, crop waste, etc., for household activities, were considered as exposed to a high level of HAP. These data were also entered from the case report form. Those who used LPG were considered to be exposed to a low level of HAP and were utilized as the internal comparison group. Information was obtained from the respective mothers as to whether the cooking room was same as the living room and whether they are involved in smoking cigarette/bidis or tobacco inside the house.

The screening was done in all preterm infants on the 24.5 postnatal days of life (mean) for their first screening and subsequent second (follow-up) screening, which varied depending on their ROP stages in the first visit. Screening of ROP was done by indirect ophthalmoscope using 20D lens by an experienced ophthalmologist. Pupils were dilated with 2.5% phenylephrine and 0.5% tropicamide. One drop of tropicamide was instilled every 10–15 min up to 4 times, starting 1 h before the scheduled time for the examination, followed by 1 drop phenylephrine. After each examination, the neonates received a mild topical antibiotic eye drops for a couple of days.

International classification of ROP was used for classifying ROP. Ophthalmological notes were made after each ROP examination, detailing zone, stage, and extent in terms of clock hours of any ROP and the presence of any pre-plus or plus disease. The neonate was classified as having plus disease by the presence or absence of dilated and tortuous vessels at the posterior pole. Whereas, the pre-plus disease was defined as an intermediate level of vascular dilation and tortuosity. The presence of ROP was categorized into five stages based on the retinal examination. The first stage of ROP consists of a line of demarcation formed between the vascular and avascular zones of the retina. When the demarcation line further developed into a ridge with a prominent width and height extending above the retinal plain, it was considered as the second stage of ROP. The third stage was characterized by extraretinal fibrovascular proliferation or neovascularization from the ridge into the vitreous. Stage 4 disease was said to be present if partial retinal detachment took place, whereas Stage 5 was the stage of total retinal detachment.

The sample size was based on the incidence of ROP of 15.0% in a similar population of neonates admitted to the NICU of a tertiary care unit at Delhi [12]. With a population proportion estimate at $(1 - \alpha)$ confidence level with a two-tailed alternative, hypothesis, and power of 80%, the sample size was estimated to be 196 neonates. Data were analyzed using the STATA 13.1 statistical package (Stata Corp, College Station, Texas, USA). Study variables of interest and their combinations were cross-tabulated in Stata and were transformed to graphs either in Stata itself or in Microsoft Excel.

RESULTS

This study showed an incidence of ROP in 44.4% (87/196) among neonates. Stage 1 was found among 72.41% (63/87), Stage 2 was found in 13.79% (12/87), Stage 3 was found in 1.14% (1/87), and immature vessels were found in 12.64% (11/87). Of these, 51 neonates were available for a second follow-up visit while the rest failed to attend the same. Of these 48 cases regressed (normal), 2 neonates underwent laser and 1 neonate expired. The factors that were significantly associated ($p<0.05$) with the development of ROP are elucidated in Table 1.

The incidence of ROP was significantly higher (51%) among the high polluting fuel (HPF) users, those who cooked on an open fire as compared to 30% among the LPG stove users ($p<0.01$) (Fig. 1). Among the users of HPF, risk ($p<0.01$) was observed for those who cooked in the living area itself (60%), as compared to those cooking in a separate kitchen/room (39%) or cooking outdoors (16%) as shown in Fig. 2. It was observed that smoking in the household either by mother or any other family member was significantly associated with the occurrence of ROP (89%) with $p<0.01$.

The risk factors that persisted to be significant on multivariate analysis after adjusting for covariates were the presence of sepsis (odds ratio [OR]: 5.75; 95% confidence interval [CI]: [1.14, 28.91]), low hemoglobin (OR: 0.36; 95% CI: [0.19, 0.65]), longer periods of providing oxygen to the neonate (OR: 1.44; 95% CI: [1.05, 1.97]), smoking in the household, and indoor household cooking especially if done in the same room where the family lived (OR: 10.15; 95% CI: [1.3, 79.43]), as shown in Table 2.

DISCUSSION

This study interestingly sheds light on the fact that environmental factors such as prenatal exposure to smoking in the house, or use of HPF that result in HAP, especially if the cooking area was in the living room, were found to significantly increase the risk of ROP. GA no longer remained a risk factor when it was adjusted for these exposures and for neonatal complications. This might be due to the fact that respiratory system of the fetus is matured gradually as they approach term may be in a better position to handle the HAP toxins that might be acting synergistically in preterm babies to lead to ROP [13].

The cryotherapy for ROP study [6] in the USA reported a ROP incidence of 65.8% in infants weighing <1.251 g. The overall incidence of any ROP in Canada between July 2006 and July 2010 was found to be 40.4% in all infants admitted to the NICU with a birth weight <1.500 g or GA <32 weeks (171 of 423 infants) [7]. Studies from India have reported ROP in the range of 20–52% of screened neonates [12,14-16], which was consistent with the findings of the current study.

The findings from the univariate analysis reveal a decrease in GA, decrease in birth weight, and the presence of complications in the preterm neonates such as respiratory distress, apnea, seizures, sepsis, jaundice, shock, anemia, prolonged administration of oxygen, and blood transfusion increased the risk of ROP. Low GA and LBW are known risk factors for the development of

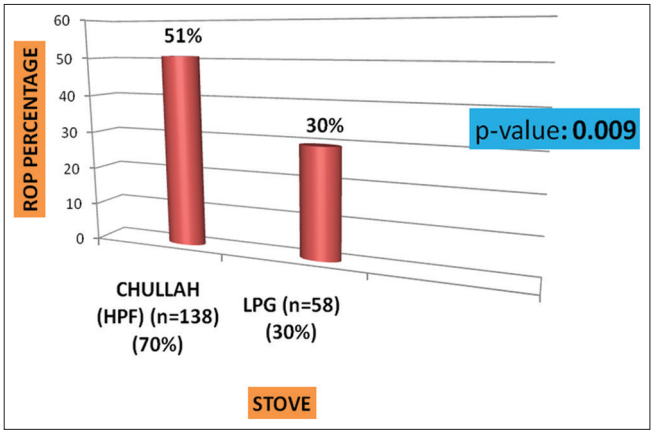

Figure 1: Bar chart showing the percentage of neonates with retinopathy of prematurity according to the type of stove used for cooking

Table 1: Distribution of cases according to neonatal risk factors/maternal risk factors and ROP (univariate analysis)

Neonatal risk factors (n=196)	No. (%)		Total study population n (%)	p-value
	ROP	No ROP		
Mode of delivery (LSCS)	41 (47.13)	59 (54.13)	100 (51.02)	0.0719
Resuscitation required	16 (18.39)	4 (3.67)	20 (10.93)	0.0073
Requirement of oxygen	62 (71.26)	33 (30.28)	95 (48.47)	0.0029
Respiratory distress	61 (75)	20 (25)	81 (41.33)	<0.0001
Apnea	22 (81)	5 (19)	27 (13.92)	0.0011
Seizures	19 (66)	10 (34)	29 (14.87)	0.0243
Jaundice	52 (62)	32 (38)	84 (42.86)	0.0291
Cyanosis	4 (100)	0	4 (2.80)	0.0455
Sepsis	57 (73)	21 (27)	78 (39.80)	<0.0001
History of blood transfusion	20 (80)	5 (20)	25 (12.76)	0.0027
HIE	13 (81)	3 (19)	16 (8.60)	0.0124
Shock	45 (80)	11 (20)	56 (28.57)	<0.0001
Anemia (Hb ≤13 g%)	24 (77.42)	7 (22.58)	31 (23.48)	0.0023
Mean Hb (in g%)	13.45	14.59	132 (67.34)	<0.0001
Mean GA (in weeks)	31.28	32.43	196 (100)	<0.0001
Mean birth weight (in g)	1232.76	1345.41	196 (100)	<0.0001
Mean NICU stay (in days)	17.49	14.13	196 (100)	<0.0001
Duration of O_2 therapy (in days)	6.66	2.07	196 (100)	<0.0001
Maternal characteristics				
Any complications	52 (55.32)	42 (44.68)	94 (100)	0.3023
Use of steroid	39 (43.33)	51 (56.67)	90 (45.92)	0.2059
Blood transfusion	44 (44.44)	55 (55.56)	99 (50.51)	0.2689

Figures indicate proportions. Hb: Hemoglobin, NICU: Neonatal intensive care unit, GA: Gestational age, ROP: Retinopathy of prematurity, LSCS: Lower segment cesarean section, HIE: Hypoxic ischaemic enchephalopathy

Table 2: Multivariate analysis

Variables	Risk ratio (95%CI)	p-value
Gestational age at birth (NBS)	0.89 (0.6, 1.31)	0.55
Hemoglobin	0.36 (0.19,0.65)	0.001
Length of time oxygen received	1.44 (1.05,1.97)	0.02
Oxygen given	0.30 (0.03, 2.98)	0.31
Seizures present	0.73 (0.13, 4.15)	0.72
Sepsis present	5.75 (1.14, 28.91)	0.03
Blood transfusion given	6.88 (0.38, 123.30)	0.19
Jaundice present	1.27 (0.28, 5.79)	0.76
Shock present	1.02 (0.16, 6.35)	0.98
History of smoking cigarette/bidi or tobacco in family	11.23 (1.3, 96.85)	0.03
Stove		
LPG	1.00	0.45
Chullah	1.66 (0.45, 6.17)	
Cooking area		
Not in a separate room	10.15 (1.3, 79.43)	0.03
In a separate room	4.46 (0.49, 40.40)	0.18
Outdoors	1.00	

LPG: Liquefied petroleum gas, NBS: New ballard score

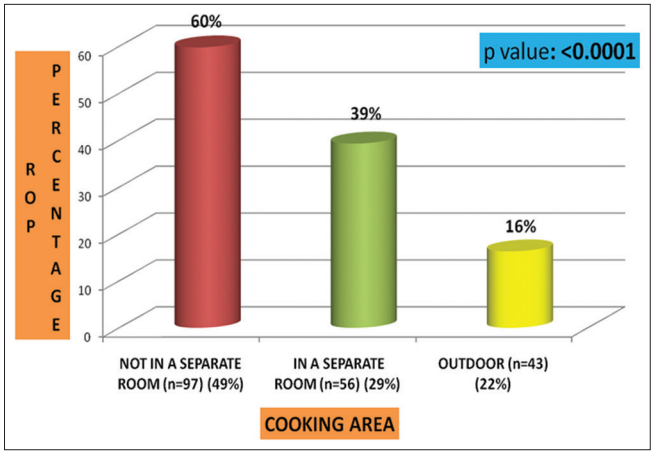

Figure 2: Bar chart showing the percentage of neonates according to cooking area and retinopathy of prematurity

ROP; many studies have reported sepsis, respiratory distress, intraventricular hemorrhage, blood transfusion, apnea, and oxygen therapy as significant risk factors associated with ROP [17-21].

The most interesting finding of this study was the confirmation of our hypothesis that prenatal exposure of a pregnant woman to HAP is likely to increase the risk of ROP independent of the GA. The impact of prenatal environmental exposure such as, HAP due to the use of solid fuels for household cooking by the pregnant women, on the risk of ROP in the neonate that is born prematurely has never been assessed. HAP has been previously reported to be a significant risk factor for adverse pregnancy outcomes including prematurity.

One of the pathways to increase the risk of ROP, in neonates born to mothers with prenatal exposure to tobacco smoke or HAP, is by increasing the risk of premature deliveries which will increase the rates of ROP in live births. Our study, however, found that these environmental exposures increased the risk of ROP after controlling for prematurity in the multivariate model. Particulate matter present in the smoke from the use of solid fuels causes oxidative stress, pulmonary and placental inflammation, blood coagulation, alteration of endothelial function, and hemodynamic responses. This ultimately leads to adverse pregnancy outcomes and can also potentially lead to abnormal retinal vasculogenesis in the fetus in addition to premature delivery. Other pollutants from household cooking, such as carbon monoxide, cross the placenta and decrease oxygen supply to tissue which limits the ability of the placenta to transfer nutrients to the fetus. Thus, the fetus can be subjected to chronic hypoxic stress when the mother spends long hours in household cooking. Chronic hypoxic stress experienced in utero may augment the sensitivity to oxygen received after birth in preterm neonates.

According to the classical theory [22] proposed by Ashton and Patz of the pathogenesis of ROP, supplemental oxygen administration was considered as the main causative factor. Elevated arterial PO_2 causes retinal vasoconstriction, leading to vascular closure, and if vasoconstriction is sustained, subsequent permanent vascular occlusion occurs. Endothelial cell proliferation adjacent to closed capillaries is followed when neonate returns to room air thus leading to neovascularization. The subsequent extension of this neovascularization may reach vitreous, producing hemorrhage leading to fibrosis and causing vitreous traction and retinal detachment. The other mechanism could be increased sensitivity of the spindle cells to the toxic effect of oxygen due to a prior prenatal chronic hypoxic state.

This theory proposed by Kretzer *et al*. [23] postulated that there is induction of retinal and vitreal neovascularization by spindle cell insult due to exposure to the hyperoxic environment when oxygen diffusion occurs from choroidal vasculature. Oxygen-free radical: A cytotoxic agent attacks compromised spindle cells, which has a deficient antioxidative defense mechanism. This abnormal spindle cells stop migration and canalization. Another possible mechanism could be the role of vasoformative factors that help the normal

development of retinal vasculature. If the avascular zone is larger, which may occur in prenatal chronic hypoxic states, and when this is exposed to the hyperoxic state, vascular endothelial growth factor (VEGF) expression is decreased leading to vasobliteration. This causes hypoxia and ischemia in the non-perfused area if the insult is sustained. This again stimulates VEGF production and thus neovascularization. Over time, if VEGF production decreases, ROP will regress and vice versa. Flynn *et al*. [24-29] explained that injury to the endothelium occurs where it has just differentiated from mesenchyme to form the primitive capillary meshwork. The work of Alon *et al.* suggests that reduced VEGF results in the death of endothelial cells [30] because of its role as a survival factor.

This study is the first to examine the association between HAP and ROP and provides an opportunity to further explore the effects of prenatal exposure of mothers to HAP, so as to decrease the incidence of ROP. Further studies for the quantification of the duration and magnitude of exposure that leads to ROP are essential to determine the possible preventive measures and to develop guidelines for avoiding exposure in the antenatal period to prevent HAP-associated ROP in the newborns.

CONCLUSION

Our study was the first to examine the association between biomass fuel use and ROP. The rate of ROP is significantly higher in premature infants of mothers who were exposed to HAP as compared to premature infants whose mothers were not using polluting fuels for household cooking. Given the high prevalence of ROP and the widespread use of biomass fuel for cooking in India and other developing countries, there is an urgent need to reduce HAP exposure from biomass fuels.

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