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# Severe Perinatal Asphyxia and Risk of Neonatal Jaundice at a Tertiary Hospital in Northern Nigeria

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***Authors' contributions***

*This work was carried out in collaboration among all authors. Author IAI conceptualization of the study, design, performed the statistical analysis and interpretation of data, drafting of the manuscript. Author MOY managed the data entry and statistical analysis. Authors ATA, PEA and ZMW managed the data collection. All authors read and approved the final manuscript.*

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## ABSTRACT

**Background:** The risk factors of neonatal jaundice are largely known, yet there is little agreement on the association between it and perinatal asphyxia.
**Aim:** To investigate the association between severe perinatal asphyxia (SPA) and the risk of clinical jaundice (NNJ) among neonates managed at the Federal Medical Centre, Azare, Nigeria.
**Methodology:** Case control design was employed. Medical records of 315 babies managed at the special care baby unit from 1st January, 2011 to 31st December, 2018 were analysed. The exposure of interest was SPA and the outcome was jaundice. Logistic regression was applied to demonstrate the relationship between neonatal jaundice and SPA. Relative risk was provided as odds ratio and 95% confidence interval.
**Results:** Sixty-three cases and 252 controls were enrolled in the study. The mean age of the cases ($4.39 \pm 4.04$ days) and that of the controls ($4.95 \pm 7.52$ days ) did not differ significantly (t= -0.52, *P*= 0.30). One hundred and fifty-six (61.9%) of the controls were males while 34 (54.0%) of the cases were females. For 59 (93.7%) of the cases treatment for jaundice was done with phototherapy and 1.6% required exchange blood transfusion. SPA significantly reduced the risk of developing NNJ (adjusted OR = 0.27, *P*-value < 0.01).

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**Conclusion:** We demonstrated a significantly reduced risk of developing neonatal jaundice with prior exposure to severe perinatal asphyxia. Prospective multicenter and community based studies correlated with serum bilirubin levels are recommended.

*Keywords: Severe perinatal asphyxia; neonatal jaundice; risk; phototherapy.*

## 1. INTRODUCTION

While the risk factors of neonatal jaundice (NNJ) have been extensively studied, [1] there is little agreement on the association between perinatal asphyxia and NNJ. Whereas, there is some evidence that perinatal asphyxia may raise hepatic enzymes in the newborn, there is no consensus on its clinical consequence in the context of jaundice [2,3]. There are also indications that severe perinatal asphyxia (SPA) may be associated with a rise in total serum bilirubin (TSB) in the newborn [4]. SPA inducing higher levels of hepatic enzymes and raising total serum bilirubin sends conflicting signals as higher levels of the hepatic bilirubin conjugating enzyme uridine diphosphoglucuronate glucuronosyltransferase 1A1 (UGT) have been shown to result in diminished levels of TSB [5]. The need to further scrutinize this association to establish the risk of NNJ in the context of SPA is thus of huge significance.

To the best of our knowledge there is as yet no comprehensive study that explores the clinical consequences of the effect of SPA on neonatal bilirubin metabolism. Hence with the notion that transcutaneous assessment of jaundice correlates satisfactorily with serum bilirubin, [6,7] we have elected to conduct this study to determine the risk of developing clinical jaundice in neonates with perinatal asphyxia. The primary objective of this study was to investigate the association between severe perinatal asphyxia and the risk of clinical jaundice among neonates managed at the Federal Medical Centre, Azare in North-Eastern Nigeria. Therefore, the research question arose: Does severe perinatal asphyxia increase the risk of contracting clinical jaundice amongst newborns in Azare? We hypothesized that there is no association between severe perinatal asphyxia and clinical jaundice in the newborn.

## 2. MATERIALS AND METHODS

This was a case control study of neonates admitted and managed at the special care baby unit (SCBU) of the Federal Medical Centre, Azare of Bauchi state in North-Eastern Nigeria from 1st January, 2011 to 31st December, 2018 (an 8-year period). Medical records were the sole source of data for this study. The minimum sample size was calculated with the formula: [8]

$$\text{Sample size} = \frac{r+1}{r}\frac{P^*(1-P)(Z_\beta + Z_2^\alpha)^2}{(P_1-P_2)^2}$$

(Where r = ratio of control to cases, P*= average proportion exposed, $Z_\beta$ =standard normal variate for power, $Z_2^\alpha$ =standard normal variate for level of significance, $P_1 - P_2$= effect size or difference in proportion based on previous studies). The proportion of controls to cases was 4:1. Medical records of sixty-three (63) newborns diagnosed with neonatal jaundice were retrieved retrospectively as cases. The control subjects were two hundred and fifty-two (252) newborns whose records were obtained from among those who did not have neonatal jaundice and were managed during the study period. Selection of controls was done with the simple random sampling method utilizing a sampling frame. Information was extracted from the records with the use of a structured questionnaire. Data obtained included, age, gender, gestational age, birth weight, place of birth, presence or absence of perinatal asphyxia, method applied in the treatment of jaundice (for cases), and management outcome. All data were collected by the authors. Newborns with major congenital anomalies/syndromes and preterm babies < 35 completed weeks of gestation were excluded from the study with the intention of lessening the drawbacks of the Apgar score for perinatal asphyxia diagnosis. Babies with confirmed obstructive jaundice were also excluded. The exposure of interest was severe perinatal asphyxia and it was defined as Apgar score of ≤ 3 at 1 minute and ≤ 5 at 5 minutes. Outcome of interest was clinical jaundice which was assessed visually by consultant Paediatricians. In every case, assessment for clinical jaundice was done in bright light (natural and electric) before commencement of phototherapy. Jaundice was assessed on the conjunctiva and the tip of the nose [9]. For each site, it was subjectively assessed as absent or present.

### 2.1 Statistical Analysis

Data was analyzed with the statistical package for social sciences (SPSS) version 20.0 and presented in prose, tables and a figure. Means were compared with the student t-test. Logistic regression was used to demonstrate the relationship between neonatal jaundice and severe perinatal asphyxia. Relative risk of NNJ was made available as odds ratio (OR) and 95% confidence interval (CI). The association between SPA and NNJ was assessed with the chi –square test. We established potential confounders based on biological possibility and their association with both NNJ and SPA. These were, gender, gestational age and birth weight. For these variables the Mantel- Haenszel chi-square test was used for adjustment. A *P*-value < 0.05 was regarded as statistically significant.

## 3. RESULTS

A total of 2501 neonates were managed at the SCBU during the study period. Seventy-six (76) patients had NNJ, giving a prevalence of 3.04%. However, 13 were excluded because their clinical records could not be obtained from the records library. Hence 63 subjects were enrolled as cases. Two hundred and fifty-two control subjects were recruited. Therefore, our sample size was 315. Our study subjects were newborn babies within the first 28 days of life. The mean age of the cases ($4.39 \pm 4.04$ days) and that of the controls ($4.95 \pm 7.52$ days ) did not differ significantly (t= -0.52, *P*= 0.30). Table 1 outlines the general characteristics of the study participants. It shows that 124 (49.2%) of the controls and 12 (19.0%) of the cases were < 1 day old. One hundred and fifty-six (61.9%) of the controls were males while 29 (46.0%) of the cases were males. Forty-seven (71.4%) of the cases and 177 (70.2%) of the controls were delivered at term, 33 (52.4%) of the cases and 130 (52.2%) of the controls had birth weights within the range of 2500- 3999g. The table also shows that 11.9% of cases and 22.2% of controls died while on admission.

Fig. 1 displays the treatment modalities applied in the management of NNJ, 59 (93.7%) were treated with phototherapy while 1 (1.6%) baby with NNJ had required an exchange blood transfusion. Table 2 demonstrates the relative risk of developing NNJ when SPA was diagnosed in a neonate. It shows an adjusted OR 0.27 and *P* value of < 0.01. Thus exposure of a newborn to SPA significantly reduced the risk of developing NNJ. Therefore, we rejected the null hypothesis that there is no association between SPA and NNJ.

## 4. DISCUSSION

With the aim of investigating the relationship between prior exposure to SPA and the risk of jaundice among neonates managed at the Federal Medical Centre Azare, Nigeria, we hypothesized that 'there is no association between SPA and NNJ. Nevertheless, our findings indicated that exposure of a newborn to SPA significantly reduced the risk of developing NNJ at FMC Azare during the study period. We also demonstrated that NNJ was predominantly managed successfully with phototherapy alone.

To our knowledge there is as yet no other study that has investigated the direct impact of SPA on NNJ. However, a few surveys have looked at the effects of SPA on serum bilirubin with inconsistent results. While some reports have indicated that SPA is associated with a low risk of hyperbilirubinaemia, [2,3,10-12] others have postulated that SPA is often accompanied with a rise in serum bilirubin [4,13,14]. Our findings are more correlated to the former. Nonetheless, the later studies were limited in design, and scope. These studies were also largely done with inadequate number of subjects hence their findings are less likely to be robust. The exact mechanism behind the reduced risk of developing NNJ in the presence of SPA is unknown. However, there is evidence that bilirubin may be involved and hence used up in the physiologic defense against oxidative stress in the neonate [15]. One could also surmise that the hypoxic state impairs neonatal cutaneous expression of hyperbilirubinaemia.

This is the pioneer Nigerian report on the effects of SPA on the risk of NNJ. It enhances the body of knowledge on the concept of hypoxia reducing the risk of NNJ, and makes it imaginable for some form of controlled hypoxia to be applied in the prevention and treatment of NNJ. Some of the other strengths of this study include; a large sample size and the case control design which is ideal for studying rare outcomes (NNJ is uncommon in our setting).

### 4.1 Study Limitations

The limitations of our study are, the retrospective design, a lack of inclusion of milder forms of perinatal asphyxia to ascertain their effects on the risk of NNJ, it been hospital based and a lack of correlation with serum bilirubin levels.

**Table 1. General characteristics of study participants**

| | Cases N= 63 (%) | Controls N= 252 (%) | *P*-value |
|---|---|---|---|
| **Age (Days)** | | | |
| < 1 | 12 (19.0) | 124 (49.2) | 0.00 |
| 1-7 | 39 (61.9) | 64 (25.2) | |
| 8-14 | 11 (17.5) | 26 (10.3) | |
| 15-28 | 1 (1.6) | 38 (15.1) | |
| **Gender** | | | 0.02 |
| Male | 29 (46.0) | 156 (61.9) | |
| Female | 34 (54.0) | 96 (38.1) | |
| **Gestational age (weeks)** | | | 0.12 |
| < 37 | 18 (28.6) | 60 (23.8) | |
| 37- 41 | 45 (71.4) | 177 (70.2) | |
| > 41 | 0 (0.0) | 15 (6.0) | |
| **Birth weight (grams)** | | | 0.27 |
| < 1000 | 0 (0.0) | 4 (1.6) | |
| 1000- 1499 | 6 (9.5) | 20 (8.0) | |
| 1500- 2499 | 24 (38.1) | 81 (32.5) | |
| 2500- 3999 | 33 (52.4) | 130 (52.2) | |
| ≥ 4000 | 0 (0.0) | 14 (5.6) | |
| **Birth place** | | | 0.12 |
| Home (unsupervised) | 15 (24.2) | 63 (25.2) | |
| Hospital | 45 (72.6) | 186 (74.4) | |
| TBA supervised | 2 (3.2) | 1 (0.4) | |
| **Outcome** | | | 0.10 |
| Discharged | 38 (60.3) | 181 (71.8) | |
| Death | 14 (22.2) | 30 (11.9) | |
| Referral | 0 (0.0) | 5 (2.0) | |
| DAMA | 11 (17.5) | 36 (14.3) | |

*TBA = Traditional birth attendant, DAMA = Discharged against medical advice*

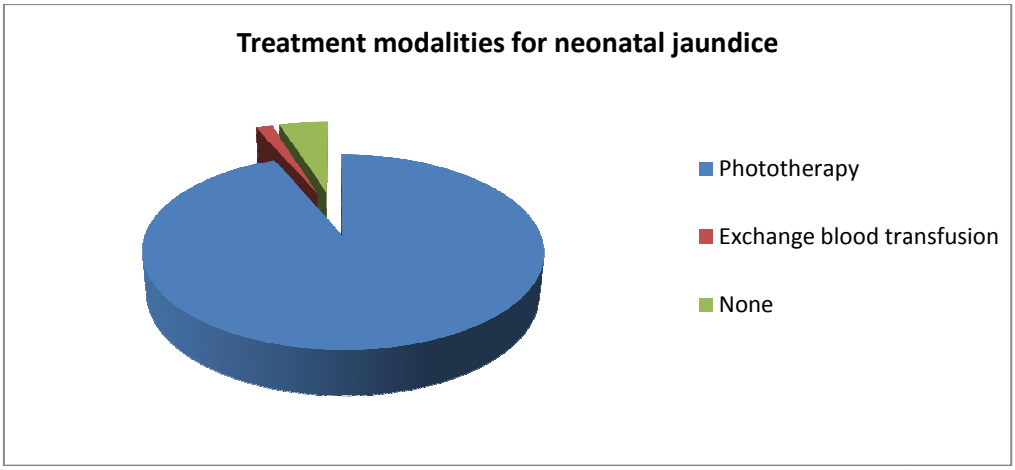


**Fig. 1. Treatment modalities for neonatal jaundice**

**Table 2. Relative risk of neonatal jaundice in relation to prior exposure to severe perinatal asphyxia**

| | Cases N= 63 (%) | Controls N = 252 (%) | Crude OR (95% CI) | Adjusted OR (95% CI) |
|---|---|---|---|---|
| SPA | | | 0.25 (0.10-0.64) | 0.27 (0.11- 0.71) |
| Present | 5 (7.9) | 62 (24.6) | *P* < 0.01 | *P* < 0.01 |
| Absent | 58 (92.1) | 190 (75.4) | | |

*Relative risk is provided as odds ratio (OR) with 95% confidence interval (CI) and adjusted for gender, gestational age and birth weight*

## 5. CONCLUSION

The study demonstrated a significantly reduced risk of NNJ in newborns with SPA, and also that phototherapy is the mainstay of the management of NNJ at FMC Azare. We recommend prospective multicenter and community based studies including a correlation with serum bilirubin levels as well as an expansion of the scope of exposures to include mild, and moderate perinatal asphyxia.

## CONSENT

It is not applicable.

## ETHICAL APPROVAL

The study was approved by the Research Ethics and Review Committee of the Federal Medical Centre, Azare, Nigeria.

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## COMPETING INTERESTS

Authors have declared that no competing interests exist.

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