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Prevalence And Factors Associated With Neonatal Jaundice: A Case Study Of University College Hospital, Ibadan.

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Abstract; *Neonatal jaundice occurs frequently in new born babies in the first week of life. It may be harmless but results in "Kernicterus" or "bilirubin brain damage" when it is severe. This study examined prevalence and associated risk factors affecting neonatal jaundice among neonates born between 2005 and 2010 in University College Hospital, Ibadan. The study is a retrospective study where data were retrieved from neonates' case notes frommedical records unit of the University College Hospital, Ibadan.A total of 232 neonatal jaundice cases wereanalysed and categorized into mild and severe jaundice. Qualitative response regression models was proposed to obtain the precise estimates of the probabilities of a neonatal having neonatal jaundice. Binary Logistic regression analysis which model neonatal jaundice as a response variable while Neonate age, neonate sex, birth weight, mode of delivery, place of delivery, settlement, G6PD, Mothers' Rhesus factor, mother illness during pregnancy, mother level education, parity of the mother and gestational age were the risk factors. The result showed that gestational age, place of delivery, Rhesus incompatibility, and G6PD were statistically significant risk factors for neonatal jaundice. The model converges at the 4th iteration with -2log-likelihood of 267.712, and Cox & Snell R^2 is .206 with probability of 0.0000 at 5% $\propto$ level of significance, this indicated that the model fitted for the study is adequate at that level of significance.*

Keywords: *Kernicterus, bilirubin, G6PD, -2log-likelihood, Cox & Snell R^2, Logistic Regression.*

I. Introduction

Jaundice comes from the French word Jaune, which means yellow. When it is said that a baby is jaundiced, it simply means that the colour of his skin appears yellow. In fair-skinned infants, jaundiced skin may be observed at total serum bilirubin (TSB) levels of 5 to 6 mg/dl (Augustine, 1999).Jaundice in the infant appears first on the face and upper body and progresses downward towards the toes. Preterm infants are more likely to develop jaundice than full-term babies (Mead Johnson & Company, 1993, Jaundice & Your Baby, 1-4.) The incidence of jaundice in newborns varies between 20 and 80% depending on gestational age and ethnicity (Nelson textbook of paediatrics). When jaundice is severe, it has the potential of causing brain damage (kernicterus) with long term neurodevelopmental impairment in survivors or death (Practical Paediatric Problems, James H. Hutchison, 1972). This effect can however be prevented by early recognition and prompt management of those at risk. It is a health problem that bothers on proper child's birth and development which requires urgent attention. The intention is not to lay emphasis on the socio-economic problem of neonatal jaundice in our society. These might have been covered in some details elsewhere. However, this study is set to examine through existing data the prevalence and associated risk factors for neonatal jaundice.

Approximately 65% of newborn infants develop clinically evident jaundice in the first week of life (Maisels 1992).Neonatal jaundice is a very common condition worldwide occurring in up to 60% of term and 80% of preterm newborns in the first week of life (Slushier et al 2004, Haque and Rahman 2000). Prevalence and factors associated with neonatal jaundice can help guide policy makers in planning public health interventions. As a result of personal tragedies with kernicterus, the organization Parents of Infants and Children with Kernicterus (PICK) was founded in 2000 to increase awareness and education regarding kernicterus. This parental group prompted several "zero tolerance for kernicterus" national campaigns (TJC, 2004; PICK, 2007).Immature newborn brain is susceptible to toxicity from unconjugated bilirubin resulting in "Kernicterus" or "bilirubin brain damage" and this eventually leads to cerebral palsy and mental retardation. The level of intelligence has been proved to be relative to the degree of neonatal jaundice and in the long run it limits the functioning of the body organs (The development of the infant and young Child, R. S Illingworth, 1971).

This paper investigates if the neonatal jaundice data collected fits into the Logistic Regression model, (b) to model logistics regression and check for the risk factors associated with neonatal jaundiceand (c) to make some meaningful inferences from logistic regression model. The outcomes of the analyses are expected to be yardstick for experts and government alike to identify infants at risk requiring close surveillance. The rest of the paper is organized as follows: the next sections briefly review some literature and presents the literatures on neonatal jaundice treatment. Section 3 presents the model, data sources and measurements. Section 4 discusses the results. While the last section concludes the paper.

II. Review Of Some Related Literature

During the past decades, researchers have made significant progress in understanding the epidemiology of neonatal jaundice. On the part of statisticians and social scientist, they have analyzed the cultural and behavioral aspect of the epidemic as well as its impacts on families, communities and the nation.

RansomeKuti 1972,Effionget al 1975, and Coulter et al 1977 reported a lower incidence of neonatal jaundice among the Hausas (Northern Nigeria) compared to the Yoruba's (Western Nigeria) and Igbo's (Eastern Nigeria) in their series and deals with neonatal jaundice in predominantly Igbo population. They also concluded that neonatal jaundice is a common paediatric problem in various parts of Nigeria.

Dr B.S.B, Wood (1978) reported that breastfeeding was associated with a two fold increase in jaundice and also that multivariate analysis confirmed breast feeding as an independent factor associated with increased jaundice.

Louise Friedmalet al (1980) argued that what Wood (1978) reported as an independent factor has small effect and less than that of oxytocin, sex of baby, epidural anesthesia and gestational age.

KhuramArifet al (1998) employed logistic regression model with estimation of odds ratio in the analysis of risk factors and spectrum of neonatal jaundice in a birth cohort in Karachi, Pakistan. Data was analyzed using SPSS Version 6.1, out of 5570 birth during the study period, the number of newborn requiring phototherapy and / or exchange transfusion of blood was 869 (15.6/ 1000 live births) with a male to female ratio 1:1.3, the mean gestational age and birth weight were 37.2 ± 2.8 weeks and 2754 ± 735 g respectively. G6pd deficiency accounted for 2% of the study group.

Yoshihiro Maruoetal in "Association of Neonatal Hyperbilirubinemia with Bilirubin UDP-Glucuronosyltransferase Polymorphism" concluded that the missense mutation causing g71r is the first reported polymorphism for ugt1a1, and the mutation is a risk factor for nonphysiologic neonatal hyperbilirubinemia. The high incidence of hyperbilirubinemia in the Japanese may be attributable to the high frequency of this missense mutation.

Shu-Chiung Chou etal (2001) in "Management of newborns: measuring performance by using a benchmarking model". The logistic regression revealed that the risk of developing a maximum observed TSB ≥ 20 mg / dl was positively associated with lower gestational age, male gender and older maternal age. Also poison regression revealed that the incidence of severe hyperbilirubinemia (TSB ≥ 20 mg / dl) was associated positively with lower gestational age and male gender. HosmerLemeshow goodness of fit test was used to examine the model where p = 0.312.

Thomas etal (2002) used logistics multivariate regression analysis technique to study the prediction and prevention of extreme neonatal hyperbilirubinemia in mature health maintenance organization. The study showed that the strongest predictors of neonatal jaundice were family history jaundice in newborn with or = 6.0, maternal age of 25 or older (or = 3.1), lower gestational age (or = 0.6 / week).

The useof herbal medications in association with severe neonatal jaundice had been reported previously from Lagos, Southern Nigeria.Olusanyaetal., 2009 explored that significantly, mothers of the newborn babies with significant bilirubinaemia took herbal drugs.

Eneh and Ugwu(2009), Oladokunetal ., (2009),Owa and Ogunlesi, (2009) reported that unlike the developed countries where feto-maternal blood group incompatibilities are the main causes of severe neonatal jaundice, it is mostly prematurity, G6PD deficiency, infections as well as effects of negative traditional and social practices such as consumption of herbal medications in pregnancy, application of dusting powder on baby, use of camphor balls to store babies clothes are the majorcauses in developing countries.

Onyearugha C. N etal (2011)reported a high prevalence of neonatal jaundice in Abakaliki, Southeast Nigeria and recommended that effective and sustained health education of the citizenry and particularly expectant women on the need forearly booking for ANC, regular antenatal supervision of pregnancy and delivery in appropriate health facility, as well as on early signs of NNJ and prompt presentation of affected newborn for appropriate medical care be implemented forthwith to curb this unacceptable situation.

Ezham, A.et al (2011) in "Prevalence of UridineGlucuronosylTransferase 1A1 (UGT1A1) Mutations in Malay neonates with severe jaundice", discovered that out of 250 neonates that were enrolled in the study, one hundred and twenty-five neonates of Malay ethnic parentage were admitted with severe unconjugated hyperbilirubinemia. They found that there was an equal distribution of gender between the severely jaundiced neonates and the control cases.

Review of Related Literature on treatment of Neonatal Jaundice

Gibbs W.N etal (1979) in "Glucose-6-phosphate dehydrogenase deficiency and neonatal jaundice in Jamaica" observed that the most dangerous consequence of G6PD deficiency is neonatal jaundice. Neonatal Jaundice has been documented repeatedly in populations in which class 2 variants are common. Phototherapy has been used to reduce bilirubin levels, and phenobarbital has also been used prophylactically with some

success. Exchange transfusion is required if the bilirubin exceeds 20 mg/dL, but G6PD-deficient blood should not be used for this purpose.

Azubuike J.C (1985), in 'Neonatal jaundice in Eastern part of Nigeria' was able to come up with some treatments of neonatal jaundice. These treatments usually should be started with Pheno-barbitone (3mg/kg body weight per day orally, given in two divided doses) or with standard phototherapy. Exchange Blood transfusion must be performed if unconjugated bilirubin level was 20mg/dl or above in normal full term babies or above 15mg/dl in low birth weight babies especially if there was attendant asphyxia and Acidosis at birth.

Martell et al, (1999), recommended that neonatal jaundice should be monitored in the hospital nursery while mother and newborn recovered for 3 or more days after the birth. During this hospitalization, breastfeeding patterns would be established, role transition supported, and jaundice issues would be addressed.

Jackson reported 3 deaths/1000 procedures of EBT-related deaths in a previous study (Jackson, 1997), He also discovered that adverse events following intervention procedures occurred in 10.4% of the subjects comprising mostly malaria parasitaemia and occurrence of fever within 72 h. This is not surprising since malaria is endemic in the population and blood for transfusion is not screened for the presence of malaria parasites. Death that occurs about 3 hours after an EBT (Exchange blood transfusion) procedure in a newborn subject with bilirubin encephalopathy and gasping might not be categorically classified as procedure-related death since the baby was gravely ill.

Review of Some Related Literature on Logistic Regression Model

Dayton (2001) said that the model for logistic regression analysis assumes that the outcome variable, Y, is categorical (e.g., dichotomous), but LRA does not model this outcome variable directly. Rather, LRA is based on probabilities associated with the values of Y. For simplicity, and because it is the case most commonly encountered in practice, one should assume that Y is dichotomous, taking on values of 1 (i.e., the positive outcome, or success) and 0 (i.e., the negative outcome, or failure). In theory, the hypothetical, population proportion of cases for which $Y = 1$ is defined as $p = P(Y = 1)$. Then, the theoretical proportion of cases for which $Y = 0$ is $1 - p = P(Y = 0)$. In the absence of other information, we would estimate p by the sample proportion of cases for which $Y = 1$. However, in the regression context, it is assumed that there is a set of predictor variables, $X1, \ldots, Xp$, that are related to Y and, therefore, provide additional information for predicting Y. For theoretical, mathematical reasons, LRA is based on a linear model for the natural logarithm of the odds (i.e., the log-odds) in favor of $Y = 1$

Logistic regression allows one to test models to predict categorical outcomes with two or more categories where the predictor (independent) variables can either be categorical or continuous, or a mix of both in the one model. Risk Factors (predictor or independent variables) can either be categorical or continuous or a mix of both in one model. In the approach of this study, all risk factors are tested in one block to assess their predictive ability in order to pick a subset that provides the best predictive power. Binary Logistic regression is perform when Response variable has with a dichotomous response (i.e. with only two categories or values) and If your response variable has more than two categories, you will need to use the Multinomial Logistic set of procedures (Hosmer&Lemeshow 2000; Peat 2001; Tabachnick&Fidell 2007).

The logistic model says that the log–odds follow a linear model. Another way of saying this is that $\widehat{\beta_1}$ has the following interpretation: a one unit increase in x is estimated to be associated with multiplying the odds of success by $e^{\widehat{\beta_1}}$, holding all else in the model fixed. The estimated odds of success when all predictors equal zero is obtained from the constant term as $e^{\widehat{\beta_0}}$. Note that since the logit is based on natural logs, there is a clear advantage to using the natural logarithm (base e) rather than the common logarithm (base 10) if you need to log a predictor: if this is done, the coefficient $\widehat{\beta_1}$ represents an elasticity of the odds. So, for example, a coefficient $\widehat{\beta_1} = 2$ means that a 1% increase in x is associated with a (roughly) 2% increase in the odds of success. The logistic regression model is an example of a generalized linear model. The model is that $yi \sim \text{Binomial}(1, pi)$, with pi satisfying the logistic model. The parameters are estimated using maximum likelihood (OLS, WLS, and GLS are versions of maximum likelihood in Gaussian error regression models), which implies that the resultant estimated probabilities of success are the maximum likelihood estimates of the conditional probabilities of success given the observed values of the predictors (Simonoff, 2012).

Anil Dolgun (2012) confirmed that many research problems call for the analysis and prediction of a binary outcome.

III. Model Specification, Data Sources And Measurement.

In this study, we apply logistic regression model in determining factors that are affecting neonatal jaundice and to show the pattern of relationships of the factors involved.

The logistic regression model:

$$E\{Y_i\} = \pi_i = \frac{\exp(\beta_0 + \beta_i x_i)}{1+\exp(\beta_0 + \beta_i x_i)}$$

$$\text{logit } y = \propto + \sum_{i=1}^{n} \beta_i x_i$$

$$\text{logit } Y = [1 + e^{-(\beta_i x_i)}]^{-1}$$

Logistic regression analysis (LRA) extends the techniques of multiple regression analysis to research situations in which the outcome variable is categorical. In practice, situations involving categorical outcomes are quite common. In the setting of evaluating an educational program, for example, predictions may be made for the dichotomous outcome of success/failure or improved/not-improved. Similarly, in a medical setting, an outcome might be presence/absence of disease. The focus of this document is on situations in which the outcome variable is dichotomous. Logistic regression is used for predictions of probability of occurrence of an event by fitting data to a logistics curve. It is a generalized linear model used for binary response variable. Logistics makes use of several predictors' variables that may either be numerical or categorical. Logistic regression is sometimes called logit model.

Logit model as an aspects of qualitative response regression model possess interesting estimations and interpretations challenges especially in various areas of social science and medical research. In qualitative model, the objective is to find the probability of an event occurring. Hence qualitative response regression models are often known as probability models. The logistics response variable is dichotomous such as blood pressure status (high blood pressure, not high blood pressure,) or polytomous i.e. multicategory such as pregnancy duration (preterm, intermediate term and full term)

3.2 Data Source and Measurement

The data used for this work were retrieved from neonate's case note from children outpatients (CHOP) units of the University College Hospital, Ibadan from 2005 to 2010. Data includes age, sex, gestational age, birth- weight, maternal illness, mode and place of delivery, mother education, parity, settlement, Rhesus factor and G6PD which forms the eleven predictor variables. Considering the data used for this research, letting Y = 1(>340 mol/L (20 mg/dL) if a neonate have severe jaundice and Y = 0 (<85–170 mol/L (5–10 mg/dL), if a neonate have mild jaundice, which form the response variable.

IV. Empirical Results.

4.1 Descriptiveanalysis Results

A total of 232 neonatal jaundice cases was used for the study. A summary of the analysis of neonatal jaundice using SPSS, version 16 to run the descriptive analysis are presented in **Table 1a through 1c.**

Table 1a

Variable	**Category**	Frequency	Percent	Cumulative Percent
Sex	Male	107	46.1	46.1
	Female	125	53.9	100.0
Survival	Dead	79	34.1	34.1
	Alive	153	65.9	100.0
Mode of Delivery	CS	85	36.6	36.6
	SVD	147	63.4	100.0
Place of Delivery	Not Hospital	53	22.8	22.8
	Hospital	179	77.2	100.0
Mother's Education	Illiterate	83	35.8	35.8
	Literate	149	64.2	100.0
Mothers' Illness	Present	43	18.5	18.5
	Absent	189	81.5	100.0
G6PD	Normal	71	30.6	30.6
	Deficient	161	69.4	100.0
Gestational Age	Preterm	110	47.4	47.4
	Term	122	52.6	100.0
Settlement	Rural	37	15.9	15.9
	Urban	195	84.1	100.0

From the descriptive results of the data use for the study , 107 neonates were male with 46.1% and 53.9% were female, 79 (34.1%) neonates did not survive the disease. 85(36.6%) neonates were born through Caesarean Section, 53(22.8) neonates were born outside the hospital, 83 (35.8%) mothers were illiterate. 43(18.5%) mothers are presented with illness during pregnancy, 146 (62.9%) mothers are rhesus negative which leads to rhesus incompatibility with the blood group of the neonate, 161 (69.4%) neonates have G6PD

deficiency, 110 (47.4%) neonates were born prematurely while 122 (52.6%) were born with full term and 120 (51.7) neonates has severe jaundice .

Table 1b: Cross tabulation of Sex and Survival rate.

Neonate Sex * Survival Cross tabulation				
Count				
		Survival		
		Dead	Alive	Total
Neonate Sex	Male	39	68	107
	Female	40	85	125
Total		79	153	232

Fig1

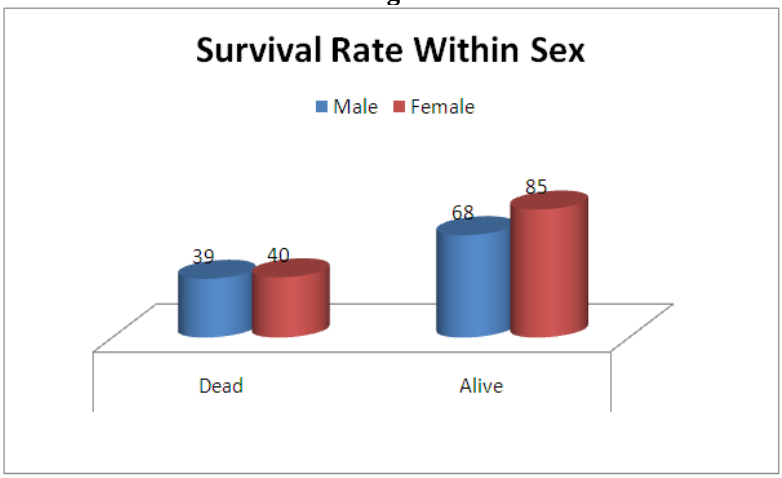
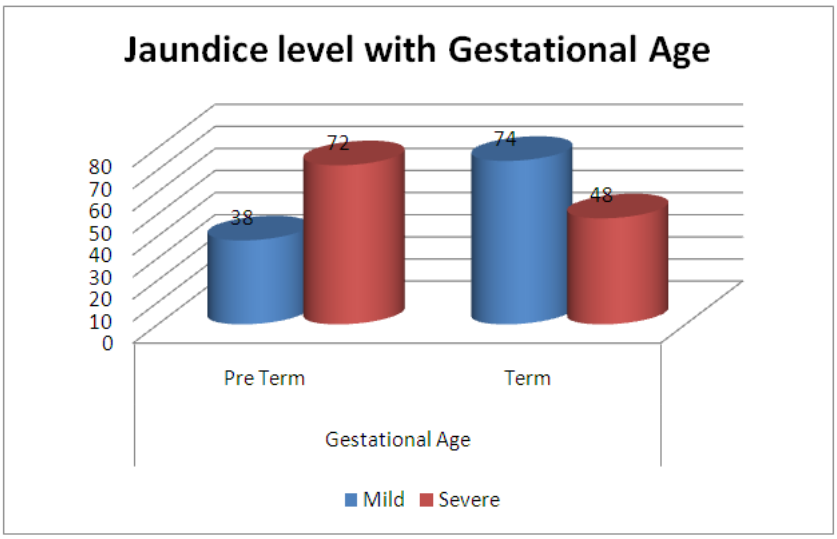


Table 1c: Cross tabulation of Jaundice Level and Gestational Age.

Jaundice Level * Gestational Age Crosstabulation				
Count				
		Gestational Age		
		Pre Term	Term	Total
Jaundice Level	Mild	38	74	112
	Severe	72	48	120
Total		110	122	232

Fig2



4.2 Logistic Regression Analysis

A summary of the analysis of neonatal jaundice using SPSS version 16 to run the Binomial Logistics Regression are presentedbelow. The model converge at the fourth iteration with -2log likelihood = 267.712 and Cox & Snell R square 0.206.

Table 2a

Model Summary			
Step	-2 Log likelihood	Cox & Snell R Square	Nagelkerke R Square
1	267.712[a]	.206	.275
a. Estimation terminated at iteration number 4 because parameter estimates changed by less than .001.			

Table 2b

Variables in the Equation										
								95.0% C.I.for EXP(B)		Sig. Decision
		B	S.E.	Wald	df	Sig.	Exp(B)	Lower	Upper	
Step 1[a]	Mode_Dummy	.512	.349	2.152	1	.142	1.669	.842	3.308	Insignificant
	Sex_dummy	-.380	.334	1.293	1	.255	.684	.355	1.316	Insignificant
	Place_dummy	-1.300	.437	8.867	1	.003	.273	.116	.641	**Significant**
	education_dummy	.202	.351	.333	1	.564	1.224	.616	2.433	Insignificant
	illness_dummy	-.675	.403	2.813	1	.093	.509	.231	1.121	Insignificant
	G6PD_dummy	-1.114	.375	8.832	1	.003	.328	.157	.684	**Significant**
	settlement_dummy	.405	.497	.664	1	.415	1.500	.566	3.975	Insignificant
	gestation_dummy	-1.300	.339	14.695	1	.000	.273	.140	.530	**Significant**
	Rhesus_dummy	.780	.321	5.902	1	.015	2.183	1.163	4.096	**Significant**
	weight_dummy	.106	.514	.043	1	.836	1.112	.406	3.046	Insignificant
	Constant	.819	.386	4.503	1	.034	2.268			

Note: Dummy variables are variables of interest which is the base category and denoted by 1 while the reference category is denoted by 0.

It can be observed that only place of delivery, G6PD, Gestational age and Rhesus factor are statistically significant factors associated with neonatal jaundice.

Interpretation of the Result

The logistics regression run on the Neonatal Jaundice data collected, shows the intercept, the coefficients of the risk factors, the standard errors, the Wald statistics, degree of freedom,Sig. value,the odds ratio [Exp(β_i)], and the 95% confidence interval of the coefficients.

The coefficient of place of delivery is -1.300 and the odds ratio is obtained simply bye^{β_i}, thus Odds ratio between place of delivery and neonatal jaundice is $e^{-1.300} = 0.273$, a value less than 1.This indicates that mothers who gave birth to child in hospitals are at a lower risk of neonatal jaundice than mothers who gave birth at home or not in an equipped hospital with qualified hands. The estimated odds of neonatal jaundice when neonates were not born in hospital are about 27.3% more than the estimated odds when neonates were born in the hospital.

Also, for G6PD, $e^{-1.114} = 0.328$ which is less than 1. The result indicated that G6PD normal babies are at lower risk of neonatal jaundice than G6PD deficient neonates. The odds ratio is 0.328 which simply means that neonates with G6PD deficient babies are 32.8% more likely to have neonatal jaundice than G6PD normal babies.

For Gestational age, $e^{-1.300} = 0.273$ which is also less than 1. The result indicated Term neonates are at lower risk than preterm neonates. The estimated odd ratio 0.273 shows that preterm neonates are 27.3% more likely to have neonatal jaundice term neonates.

For Rhesus Compatibility, $e^{0.780} = 2.183$ which is greater than 1. The result indicated that neonates with Rhesus compatibility are at lower risk than neonates with Rhesus incompatibility. The estimated odd ratio shows that Rhesus compatibility is about 218.3% less likely to have neonatal jaundice than Rhesus Incompatibility.

V. Conclusion

This paper analyzed risk factors generated from the case notes of neonates that had neonatal jaundice in the paediatrics department, University College Hospital, Ibadan between 2005 – 2011 to formulate a model that can be used to predict the probability of neonatal jaundice using those predictor variables. This paper work was able to establish that there exist a significant relationship between neonates' gestational age, place of delivery, G6PD, Rhesus factor and Neonatal Jaundice among the neonates cases studied in UCH. Thus, Literatures has proven the existence of these associations hence the Logistic regression model chosen can be used to prove such associations. One of the important of logistic regression analysis is for modeling binary responses that is response variable that are dichotomous in nature, also, the objective is to find the probability of an event occurring. Hence qualitative response regression models are often known as probability models.

Based on the outcome of this research work and available information, which has been discussed, it is recommended that:

- Expectant mothers in the country should be encouraged to use public hospital since this will reduce drastically the incidence of neonatal jaundice among our new born babies.
- Expectant mothers in the country should be encouraged to start Antenatal clinic as early as possible and attend consistently to prevent mother illness during pregnancy and to be able to address the rhesus incompatibility if the mother is rhesus negative.
- Government should provide modern health facilities in all our public hospital.

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