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CASE STUDY

NOVEL OR NEW METHOD FOR THE TREATMENT OF JAUNDICE IN PAEDIATRICS

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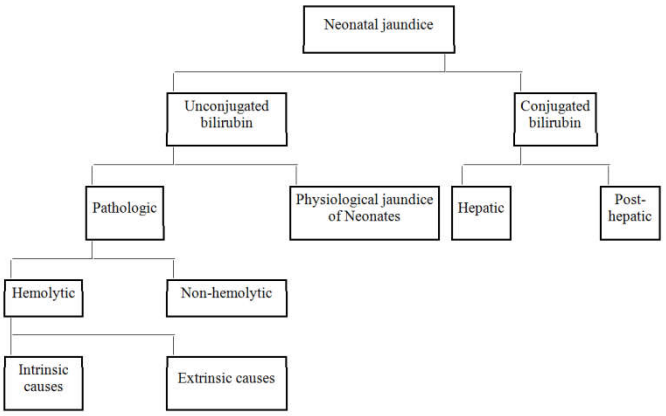
ABSTRACT

Neonatal jaundice or neonatal hyperbilirubinemia, or neonatal icterus, attributive adjective: icteric, is a yellowing of the skin and other tissues of a newborn infant. A bilirubin level of more than 85 µmol/l (5mg/dL) leads to a jaundiced appearance in neonates whereas in adults a level of 34 µmol/l (2 mg/dL) is needed for this to occur. In newborns, jaundice is detected by blanching the skin with pressure applied by a finger so that it reveals underlying skin and subcutaneous tissue. Jaundiced newborns have yellow discoloration of the white part of the eye, and yellowing of the face, extending down onto the chest. Neonatal jaundice can make the newborn sleepy and interfere with feeding. Extreme jaundice can cause permanent brain damage from kernicterus. In neonates, the yellow discoloration of the skin is first noted in the face and as the bilirubin level rises proceeds caudal to the trunk and then to the extremities. This condition is common in newborns affecting over half (50–60%) of all babies in the first week of life.[3] Infants whose palms and soles are yellow, have serum bilirubin level over 255 µmol/l (15 mg/dL) (more serious level). Studies have shown that trained examiners assessment of levels of jaundice show moderate agreement with icterometer bilirubin measurements as the new or novel method to determine.[2] In infants, jaundice can be measured using invasive or non-invasive methods. This research article focuses on a brief introduction to jaundice, its types and causes, measuring the bilirubin level, clinical approaches towards hyperbilirubinemia, different precautionary measures for the parents of babies suffering from hyperbilirubinemia and different remedial therapeutic measures for its treatment. 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 R2 is .206 with probability of 0.0000 at 5% ∝ level of significance, this indicated that the model fitted for the study is adequate at that level of significance.

INTRODUCTION

In neonates, jaundice tends to develop because of two factors the breakdown of fetal hemoglobin as it is replaced with adult hemoglobin and the relatively immature metabolic pathways of the liver, which are unable to conjugate and so excrete bilirubin as quickly as an adult. This causes an accumulation of bilirubin in the blood (hyperbilirubinemia), leading to the symptoms of jaundice. If the neonatal jaundice does not clear up with simple phototherapy, other causes such as biliary atresia, Progressive familial intrahepatic cholestasis, bile duct paucity, Alagille syndrome, alpha 1-antitrypsin deficiency, and other pediatric liver diseases should be considered. The evaluation for these will include blood work and a variety of diagnostic tests. Prolonged neonatal jaundice is serious and should be followed up promptly [1-3]. Severe neonatal jaundice may indicate the presence of other conditions contributing to the elevated bilirubin levels, of which there are a large variety of possibilities (see below). These should be detected or excluded as part of the differential diagnosis to prevent the development of complications. They can be grouped into the following categories:

Flow chart of neonatal jaundice



Unconjugated

Hemolytic

Intrinsic causes of hemolysis

1. Membrane conditions
   a. Spherocytosis
   b. Hereditary elliptocytosis
2. Enzyme conditions
   a. Glucose-6-phosphate dehydrogenase deficiency (also called G6PD deficiency)
   b. Pyruvate kinase deficiency
3. Globin synthesis defect
   a. sickle cell disease
   b. Alpha-thalassemia, e.g. HbH disease

Extrinsic causes of hemolysis

1. Systemic conditions
   a. Sepsis
   b. Arteriovenous malformation
2. Alloimmunity (The neonatal or cord blood gives a positive direct Coombs test and the maternal blood gives a positive indirect Coombs test)
   a. Hemolytic disease of the newborn (ABO)
   b. Rh disease
   c. Hemolytic disease of the newborn (anti-Kell)
   d. Hemolytic disease of the newborn (anti-Rhc)
   e. Other blood type mismatches causing hemolytic disease of the newborn

Non-hemolytic causes

1. Breastfeeding jaundice
2. Breast milk jaundice
3. Cephalohematoma
4. Polycythemia
5. Urinary tract infection
6. Sepsis
7. Hypothyroidism
8. Gilbert's syndrome
9. Crigler-Najjar syndrome
10. High GI obstruction (Pyloric stenosis, Bowel obstruction)

Conjugated (Direct)

Liver causes

1. Infections
   a. Sepsis
   b. Hepatitis A
   c. Hepatitis B
   d. TORCH infections
2. Metabolic
   a. Galactosemia
   b. Alpha-1-antitrypsin deficiency, which is commonly missed, and must be considered in DDx
   c. Cystic fibrosis
   d. Dubin-Johnson Syndrome
   e. Rotor syndrome
3. Drugs
4. Total parenteral nutrition
5. Idiopathic

Post-liver

1. Biliary atresia or bile duct obstruction
   a. Alagille syndrome
   b. Choledochal cyst

Non-organic causes

Breastfeeding jaundice

"Breastfeeding jaundice" or "lack of breastfeeding jaundice," is caused by insufficient breast milk intake, resulting in inadequate quantities of bowel movements to remove bilirubin from the body. This leads to increased enterohepatic circulation, resulting in increased reabsorption of bilirubin from the intestines. Usually occurring in the first week of life, most cases can be ameliorated by frequent breastfeeding sessions of sufficient duration to stimulate adequate milk production.

Breast milk jaundice

Whereas breastfeeding jaundice is a mechanical problem, breast milk jaundice is a biochemical occurrence and the higher bilirubin possibly acts as an antioxidant. Breast milk jaundice occurs later in the newborn period, with the bilirubin level usually peaking in the sixth to 14th days of life. This late-onset jaundice may develop in up to one third of healthy breastfed infants.

Physiological jaundice

Most infants develop visible jaundice due to elevation of unconjugated bilirubin concentration during their first week. This common condition is called physiological jaundice. This pattern of hyperbilirubinemia has been classified into two functionally distinct periods [4-11].

Diagnosis

Clinical Assessment

This method is less accurate and more subjective in estimating jaundice.

Ingram icterometer: In this method a piece of transparent plastic known as **Ingram icterometer** is used. Ingram icterometer is painted in five transverse strips of graded yellow lines. The instrument is pressed against the nose and the yellow colour of the blanched skin is matched with the graded yellow lines and bilirubin level is assigned.

Transcutaneous bilirubinometer: This is hand held, portable and rechargeable but expensive and sophisticated. When pressure is applied to the photoprobe, a xenon tube generates a strobe light, and this light passes through the subcutaneous

tissue. The reflected light returns through the second fiber optic bundle to the spectrophotometric module. The intensity of the yellow color in this light, after correcting for the hemoglobin, is measured and instantly displayed in arbitrary units.

Any of the following features characterizes pathological jaundice

1. Clinical jaundice appearing in the first 24 hours or greater than 14 days of life.
2. Increases in the level of total bilirubin by more than 8.5 µmol/l (0.5 mg/dL) per hour or (85 µmol/l) 5 mg/dL per 24 hours.
3. Total bilirubin more than 331.5 µmol/l (19.5 mg/dL) (hyperbilirubinemia).
4. Direct bilirubin more than 34 µmol/l (2.0 mg/dL).

The aim of clinical assessment is to distinguish physiological from pathological jaundice. The signs which help to differentiate pathological jaundice of neonates from physiological jaundice of neonates are the presence of intrauterine growth restriction, stigma of intrauterine infections (e.g. cataracts, small head, and enlargement of the liver and spleen), cephalohematoma, bruising, signs of bleeding in the brain's ventricles. History of illness is noteworthy. Family history of jaundice and anemia, family history of neonatal or early infant death due to liver disease, maternal illness suggestive of viral infection (fever, rash or lymphadenopathy), maternal drugs (e.g. sulphonamides, anti-malarials causing red blood cell destruction in G6PD deficiency) are suggestive of pathological jaundice in neonates[12-17].

Treatment

The bilirubin levels for initiative of phototherapy varies depends on the age and health status of the newborn. However, any newborn with a total serum bilirubin greater than 359 µmol/l (21 mg/dL) should receive phototherapy. PhenobarbitalPhenobarbital is used to treat neonatal jaundice by increasing liver metabolism and thus lowering bilirubin levels. In the 1950s, phototherapy was discovered, and became the standard treatment, however phenobarbital therapy is still in common use when access to phototherapy is inconvenient or impractical. One striking benefit of successful phenobarbital therapy is the rapid onset of recovery.[16]

Phototherapy

Fig No. 1 Newborn infant undergoing (white light) phototherapy to treat neonatal jaundice

Infants with neonatal jaundice are treated with colored light called phototherapy. Physicians randomly assigned 66 infants 35 weeks of gestation to receive phototherapy. After 15±5 the levels of bilirubin, a yellowish bile pigment that in excessive amounts causes jaundice, were decreased down to 0.27±0.25 mg/dl/h in the blue light. This suggests that blue light therapy helps reduce high bilirubin levels that cause neonatal jaundice.

Exposing infants to high levels of colored light changes trans-bilirubin to the more water-soluble cis-form which is excreted in the bile. Scientists studied 616 capillary blood samples from jaundiced newborn infants. These samples were randomly divided into three groups. One group contained 133 samples and would receive phototherapy with blue light. Another group contained 202 samples would receive room light, or white light. The final group contained 215 samples, and were left in a dark room. The total bilirubin levels were checked at 0, 2, 4, 6, 24, and 48 hours. There was a significant decrease in bilirubin in the first group exposed to phototherapy after two hours, but no change occurred in the white light and dark room group. After 6 hours, there was a significant change in bilirubin level in the white light group but not the dark room group. It took 48 hours to record a change in the dark room group's bilirubin level. Phototherapy is the most effective way of breaking down a neonate's bilirubin. Phototherapy works through a process of isomerization that changes trans-bilirubin into the water-soluble cis-bilirubin isomer. In phototherapy, blue light is typically used because it is more effective at breaking down bilirubin (Amato, Inaebnit, 1991). Two matched groups of newborn infants with jaundice were exposed to intensive green or blue light phototherapy. The efficiency of the treatment was measured by the rate of decline of serum bilirubin, which in excessive amounts causes jaundice, concentration after 6, 12 and 24 hours of light exposure. A more rapid response was obtained using the blue lamps than the green lamps. However, a shorter phototherapy recovery period was noticed in babies exposed to the green lamps .Green light is not commonly used because exposure time must be longer to see dramatic results Ultraviolet light therapy may increase the risk of skin moles, in childhood. While an increased number of moles is related to an increased risk of skin cancer, it is not ultraviolet light that is used for treating neonatal jaundice. Rather, it is simply a specific frequency of blue light that does not carry these risks. Increased feedings help move bilirubin through the neonate's metabolic system. The light can be applied with overhead lamps, which means that the baby's eyes need to be covered, or with a device called a Biliblanket, which sits under the baby's clothing close to its skin.

Exchange transfusions

Much like with phototherapy the level at which exchange transfusion should occur depends on the health status and age of the newborn. It should however be used for any newborn with a total serum bilirubin of greater than 428 µmol/l (25 mg/dL).[15]

Treatment Options for Jaundice

The treatment options for jaundice include phototherapy further subdivided to conventional, intensive and exchange transfusion, and pharmacological treatment subdivided to phenobarbitone, intravenous immunoglobulins (IVIG), metalloporphyrins and follow up remedies.

Phototherapy

Hyperbilirubinemia can be treated easily without or with a minimal adverse effect with phototherapy. The efficacy of phototherapy depends on surface area exposed to phototherapy: Double surface phototherapy may be more effective than single surface phototherapy Spectrum of light source: Special blue tubes with the mark F20T12/BB should be used rather than F20T12/B lights and Irradiance or energy output may be increased in a phototherapy unit by lowering the distance of the neonate to within 15–20 cm Continuous phototherapy is better than intermittent phototherapy. Phototherapy should not be interrupted except during breast-feeding or nappy change. [17-21]

Conventional Phototherapy

One can use conventional or fiber-optic phototherapy units provided jaundice is non-hemolytic or its progression is slow.

Intensive Phototherapy

In the circumstances including hemolytic jaundice, rapidly increasing bilirubin, or ineffectiveness of a conventional unit, using of intensive phototherapy is warranted. Placing the baby on the bili-blanket and using additional overhead phototherapy units contain blue lights and then lowering the phototherapy units to within a distance of 15–20 cm are two significant remedies

Exchange Transfusion

Through exchange transfusion bilirubin and hemolytic antibodies are removed.

a. Rh Isoimmunization: Always, Blood using for exchange transfusion should be negative Rh isoimmunization, negative for Rh factor. O (Rh) negative packed cells suspended in AB plasma will be the best choice. O (Rh) negative whole blood or cross-matched baby's blood group (Rh negative) may also be used in an emergency.
b. ABO Incompatibility: Only O-blood group should be used for exchange transfusion in newborns with ABO incompatibility. The best choice would be O group (Rh compatible) packed cells which are suspended in O group/AB plasma whole blood (Rh compatible with baby).
c. Other situations: In case of the Cross-matched with baby's blood group blood volume used or double volume exchange should be kept in mind.
    1. Blood Volume Used: Partial exchange is done at birth in Rh hemolytic disease: 50-ml/kg of packed cells.
    2. Double Volume Exchange: 2 × (80–100 ml/kg) &times birth weight (kg) [22-25]

Pharmacological Treatment

Pharmacological treatment of neonatal jaundice can further be categorized into different subheadings such as phenobarbitone, Intravenous immunoglobulins and Metalloporphyrins etc.

Phenobarbitone

Bilirubin processing including hepatic uptake, conjugation and its excretion are ameliorated by this agent thus helps in decreasing level of bilirubin. However the effect of phenobarbitone is not rapid and takes time to show. When used for 3–5 days in a dose of 5 mg/kg after birth prophylactically, it has shown to be effective in babies with hemolytic disease, extravasated blood and in pre-term without any significant side effects. There is a huge literature documenting efficacy and mechanism of action and complications of treatment for Phenobarbital.

Intravenous Immunoglobulin (IVIG)

High dose IVIG (0.5–1 gr/kg) has shown to be effective in decreasing the needs of exchange transfusion and phototherapy in babies with Rh hemolytic disease

Metalloporphyrins

These compounds are still experimental but showing promising results in various hemolytic and non-hemolytic settings without significant side effects.

Follow-up

Babies having roughly 20 mg/dl serum bilirubin and that requiring exchange transfusion should be kept under follow-up in the high risk clinic for neuro developmental outcome Hearing assessment (Brainstem Evoked Response Audiometry (BAER)) should be done at 3 months of corrected age[25-29]..

Empirical Results

Descriptive analysis 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	Frequey	Percent	Cumulative Percent
Sex	Male	107	46.1	46.1
	Female	125	53.9	100.0
Survival	Dead	4	1.72	1.72
	Alive	228	98.28	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
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 125(53.9%) were female, 4 (1.72%) 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	1	106	107
	Male	3	122	125
Total		4	228	232

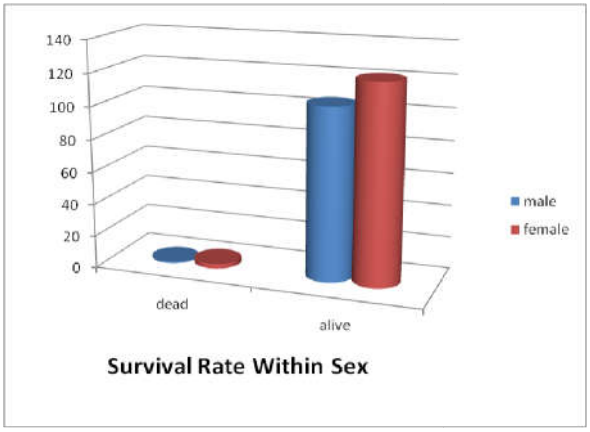
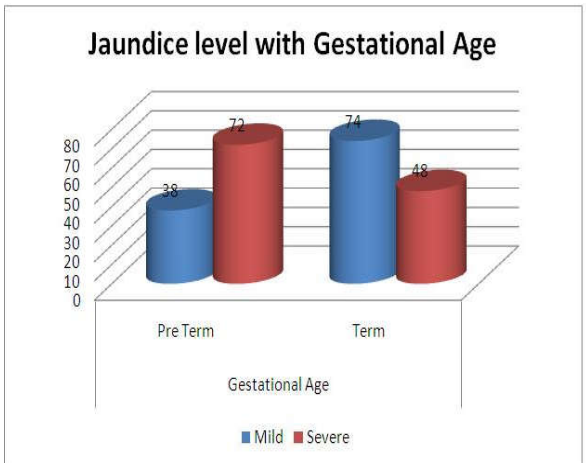


Table 1c Cross tabulation of Jaundice Level and Gestational Age

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



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
b. estimates changed by less than .001.

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$^{\beta i}$, 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. 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.

Recent Advances

Hour-specific bilirubin nomograms have been constructed based on routine pre-discharge bilirubin assessment. These charts are useful in predicting hyperbilirubinemia based on a bilirubin level done after 24 h of age. However the mentioned charts are prepared based on infants born in the West and probable need to be assessed and validated on Asian infants or on regional basis before they can be used for routine newborn care.

Complications

Prolonged hyperbilirubinemia (severe jaundice) can result in chronic bilirubin encephalopathy (kernicterus). Quick and accurate treatment of neonatal jaundice helps to reduce the risk of neonates developing kernicterus. Infants with kernicterus may have a fever or seizures. High pitched crying is an effect of kernicterus. Scientists used a computer to record and measure cranial nerves 8, 9 and 12 in 50 infants who were divided into two groups equally depending upon bilirubin concentrations. Of the 50 infants, 43 had tracings of high pitched crying. Exchange transfusions performed to lower high bilirubin levels are an aggressive treatment.

CONCLUSION

Medical scientists should search for new treatments and preventive measures having no side effects and capable of recovering babies more speedily. Partners should screen their ABO blood groups as well as Rh factor before marriage. Consanguineous marriages should be avoided. Hyperbilirubinemia is more severe in newborns. Therefore precautionary measure should be adopted by both parents, and clinicians to diagnose and treat the disease properly. Government and public health organizations should arrange seminars, workshops and trainings for mothers regarding neonatal jaundice. This paper analyzed risk factors generated from the case notes of neonates that had neonatal jaundice in the paediatrics department, Niloufer Hospital, Lakdikapul, Hyderabad, Telangana, India between 2012-2015 to formulate a model that can be used to predict the probability of neonatal jaundice using those predictor variables.

Table 2b

Variables in the Equation

		B	S.E.	Wald	df	Sig.	Exp(B)	95.0% C.I.for EXP(B) Lower	Upper	Sig. Decision
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
	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, Gestational age and Rhesus factor are statistically significant factors associated with neonatal jaundice.

This paper work was able to establish that there exist a significant relationship between neonates' gestational age, place of delivery,, 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:

1) 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.
2) 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.
3) Government should provide modern health facilities in all our public hospital.

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