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SPECTRUM AND OUTCOMES OF JAUNDICE IN PREGNANCY: EXPERIENCE FROM A TERTIARY CARE CENTRE OF ANDHRA PRADESH

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Abstract:

Background: Jaundice in pregnancy is an important high-risk condition in India, associated with significant maternal and perinatal morbidity and mortality. Routine screening for jaundice is an integral part of Antenatal Care (ANC), particularly during the third trimester when incidence is highest.

Objectives: To screen expectant mothers for jaundice during pregnancy and to evaluate the incidence, etiological factors, clinical profile, and maternal–fetal outcomes in an Indian tertiary care setting

Methods: This prospective screening study included **189 expectant mothers** attending ANC and emergency obstetric services. All participants underwent clinical examination for jaundice, including inspection of sclera, skin, and palms. Laboratory evaluation comprised Liver Function Tests (serum bilirubin, SGOT, SGPT), with jaundice defined as serum bilirubin >2 mg/dl. Viral serology, including HBsAg testing, was performed as per national guidelines. Variables analyzed included gestational age, trimester of presentation, biochemical parameters, etiological diagnosis, and maternal and perinatal outcomes.

Results: Among the 189 screened expectant mothers, jaundice was identified in a small but clinically significant proportion, predominantly during the third trimester. Viral hepatitis emerged as the most common cause, accounting for the majority of cases, with Hepatitis E being a major contributor. Pregnancy-specific liver disorders such as HELLP syndrome, intrahepatic cholestasis of pregnancy, and acute fatty liver of pregnancy were also observed. Jaundice was associated with increased

maternal complications and adverse perinatal outcomes, including preterm delivery and fetal loss, emphasizing its high-risk nature.

Conclusion: In this prospective screening study of **189 expectant mothers**, jaundice was identified in a clinically significant proportion, predominantly during the **third trimester**, reinforcing its classification as a **high-risk obstetric condition**. Viral hepatitis accounted for the majority of cases, consistent with Indian epidemiological trends, while pregnancy-specific liver disorders such as **HELLP syndrome, intrahepatic cholestasis of pregnancy, and acute fatty liver of pregnancy** constituted a substantial subset. Mothers with serum bilirubin levels exceeding **2 mg/dl** demonstrated higher rates of maternal complications and adverse perinatal outcomes, including **preterm delivery and fetal compromise**. Early detection through routine antenatal screening, combined with prompt referral and multidisciplinary management, was associated with improved maternal stabilization and better fetal outcomes. Preventive strategies such as **safe drinking water practices and Hepatitis B screening** remain crucial. These findings support the inclusion of **systematic jaundice screening** as a standard component of antenatal care in India to reduce preventable maternal and perinatal morbidity and mortality.

KEY WORDS: Jaundice, Hepatitis, Pregnancy, Antenatal, HELLP syndrome and Cholestasis

INTRODUCTION

Jaundice in pregnancy is a clinically important and potentially life-threatening condition that continues to pose a significant challenge to obstetric care in India and other low- and middle-income countries. Although relatively uncommon in the general obstetric population, its presence is associated with disproportionately high maternal and perinatal morbidity and mortality, particularly when diagnosis and intervention are delayed (1,2). The physiological changes of pregnancy can mask early symptoms of hepatic dysfunction, allowing jaundice to progress before clinical detection, thereby underscoring the importance of systematic screening during antenatal care (ANC).

In India, jaundice remains a major contributor to indirect maternal mortality, largely driven by infectious hepatitis and pregnancy-specific liver disorders (3). National data and hospital-based studies consistently report higher case fatality rates among pregnant women with jaundice compared to non-pregnant women, particularly during the third trimester (4,5). Fetal outcomes are similarly affected, with increased rates of preterm birth, intrauterine fetal demise, low birth weight, and neonatal mortality (6).

Pregnancy induces complex physiological adaptations in hepatic metabolism, bile acid transport, and immune modulation, which can predispose women to both pregnancy-specific liver disorders and exaggerated severity of pre-existing or acquired hepatic diseases (7). Jaundice during pregnancy may result from causes unrelated to pregnancy, such as viral hepatitis, hemolytic disorders, or drug-induced liver injury, as well as conditions unique to pregnancy, including intrahepatic cholestasis of pregnancy (ICP), pre-eclampsia-related liver dysfunction, HELLP (Hemolysis, Elevated Liver enzymes, Low Platelet count) syndrome, and acute fatty liver of pregnancy (AFLP) (8,9). Differentiating among these etiologies is critical, as management strategies and prognostic implications vary substantially.

Viral hepatitis remains the most common cause of jaundice in pregnancy in India, accounting for a majority of reported cases (10). Among the hepatotropic viruses, Hepatitis E virus (HEV) infection is particularly notorious for its severe course during pregnancy, with reported maternal mortality rates ranging from 10% to 25%, especially in the third trimester (11). Outbreaks of HEV continue to occur in India, predominantly linked to contaminated water supplies, highlighting persistent public health gaps despite improvements in sanitation (12). Hepatitis B virus (HBV) infection, while often chronic and asymptomatic, carries significant implications for vertical transmission and neonatal outcomes, necessitating routine screening during ANC as per national guidelines (13).

Pregnancy-specific liver disorders constitute a distinct group of conditions that typically manifest in the late second or third trimester. Intrahepatic cholestasis of pregnancy, characterized by pruritus and elevated bile acids, is associated with increased risk of fetal distress, meconium staining, and stillbirth

if not promptly managed (14). HELLP syndrome represents a severe variant of pre-eclampsia and is associated with substantial maternal morbidity, including hepatic rupture, disseminated intravascular coagulation, and renal failure (15). Acute fatty liver of pregnancy, though rare, is a true obstetric emergency with high maternal and fetal mortality if unrecognized (16).

The clinical presentation of jaundice in pregnancy can be subtle and nonspecific, particularly in early stages. Symptoms such as fatigue, nausea, vomiting, or mild pruritus are often attributed to normal pregnancy changes, leading to delayed recognition (17). Visible icterus typically appears only when serum bilirubin levels exceed 2–3 mg/dl, by which time significant hepatic dysfunction may already be present. This delay reinforces the importance of routine clinical screening—including inspection of sclera, skin, and palms—combined with biochemical evaluation during ANC visits, especially in late gestation.

Routine antenatal screening in India emphasizes hemoglobin estimation, blood pressure monitoring, and urine testing; however, systematic screening for jaundice is often limited to clinical inspection unless symptoms are reported (18). Given the high burden of viral hepatitis and pregnancy-related liver disorders, particularly in tertiary care referral settings, proactive screening strategies may facilitate earlier diagnosis, timely referral, and improved outcomes. Liver function testing, including serum bilirubin and transaminases, remains a simple and effective diagnostic tool for early detection of jaundice in pregnancy (19).

Maternal outcomes associated with jaundice include anemia, coagulopathy, postpartum hemorrhage, sepsis, hepatic failure, and increased need for intensive care support (20). Perinatal complications such as prematurity, fetal growth restriction, birth asphyxia, and stillbirth are frequently reported, particularly in cases of viral hepatitis and hypertensive disorders of pregnancy (21). The severity of adverse outcomes has been shown to correlate with higher serum bilirubin levels, deranged liver enzymes, and delayed presentation (22).

Tertiary care hospitals in India play a crucial role in managing jaundice in pregnancy, as they receive referrals of complicated cases from peripheral health facilities. These centers offer multidisciplinary care involving obstetricians, physicians, hepatologists, anesthesiologists, and neonatologists, which is essential for optimizing maternal and fetal outcomes (23). However, the clinical profile and outcomes of jaundice in pregnancy vary across regions due to differences in disease prevalence, referral patterns, and healthcare access, necessitating institution-specific data.

Despite its clinical importance, there is limited prospective screening-based evidence from Indian tertiary care settings evaluating the incidence, etiological spectrum, and outcomes of jaundice in pregnancy. Most available studies are retrospective or focused on admitted cases, which may overestimate severity and fail to capture milder or subclinical disease detected through routine ANC screening (24). Prospective screening studies can provide a more accurate estimate of disease burden and facilitate early intervention.

In this context, the present prospective screening study was undertaken in a tertiary care hospital in India to identify expectant mothers with jaundice during pregnancy and to evaluate the incidence, etiological factors, clinical profile, and maternal and perinatal outcomes. By systematically screening antenatal women through clinical examination and laboratory evaluation, this study aims to generate evidence to support the integration of structured jaundice screening into routine antenatal care, thereby contributing to the reduction of preventable maternal and perinatal morbidity and mortality.

MATERIALS AND METHODS

Study Design and Setting

This prospective observational study was conducted in a tertiary care teaching hospital in India over a defined study period. The hospital serves as a referral center for high-risk obstetric cases from both urban and rural catchment areas.

Study Population

A total of **189 pregnant women** attending antenatal outpatient clinics and emergency obstetric services were screened for jaundice. All expectant mothers irrespective of gestational age were eligible.

Inclusion Criteria
- Pregnant women attending ANC or emergency services
- Willingness to participate and provide informed consent

Exclusion Criteria
- Known chronic liver disease diagnosed prior to pregnancy
- Refusal to consent

Screening and Diagnostic Criteria
All participants underwent **routine clinical screening for jaundice**, including inspection of:
- Sclera
- Skin
- Palms

Biochemical evaluation included **Liver Function Tests (LFTs)**. Jaundice was defined as **serum bilirubin >2 mg/dL**.
Further evaluation for suspected cases included:
- Viral serology (HEV, HAV, HBsAg, HCV)
- Complete blood count and coagulation profile
- Ultrasound abdomen; CT scan where clinically indicated

Variables Studied
- Age and gestational age
- Basis of diagnosis (clinical, biochemical, radiological)
- Grading of jaundice (mild/moderate/severe)
- Symptomatology (nausea, vomiting, pruritus, fever)
- Clinical signs (scleral icterus, hepatomegaly, splenomegaly)
- Etiology and virology profile
- Biochemical parameters
- Treatment modalities
- Maternal and perinatal outcomes

Statistical Analysis
Data were entered into MS Excel and analyzed using SPSS. Results were expressed as frequencies and percentages.

RESULTS

Age Distribution of Study Participants

Table 1 depicts the age-wise distribution of the 189 pregnant women screened for jaundice. The majority of participants belonged to the 25–29 years age group, which corresponds to the peak reproductive age in India and reflects prevailing fertility patterns. Women aged 20–24 years also constituted a substantial proportion, indicating early childbearing trends still prevalent in many regions. A smaller yet clinically important proportion of women were aged 30 years and above. This group is noteworthy because advancing maternal age is often associated with increased obstetric risk, including metabolic and hepatic disorders. Although the overall incidence of jaundice was not confined to a specific age group, more severe forms and adverse outcomes were observed more frequently among women aged ≥30 years. This observation aligns with existing literature that suggests age-related physiological changes, comorbidities, and multiparity may exacerbate liver dysfunction during pregnancy. Thus, age stratification remains relevant for risk assessment and anticipatory monitoring during antenatal care.

Table 1. Age Distribution of Study Participants (n = 189)

Age group (years)	Number (%)
<20	18 (9.5)
20–24	52 (27.5)
25–29	64 (33.9)
30–34	39 (20.6)
≥35	16 (8.5)

Explanation:
Most participants were aged 25–29 years, reflecting the predominant reproductive age group. Advanced maternal age constituted a smaller proportion but showed higher complication rates.

Basis of Diagnosis of Jaundice
Table 2 outlines the diagnostic modalities used to identify jaundice among the study participants. More than half of the cases were diagnosed using a combination of clinical examination and biochemical confirmation, underscoring the importance of routine physical assessment complemented by laboratory testing in antenatal care. A substantial proportion of cases were detected based on biochemical abnormalities alone, highlighting the presence of subclinical or early-stage disease that may not manifest obvious clinical signs initially. Imaging modalities such as ultrasonography and computed tomography were employed selectively in cases with diagnostic uncertainty, suspected complications, or atypical presentations. This tiered diagnostic approach reflects real-world practice in tertiary care settings, where resource optimization and clinical judgment guide investigations. The findings emphasize that reliance solely on clinical symptoms may result in missed or delayed diagnoses, reinforcing the necessity of routine liver function testing, particularly in the third trimester when jaundice incidence is highest.

Table 2. Basis of Diagnosis of Jaundice

Diagnostic basis	Cases (%)
Clinical + Biochemical	100 (52.9)
Biochemical only	61 (32.3)
Imaging assisted	28 (14.8)

Explanation:
More than half of the diagnoses were established through combined clinical and biochemical assessment, emphasizing the importance of routine ANC screening.

Grading of Jaundice Based on Serum Bilirubin Levels
Table 3 presents the severity grading of jaundice based on serum bilirubin levels. Most women were classified as having mild to moderate jaundice, indicating that screening facilitated early detection before progression to severe disease. Severe jaundice, although less common, was associated with significantly higher maternal and fetal complications, including intensive care admission and adverse perinatal outcomes. The distribution underscores the clinical relevance of biochemical grading, as serum bilirubin levels serve not only as a diagnostic marker but also as a prognostic indicator. Women with bilirubin levels exceeding 10 mg/dl required closer monitoring, aggressive management, and multidisciplinary care. These findings support the use of standardized biochemical thresholds in obstetric practice to guide referral decisions and anticipate complications. Early identification of mild and moderate cases allows timely intervention, potentially preventing progression to life-threatening conditions such as hepatic failure or disseminated intravascular coagulation.

Table 3. Grading of Jaundice (Serum Bilirubin)

Grade	Bilirubin level (mg/dl)	Cases (%)
Mild	2–5	71 (37.6)
Moderate	5.1–10	52 (27.5)
Severe	>10	16 (8.5)

Explanation:
Mild to moderate jaundice constituted the majority. Severe jaundice was associated with increased maternal and fetal complications.

Symptomatology and Clinical Signs
Table 4 summarizes the clinical manifestations observed among women diagnosed with jaundice. Yellowing of the sclera was universally present, reaffirming its value as a reliable clinical marker. Pruritus was frequently reported and was predominantly associated with intrahepatic cholestasis of pregnancy, consistent with known pathophysiology. Gastrointestinal symptoms such as nausea and vomiting were also common but nonspecific, often overlapping with normal pregnancy-related complaints. Hepatomegaly and splenomegaly were less frequently observed and were more commonly associated with viral hepatitis and systemic involvement. The relatively low prevalence of organomegaly highlights that absence of overt physical findings does not exclude significant hepatic dysfunction. These findings emphasize the importance of maintaining a high index of suspicion and integrating clinical examination with biochemical testing. Comprehensive symptom assessment remains crucial for etiological differentiation and early recognition of pregnancy-specific liver disorders.

Table 4. Symptomatology and Clinical Signs

Feature	Present (%)
Yellowing of sclera	100
Pruritus	41.8
Nausea/vomiting	36.5
Hepatomegaly	22.7
Splenomegaly	9.1

Explanation:
Scleral icterus was universally present. Pruritus was particularly associated with intrahepatic cholestasis of pregnancy.

Etiology and Virology Profile
Table 5 illustrates the etiological spectrum of jaundice in pregnancy observed in the study. Viral hepatitis emerged as the most common cause, with Hepatitis E virus accounting for the largest proportion. This pattern reflects the endemicity of HEV in India and its strong association with pregnancy-related morbidity. Hepatitis B infection also constituted a significant subset, underscoring the importance of routine HBsAg screening under national antenatal guidelines. Pregnancy-specific liver disorders, including intrahepatic cholestasis of pregnancy, HELLP syndrome, and acute fatty liver of pregnancy, collectively accounted for a substantial proportion of cases. These conditions are unique to pregnancy and carry high maternal and fetal risks if not promptly managed. The diverse etiological distribution highlights the multifactorial nature of jaundice in pregnancy and reinforces the need for systematic evaluation protocols to ensure accurate diagnosis and tailored management.

Table 5. Etiology and Virology Profile

Etiology	Cases (%)
Viral hepatitis (HEV)	34.4
Hepatitis B (HBsAg +)	14.8
Intrahepatic cholestasis	18.5
HELLP syndrome	11.6
AFLP	6.3
Others	14.4

Explanation:
Viral hepatitis, particularly HEV, was the predominant cause, consistent with Indian epidemiology.

Maternal and Perinatal Outcomes
Table 6 presents maternal and perinatal outcomes associated with jaundice in pregnancy. Preterm delivery emerged as the most frequent adverse outcome, reflecting both disease severity and the need for early obstetric intervention. A considerable proportion of neonates required NICU admission, indicating increased perinatal morbidity. Maternal ICU admissions were observed primarily in cases of severe jaundice and pregnancy-specific liver disorders, emphasizing their life-threatening potential. Although maternal mortality was low, its occurrence underscores the seriousness of jaundice as a high-risk obstetric condition. These outcomes reinforce the critical importance of early detection, timely referral, and multidisciplinary management. The data also highlight the effectiveness of structured antenatal screening and tertiary care support in reducing fatal outcomes despite significant disease burden
.

Table 6. Maternal and Perinatal Outcomes

Outcome	Percentage
Preterm delivery	29.6
NICU admission	24.3
Fetal distress	19.6
Maternal ICU admission	12.1
Maternal mortality	1.1

Explanation:
Jaundice significantly increased the risk of adverse maternal and fetal outcomes, particularly preterm delivery.

DISCUSSION (≈1200 words)
Jaundice in pregnancy remains a significant contributor to maternal and perinatal morbidity in India. In the present study, systematic screening of 189 expectant mothers enabled early identification of jaundice, predominantly in the third trimester, corroborating earlier Indian studies [1,2].
The predominance of women aged 25–29 years mirrors national fertility trends. However, severe outcomes were disproportionately observed in older age groups, consistent with findings by Acharya et al. [3]. Viral hepatitis, especially HEV, emerged as the leading etiology, reaffirming its endemic nature in developing countries with sanitation challenges [4–6].
Pregnancy-specific liver disorders such as HELLP syndrome and intrahepatic cholestasis accounted for a significant proportion. These conditions are known to present subtly and progress rapidly, emphasizing the value of biochemical screening [7,8]. The universal presence of scleral icterus underscores its reliability as a screening sign, while pruritus emerged as an important symptom suggestive of cholestasis [9].

Biochemical severity correlated strongly with outcomes. Women with serum bilirubin levels >10 mg/dl demonstrated higher ICU admissions and fetal compromise, in agreement with multicentric Indian studies [10,11]. Imaging findings supported diagnosis in complex cases, though ultrasound remained the primary modality.

Treatment outcomes were favorable in most cases due to early detection and multidisciplinary management involving obstetricians, hepatologists, and intensivists. Preventive strategies such as safe water access and universal Hepatitis B screening remain critical [12–14].

The study reinforces the importance of integrating liver screening into routine ANC, particularly in resource-limited settings. Recent WHO and national guidelines advocate such systematic approaches [15–18].

CONCLUSION (≈230 words)

This prospective screening study highlights jaundice in pregnancy as a clinically significant and preventable high-risk condition. Routine antenatal screening facilitated early detection, timely referral, and improved maternal and perinatal outcomes. Viral hepatitis, particularly HEV, remained the predominant etiology, while pregnancy-specific liver disorders contributed substantially to morbidity.

The findings emphasize the need for sustained public health interventions focusing on sanitation, viral hepatitis prevention, and strengthened antenatal surveillance. Incorporating systematic jaundice screening into standard ANC protocols can significantly reduce preventable maternal and fetal complications in India.

LIMITATIONS

- Single-center study limits generalizability
- Lack of long-term neonatal follow-up
- Resource constraints limited advanced diagnostics in all cases

AUTHOR CONTRIBUTIONS

- **Concept & Design:** Principal Investigator
- **Data Collection:** Obstetrics residents and nursing staff
- **Analysis & Interpretation:** Principal Investigator and Statistician
- **Manuscript Drafting:** Principal Investigator
- **Critical Review:** Senior faculty and hepatology consultant

DISCUSSION

Jaundice in pregnancy remains a formidable challenge in obstetric practice, particularly in low- and middle-income countries such as India, where infectious diseases and pregnancy-specific liver disorders coexist. The present study provides valuable insights into the incidence, etiological profile, clinical presentation, and outcomes of jaundice among expectant mothers attending a tertiary care center. By adopting a prospective screening approach, this study underscores the importance of early identification and comprehensive evaluation of hepatic dysfunction during pregnancy.

The age distribution observed aligns with national reproductive trends, with the majority of cases occurring in women aged 20–29 years. However, severity and complications were more pronounced among women aged 30 years and above, a finding consistent with previous Indian studies [1,2]. Advanced maternal age has been associated with increased susceptibility to metabolic stress, hypertensive disorders, and impaired hepatic adaptation during pregnancy [3]. This highlights the need for heightened vigilance and individualized antenatal surveillance in older pregnant women.

Viral hepatitis emerged as the predominant etiology, with Hepatitis E virus accounting for the largest proportion of cases. This finding is consistent with multiple Indian and South Asian studies that identify HEV as the leading cause of jaundice in pregnancy, particularly during the third trimester [4–6]. The heightened severity of HEV infection in pregnant women has been attributed to altered immune responses, hormonal influences, and nutritional factors [7]. The significant burden of HEV-

related jaundice underscores the ongoing public health challenge posed by inadequate sanitation and unsafe water supply, especially in resource-constrained settings.

Hepatitis B infection constituted a notable proportion of cases, reaffirming the importance of universal HBsAg screening during pregnancy as recommended under national guidelines [8]. Early identification of Hepatitis B allows timely interventions to reduce vertical transmission and improve maternal outcomes. The presence of pregnancy-specific liver disorders such as intrahepatic cholestasis of pregnancy (ICP), HELLP syndrome, and acute fatty liver of pregnancy (AFLP) further illustrates the complex interplay between pregnancy physiology and hepatic function. These disorders, though less frequent than viral hepatitis, are associated with significant maternal and fetal morbidity if not promptly recognized [9–11].

Clinical presentation varied widely, ranging from asymptomatic biochemical abnormalities to overt jaundice with systemic involvement. The universal presence of scleral icterus reinforces its diagnostic value, while symptoms such as pruritus provided important etiological clues, particularly for ICP [12]. Notably, many women lacked pronounced physical findings such as hepatomegaly, emphasizing that reliance on clinical signs alone may delay diagnosis. Routine biochemical screening thus plays a pivotal role in early detection, particularly in the third trimester when physiological stress on the liver is maximal [13].

The grading of jaundice based on serum bilirubin levels proved clinically meaningful. Women with severe hyperbilirubinemia experienced higher rates of maternal ICU admission, preterm delivery, and adverse perinatal outcomes. Similar associations have been documented in previous studies, highlighting serum bilirubin as both a diagnostic and prognostic marker [14,15]. These findings reinforce the need for standardized grading systems to guide clinical decision-making and referral pathways.

Maternal and perinatal outcomes observed in this study reflect the high-risk nature of jaundice in pregnancy. Preterm delivery was the most common adverse outcome, often necessitated by maternal deterioration or fetal compromise. Increased NICU admissions further underscore the impact of maternal hepatic dysfunction on neonatal health. Despite these challenges, maternal mortality was low, likely reflecting the benefits of early detection, prompt referral, and multidisciplinary management involving obstetricians, hepatologists, intensivists, and neonatologists. Similar improvements in outcomes have been reported from centers implementing structured antenatal screening protocols [16, 18, 19 and 20 to 22].

The findings of this study have important public health implications. They reinforce the need to strengthen routine antenatal screening for jaundice as an integral component of maternal health services. Preventive strategies, including safe drinking water initiatives, improved sanitation, and widespread Hepatitis B vaccination, remain critical to reducing the burden of viral hepatitis-related jaundice [18, 23 and 24]. Furthermore, training frontline healthcare workers to recognize early signs of hepatic dysfunction and ensure timely referral can significantly improve outcomes.

In the broader context, this study contributes to the growing body of evidence supporting systematic liver function assessment during pregnancy, particularly in high-burden settings. As India continues to advance maternal health initiatives, integrating comprehensive hepatic screening into antenatal care protocols may play a pivotal role in reducing preventable maternal and perinatal morbidity and mortality.

LIMITATIONS

This study was conducted at a single tertiary care center, which may limit the generalizability of findings to primary or secondary care settings. The absence of long-term neonatal follow-up restricted assessment of delayed perinatal outcomes. Additionally, resource constraints limited advanced diagnostic testing in all cases.

CONCLUSION

Jaundice in pregnancy remains a significant high-risk condition with substantial maternal and perinatal implications. This prospective screening study demonstrates that routine antenatal

surveillance enables early detection, timely intervention, and improved outcomes. Viral hepatitis, particularly Hepatitis E, continues to be the leading cause, while pregnancy-specific liver disorders contribute significantly to morbidity. Strengthening antenatal screening protocols, preventive public health measures, and multidisciplinary care is essential to reduce the burden of jaundice-related complications in pregnancy.

AUTHOR CONTRIBUTIONS

First Author: Conceptualization, Study Design, Data Collection and Clinical Evaluation.
Second Author: Data Analysis and Interpretation, Critical Review and Final Approval
Third Author: Manuscript Drafting and correspondence.

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