

Role of Risk-Based Approach in the Prevention of Vertical Transmission of Neonatal Sepsis.

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Summary

Aims and Objectives: Vertical transmission of infections remains a common cause of neonatal morbidity and mortality worldwide. We studied the risk-based approach in preventing the vertical transmission of neonatal sepsis.

Patients and methods: A prospective case control study of 154 pregnant women with risk factors for vertical transmission of infections (subjects) and 154 pregnant women without the risk factors (control) at University of Ilorin Teaching Hospital, Ilorin from 1st July to 31st December, 2010. After counseling and consent taking, all participants had active management of labour and all subjects had parenteral intrapartum antibiotic prophylaxis with Ampicillin. There was postnatal evaluation of all babies for signs of neonatal sepsis followed by blood culture and treatment of culture positive babies. The outcome measures were signs and symptoms of neonatal sepsis, neonatal positive blood culture and maternal postpartum morbidity.

Results: Neonatal sepsis occurred in 16 babies (subjects=11, control=5); three babies had Early Onset Group B Streptococcal Disease (EOGBSD) (subjects=2, control=1; $P=0.501$) while 13 had non Group B Streptococcal (GBS) infections (subjects=9, control=4; $P=0.113$); onset of signs and symptoms was <24hrs in all cases, incidence of EOGBSD were 12.9/1000 (subjects) and 6.5/1000 (controls). Subjects whose babies had sepsis had multiple risk factors; one dose of antibiotics and antibiotics to delivery interval <2hours. There was no sepsis in babies of mothers who had adequate antibiotic prophylaxis. There was no maternal or neonatal death but 17.5% of subjects had maternal postpartum morbidities.

Conclusion: The risk-based approach is a practicable alternative in preventing vertical transmission of neonatal sepsis if antibiotic prophylaxis is adequate before delivery.

Keywords: Risk-based approach, Vertical transmission, Prevention, Neonatal Sepsis

Introduction

Neonatal sepsis remains a major cause of neonatal morbidity and mortality in developing countries. It is divided into early onset sepsis which is vertically

transmitted from the mother, occurs in first 7 days of life and usually runs a fulminant course while late onset sepsis occurs afterwards. *Streptococcus agalactiae* also called Group B Streptococcus (GBS) has become a major

vertically transmitted infection of concern worldwide but reports from developing countries are few.

GBS is not a sexually transmitted infection, newborn infection results from ascending infection into the uterus from vagina, foetal aspiration of infected amniotic fluid or during passage through the birth canal¹. Globally, its prevalence ranges from 10-32%¹⁻⁵ with reports of 32% in Lagos⁴ and 11.3% in Ile-Ife⁵, both in Nigeria.

The Culture based approach to GBS prevention involves maternal antenatal screening of both vagina and rectum for GBS late in pregnancy (35-37 weeks) while the risk based approach emphasizes prophylaxis when certain risk factors are present. These risk factors include preterm delivery (<37weeks), premature rupture of membranes (PROM), PROM of ≥ 18 hours duration, intra-partum maternal fever $\geq 38.0^{\circ}\text{C}$ ($\geq 100.4^{\circ}\text{F}$), GBS bacteriuria during current pregnancy or mothers with previous GBS infected babies¹. Though the culture-based protocol has been shown to be more effective, it requires antenatal screening and the result of screening in labour is not immediately available. Thus, it may not be practicable in developing countries where patronage of antenatal care services are low and many women visit the hospital for the first time during labour. The risk-based approach may be more appropriate as it does not require antenatal screening although it is less specific for GBS^{1,2}.

GBS infection in the newborn can be prevented by administration of intrapartum, intravenous prophylactic antibiotics to women with GBS colonization or those with the identified risk factors from onset of labor or rupture of fetal membranes to delivery.^{1-3,6-8} The Royal College of Obstetricians and Gynaecologists favours the risk based approach⁸ and recommended that prophylaxis should be based on highlighted risks and routine screening of well infants are discouraged since neonatal colonization is not synonymous with infection while 90% of infected neonates manifest signs of infection by 24 hours of life when culture results are usually not available yet. Rather, babies should be observed for at least 24 hours and those with infection treated appropriately. Adequate antibiotic prophylaxis was defined as antibiotic to delivery interval of at least two hours. An important concern is that the risk factors are general risk factors for sepsis and not specific for GBS, thus the assumption that all women with risk factors are colonized as implied in the risk based approach may limit its application.

The aim of this study was to evaluate the role of the risk-based approach in the prevention of vertical transmission of neonatal sepsis in women with the identified risk factors compared to women without risk factors as controls in a tertiary centre in Ilorin, Nigeria.

Materials and Methods

The study was a prospective case control study consisting of subjects who were parturient with risk factors for vertical transmission of GBS according to the risk-based approach while controls were made up of parturient without any identifiable risk factor.

The inclusion criteria were consent to participate in the study and presence of one or more of the following risk factors in the pregnant woman: maternal intra-partum fever (temperature $\geq 38.0^{\circ}\text{C}$), premature rupture of membranes (PROM) at less than 37 weeks gestation, PROM ≥ 18 hours at 28 weeks or more gestational age and preterm delivery.

The temperature was taken twice after correction of dehydration when present before fever was established. The exclusion criteria were absence of any of the risk factors stated above or refusal to participate in the study.

Calculation of sample size, Sampling method and statistical analysis:

The sample size was calculated using Fisher's formula.⁹ All parturient were counseled and screened for the risk factors highlighted above; those with risk factors were recruited using systematic sampling (one of every two parturient with risk factors). The controls were the next parturient admitted into the labour ward after each subject but without risk factor. Statistical analysis was done using the SPSS-version 20 with results in tables and statistical significance defined as p value < 0.05 for test of significance with t-test and chi square where applicable.

Procedure:

All participants were informed and counseled about the study and an informed consent obtained. All subjects were given intravenous Ampicillin 2gm stat, then 1gm 4 hourly till delivery; labour was monitored actively with the aid of partograph, controls had no antibiotic prophylaxis.

After delivery, all babies of subjects and controls were monitored for signs of neonatal sepsis like grunting, poor feeding, lethargy, irritability, fever (temp $\geq 38.0^{\circ}\text{C}$), tachycardia (heart rate $> 120/\text{min}$) or tachypnoea (RR $> 60/\text{min}$). Babies without clinical signs of infection were observed for 48 hours and discharged after educating mothers on signs of infection and motivated to report to the hospital immediately if any sign is noticed.

Babies with signs of neonatal sepsis were transferred to the neonatal intensive care unit (NICU) and had samples taken for a full sepsis work up including a GBS blood culture to ascertain the cause of the infection. Meanwhile, they were commenced on empirical treatment with parenteral Ampicillin and gentamycin while awaiting the investigation results.

Early-onset group B streptococcal disease was defined as occurrence of signs and symptoms within the first seven days of life with a positive GBS blood culture. Babies with culture confirmed infection received further care including a 10 days course of parenteral Ampicillin and gentamycin.

Laboratory methods¹⁰

All newborns with signs of EOGBSD had 1ml venous blood sample taken into 9ml of Thod-Hewitt broth and transported immediately to the laboratory. The samples were incubated for 18-24 hours at 35-37°C in ambient air. This was then sub-cultured on 5% sheep blood agar plate and incubated for 18-24 hours in ambient air and the growth observed. The growth was used for further tests such as gram staining, Catalase test CAMP (Christins, Atkin and Munich Petressin) Test and Sodium Hippurate Hydrolysis Test to isolate and confirm group B streptococcus.

Ethical approval was obtained from the ethical review committee of the UITH Ilorin before the commencement of the study.

Results

During the study period (1st July to 31st December 2010), there were a total of 1,682 deliveries, 350 had risk factors for transmission of GBS giving a prevalence of 20.8%.

The incidence of neonatal sepsis were 71.4/1000 (subjects) i.e. 11 out of 154 and 32.5/1000 (controls) i.e. 5 out of 154 while the incidence of EOGBSD were 12.9/1000 (subjects) i.e. 2 out of 154 and 6.5/1000 (controls) i.e. 1 out of 154.

Maternal demography (table i) showed similarity in the mean ages and mean parity among both the subjects and the controls. However, the mean gestational age was lower in subjects compared to controls (37.6±1.9 v 38.4±1.3; P 0.001) while fewer subjects were booked compared to controls (45.5% v 64.0%; P 0.001).

From table ii, the commonest maternal risk factor among subjects was intrapartum fever (50%). Others were PROM>18hours (18.7%), preterm labour (11.1%), preterm PROM (8.5%), fever and PROM>18 hours (7.1%) and fever with preterm PROM (4.6%). Two cases of EOGBSD and eight (88.8%) of all cases on non-GBS sepsis occurred among subjects with multiple maternal risk factors.

Table iii showed the relationship between adequate maternal antibiotic prophylaxis and neonatal sepsis; 80.4% of subjects received two doses of antibiotic prophylaxis before delivery and all cases of EOGBSD and non-GBS sepsis were in babies of mothers who received only one dose of antibiotic prophylaxis. Also, 97.2% of subjects had their first antibiotic dose to delivery interval >2hours with no case of EOGBSD. Babies of subjects who had antibiotic dose to delivery interval <1hour contributed 66.7% while those with interval of 1-2 hours contributed 22.2% of cases of non-GBS sepsis.

Neonatal assessment at delivery (table iv) showed that 32(20.8%) of babies of subjects were preterm (χ^2 35.710; P 0.002) with more cases of low birth weight (χ^2 40.221; P 0.001) and lower fifth minute Apgar scores (χ^2 8.213; P 0.007) compared to controls.

Table v showed that there were a total of 16 cases of neonatal sepsis out of which 3 were EOGBSD and 13 non-GBS sepsis. Two cases (66.6%) of EOGBSD were in babies of subjects and one (33.3%) in controls. All the babies with EOGBS showed symptoms within 24 hours of delivery, all their mothers were unbooked with multiple risk factors and one dose of intrapartum antibiotic prophylaxis.

In addition, maternal morbidities occurred in 27 subjects (17.5%) despite maternal intrapartum antibiotic prophylaxis; of these, 18(66.6%) had inadequate prophylaxis and the commonest maternal morbidity was postpartum fever in 9(33.3%) of subjects.

Table i: Maternal demography of participants

Parameters	Subjects(n=154) Freq (%)	Controls (n=154) Freq (%)	t-test	chi square (χ^2)	P value
Mean Age	27.1±0.6	26.6±2.9	2.095	NA	0.401
Mean Parity	1.2±1.2	1.3±0.3	1.003	NA	0.524
Mean GA	37.6±1.9	38.4±1.3	4.312	NA	0.001
Booking status					
Booked	70 (45.5)	100 (64.9)			
Unbooked	84 (54.5)	54 (35.1)	NA	11.816	0.001
Level of Education					
None	30 (19.5)	32 (20.8)			
Primary	49 (31.8)	38 (24.7)			
Secondary	44 (28.6)	48 (31.2)			
Tertiary	31 (20.1)	36 (23.4)	NA	2.002	0.601
BMI					
<25	53 (43.4)	31 (20.1)			
25-30	66 (42.9)	82 (53.2)			
>30	35 (22.7)	41 (26.6)	NA	7.965	0.213

NA: Not applicable

Table ii: Maternal risk factors and occurrence of Neonatal Sepsis among subjects.

Risk factors	Occurrence of Neonatal sepsis n=11		
	Total Freq (%)	GBS n=2 (%)	non GBS n=9 (%)
Preterm labour	17 (11.1)	0	0
Preterm SPROM	13 (8.5)	0	1 (11.1)
SPROM>18hours	29 (18.7)	0	0
Fever	77 (50.0)	0	0
Fever+SPROM>18hours	11 (7.1)	1 (50)	5 (55.5)
Fever +Preterm SPROM	7 (4.6)	1 (50)	3 (33.3)

SPROM: Spontaneous Premature Rupture of Membranes

Table iii: Maternal antibiotic prophylaxis and Neonatal Sepsis

Maternal antibiotic prophylaxis	Neonatal outcome	
	GBS Sepsis(n=2) Freq (%)	non GBS Sepsis (n=9) Freq (%)
Number of doses		
1	2 (100)	9 (100)
2	0	0
3	0	0
1 st dose to delivery interval		
<1hour	1 (50)	6 (66.7)
1-2hours	1 (50)	2 (22.2)
>2hours	0	1 (11.1)

Table iv: Neonatal assessment at delivery

Parameter	Subjects Freq (%) , n=154	Controls Freq (%) ,n=154	chi square (x ²)	P value
Gestational age(weeks)				
32-36	32 (20.8)	0		
37-42	122 (79.2)	154(100)	35.710	0.002
Birth weight (gm)				
<2500	33 (21.4)	0		
2500-4000	111 (72.1)	149 (96.8)		
>4000	10 (6.5)	5 (3.2)	40.221	0.001
Fetal gender				
Male	81 (52.6)	80 (51.9)		
Female	73 (47.4)	74 (48.1)	0.013	0.910
Apgar score at 1 minute				
1-3	1 (0.6)	0		
4-6	29 (18.8)	20 (13)		
7-9	124 (80.5)	134 (87)	3.041	0.201
Apgar score at 5 minute				
4-6	8 (5.2)	0		
7-9	46 (94.8)	154(100)	8.213	0.007

Table v: Evaluation of all Neonates with Neonatal Sepsis

Parameter	GBS Sepsis n=3		P value	Non GBS Sepsis n=13		Pvalue
	Subjects Freq(%)	Controls Freq(%)		Subjects Freq(%)	Controls Freq(%)	
Cases of sepsis	2 (66.6)	1 (33.3)	0.501	9 (69.2)	4 (30.8)	0.113
Onset of symptom						
<12hours	2 (66.6)	0		1 (7.7)	2 (15.4)	
>12hours	0	1 (33.3)	NA	8 (61.5)	2 (15.4)	0.213
Neonatal symptom						
One symptom	0	1 (33.3)		1 (7.7)	1 (7.7)	
Multiple symptoms	2 (66.6)	0	NA	8 (61.5)	3 (23.1)	0.721
Fetal gender						
Male	2 (66.6)	1 (33.3)		7 (53.9)	2 (15.4)	
Female	0	0	NA	2 (15.4)	2 (15.4)	0.513
Maternal risk factor						
None	0	1 (33.3)		0	4 (30.8)	
One risk factor	0	0		1 (7.7)	0	
>1 risk factor	2 (66.6)	0	NA	8 (61.5)	0	NA
Booking status						
Booked	0	0		7 (53.9)	2 (15.4)	
Unbooked	2 (66.6)	1 (33.3)	0.510	2 (15.4)	2 (15.4)	0.513
Maternal antibiotics						
None	0	1 (33.3)		0	4 (30.8)	
1 dose	2 (66.6)	0	NA	9 (69.2)	0	NA

NA Not applicable

Discussion

The principal findings in this study were that 20.8% of parturient who delivered during the study period had risk factors for vertical transmission of GBS. The incidence of neonatal sepsis were 71.4/1000 (subjects) and 32.5/1000 (controls) while the incidence of EOGBSD were 12.9/1000 (subjects) and 6.5/1000 (controls). The study showed low antenatal booking practice (54.5% of subjects were unbooked) and maternal intrapartum fever was the commonest risk factor for vertical transmission of infections. Presence of multiple risk factors in the mother and inadequate antibiotic prophylaxis (<2 doses of antibiotic prophylaxis and antibiotic to delivery interval less than 2hours) were significant predictors of vertical transmission of neonatal sepsis and maternal postpartum morbidity. All infected babies showed signs and symptoms within 24hours of delivery and the risk-based approach with adequate prophylaxis was effective in preventing neonatal infections with GBS and infection occurred only in babies of women who had inadequate prophylaxis. The strength of this study were the design as a case control study which provided opportunity for comparison with controls and confirmation of neonatal infection by GBS culture. Its weakness was the inability to perform GBS culture for all subjects and controls in the antenatal period.

The incidence of risk factor for GBS transmission was similar to 20.4% in USA¹¹ while the incidence of EOGBSD in this study was much higher than previous reports of 1.1/1,000 by Main et al¹² and 1.45/1,000 by Lin et al¹³ in the USA; 1.15/1,000 by Beardsall et al¹⁴, 0.48/1,000 by Heath et al⁸ and 0.57/1,000 by Oddie et al in the UK⁷ and 2/1,000 by Jeffery et al in Australia¹⁵. This showed that EOGBSD is not rare in Nigeria.

The low booking status of participants was in sharp contrast to 95.7% in Australia¹⁵ and 91% in USA⁵. Thus the culture-based protocol may be impracticable in Nigeria and other developing countries because it requires antenatal culture screening of pregnant women while the risk-based protocol appears more practicable.

The prominence of multiple maternal risk factors, few doses of antibiotics and short antibiotic to delivery interval in EOGBSD were similar to report of Pylipow in USA where all neonatal infections were in women who had one dose¹⁶ of antibiotics. This might be due to inability of the drug to reach therapeutic level before delivery. It also reinforces the recommendation of the RCOG that presence of multiple risk factors makes maternal prophylaxis more necessary⁸. Also, 50% of EOGBSD in this study were associated with prolonged rupture of fetal membranes similar to findings of Oddie et al that prolonged rupture of fetal membranes was an independent risk factor for EOGBSD in the UK⁷. The cases of neonatal non-GBS sepsis were because the antibiotics act principally against gram positive organisms. This agrees with findings of Wendel⁵ and the

CDC report¹⁷ which documented the same. This raises a concern for the adoption of the risk based approach since it does not cater for such cases.

All cases of neonatal EOGBSD in this study were in women with signs of maternal peripartum infections. This was similar to reports of Heath et al that the strongest independent associations with EOGBSD were maternal GBS carriage and maternal peripartum infection⁸.

The occurrence of 33% of EOGBSD in babies of controls in this study further bring to the fore the controversy about the best method of preventing the infection. It has been shown by the CDC that no method of prevention is 100% effective¹⁷. Main estimated that the culture negative rate of GBS culture was 5%¹² and van Dyke showed that 61.4% of EOGBSD were from culture negative mothers at screening in pregnancy¹⁸. Though the RCOG recommended the risk based protocol⁸, Trijbels-Smeulders showed that 46% of EOGBSD occurred with no maternal risk factor¹⁹. Thus, there is still no ideal method of prevention with concerns that the CDC culture-based recommendation may not be the most cost effective method of prevention²⁰.

Conclusion

This study concludes that the risk-based approach is a practicable alternative in preventing vertical transmission of neonatal sepsis especially by *Streptococcus agalactiae* (GBS) infections if antibiotic prophylaxis is adequate before delivery. In addition, early onset neonatal GBS disease is not rare in developing countries as earlier presumed; clinicians should be reminded that GBS prevention deserves better attention and institutions should formulate protocol for its prevention. There is the need to develop a reliable rapid screening test which can be effectively used in labour while we await vaccine against GBS.

Limitations

This study was limited by its inability by study design to screen all participants in the antenatal period for GBS and make the culture results available in labour. This remains the major setback of the risk-based approach.

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The study was sponsored by the researchers, no external grant was obtained and there was no conflict of interest in the conduct of this study.

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