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■ Original Research Article

An Evaluation of The Success Rate and Pregnancy Outcome of Tocolysis for Preterm Contractions at Lagos University Teaching Hospital: A 5-Year Review

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ABSTRACT

Preterm contraction and resultant preterm delivery are a major contributor to perinatal morbidity and mortality. This necessitates decision to tocolyze when there is no significant cervical change, to prolong pregnancy and enhance fetal maturity. Several tocolytic agents are available but there may be need to switch tocolytic agents when one is considered ineffective. This study aimed to determine prevalence of preterm contractions at Lagos University Teaching Hospital (LUTH) and success rate of various tocolytic agents used in the last five years. It was a retrospective cohort study. Data from medical records of 273 eligible women managed for preterm contractions at the health facility between April 1, 2015, to March 31, 2020, were analyzed using SPSS version 25.0. Chi-square test was used to test for association between categorical variables. Prevalence of preterm contractions during study period was 68.1 per 1,000 obstetric admissions. Uterine inhibition was successfully achieved in 81.7% of cases following tocolysis. Tocolytic agents used during study period were oral Salbutamol, oral Nifedipine, parenteral Magnesium Sulphate and Atosiban. Atosiban was found to be most effective and Magnesium Sulphate least effective ($p < 0.001$). Atosiban was also found to be safest in terms of side effects compared to other tocolytic agents used ($p = 0.002$). In conclusion, the prevalence of preterm contractions is high. Outcome of tocolysis is good and should be encouraged. Oxytocin receptor antagonist such as Atosiban was found to be the most effective and safest tocolytic agent but this finding needs to be evaluated in a randomised controlled trial.

Keywords: Preterm Contractions, Tocolysis, Uterine Inhibition, Effectiveness, Safety, Side Effects.

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INTRODUCTION

An estimated fifteen million babies are born prematurely every year and approximately one million children die each year due to complications of preterm birth.[1] Preterm delivery, which refers to delivery after the age of viability and before 37 weeks of gestation, is a major cause of perinatal morbidity and mortality. In Africa, the number of pregnancies affected by preterm delivery is increasing with a prevalence of 7.4% with 68.2% of preterm births occurring spontaneously.[2]

Preterm labor, which culminates in preterm delivery, is defined as regular uterine contractions accompanied by a change in cervical dilatation, effacement, or both prior to term gestation.[3] Threatened preterm labor is defined as regular uterine contractions occurring at the frequency of at least once in every 10 minutes during 30 minutes of monitoring, with no dilatation and effacement of the cervix prior to term gestation.[3]

Preterm birth is fraught with a lot of complications to the newborn, commonest of which is respiratory distress. Other complications are increased risk of intraventricular hemorrhage, neonatal hypoglycemia, sepsis, neonatal jaundice, and increased risk of still births and early neonatal deaths.[4] The complications of preterm births arise from immature organ systems that are not yet ready to support life in the extra uterine environment.

Antenatal steroids ameliorate the risk of lung disease, intracranial bleeding, and death; while magnesium sulphate reduces the risk of cerebral palsy.[5,6] The use of tocolytic agents to suppress preterm uterine contraction can delay delivery for at least 48 hours, and this prolongation enable the complete administration of corticosteroids to obtain their maximum effect for pregnancies between gestational ages of 24–34 weeks.[3,7] It also enables transfer of the pregnant mother with the fetus still in utero, to facilities where they can access prompt and optimal neonatal care in case of preterm delivery.[8]

Tocolysis is the relaxation of the pregnant uterus to postpone delivery. Tocolytics are a wide variety of agents used to suppress uterine contraction and are given when delivery would result in preterm birth.[8] The tocolytic agents commonly used at our facility are oral Nifedipine, oral Salbutamol, parenteral Magnesium sulphate and recently, Atosiban.

Nifedipine is a calcium channel blocker which acts as a tocolytic on T-type calcium channels by inhibiting the entry of calcium into the uterine smooth muscle reducing its contractility.[9] Salbutamol is a beta sympathomimetic which causes relaxation of uterine smooth muscle fibers by stimulating the beta receptors present on the cell membrane.[9] Magnesium sulphate has an unresolved mechanism of action regarding uterine contractions, but it has been described as antagonizing the action of calcium within the myometrial cells to reduce its contractility.[10] Atosiban which is an oxytocin receptor antagonist inhibits oxytocin-mediated release of inositol triphosphate from the myometrial cell membrane.[9] As a result, there is reduced release of intracellular, stored calcium from the sarcoplasmic reticulum of myometrial cells, and reduced influx of Ca^{2+} from the extracellular space through voltage gated channels.

If a pregnant woman having preterm contractions still has uterine contractions while using these drug regimens, she is classified as having "inhibition failure". A significant risk factor for inhibition failure is preterm uterine contractions with cervical changes.[9] When a decision is made to use tocolytics, the clinician is faced with a multitude of choices with side effects, efficacy and ease of administration being important considerations. Calcium channel blockers have a better safety profile than the β agonists, but there are still significant cardiovascular side effects associated with their use.[10]

Despite the available modalities to prevent preterm birth and its consequences, the proportions of preterm birth have not reduced.[2] A number of our women still progress to preterm delivery despite the use of these tocolytic agents which are fraught with side effects of varying severity. We have not assessed the effectiveness of the various tocolytic agents for uterine inhibition to ascertain which agent is better for our women. This study thus sought to determine the prevalence of preterm uterine contractions in our facility and to evaluate the success rate of preterm uterine contraction inhibition with various tocolytic agents. The outcome of this study may influence our labour ward protocol for the management of preterm contractions.

SUBJECTS AND METHODS

This was a retrospective cohort study conducted at our facility after obtaining ethical approval from the hospital's Health Research and Ethics Committee (ADM/DCST/HREC/APP/3711). All singleton pregnancies at 28 weeks' gestation to less than 37 completed weeks complicated by preterm contractions managed in the hospital over 5-year period from April 1, 2015, to March 31, 2020, were included in this study. The exclusion criteria included multiple pregnancies, women with diagnosis of dead foetus in utero on admission, women already in labour on admission irrespective of the gestational age, and women with diagnosis of foetal anomalies. Information was obtained from the Labour Ward and Accident and Emergency admission books, Labour Ward, and Labour Ward theatre delivery registers.

All traceable case notes were retrieved from the Health Records Department for additional information. Information retrieved included maternal age, parity, gestational age at which patient had preterm contractions, gestational age at delivery, type of tocolytic agent administered, time from resolution of uterine contractions to delivery, observed side effects of tocolytic agent, failure or success of uterine inhibition, foetal survival, and APGAR scores. Information retrieved was recorded in a study proforma and data was transferred to Excel spread sheet and analysed using SPSS version 25.0 (Armonk, NY: IBM Corp. Released 2017).

Descriptive statistics was done. Normality testing was done using Komolgorov Smirnov test. Continuous variables were presented as mean ± S.D if normally distributed or as median and interquartile range if not normally distributed. Categorical variables were presented as frequency and percentage. The prevalence of preterm contraction was presented as a percentage. Prevalence of side effects for each tocolytic agent used was presented as frequency and percentage. Hypothesis testing to determine the association between type of tocolytic agent and success of inhibition was determined using Chi Square test, and Fishers Exact test values reported where the expected value in >25% of the cells was less than 5. Statistical significance was set at $p < 0.05$.

RESULTS

During the study period, a total of 4,007 women were managed in facility for various obstetric indications. Of these, 273 women had preterm contractions. This put

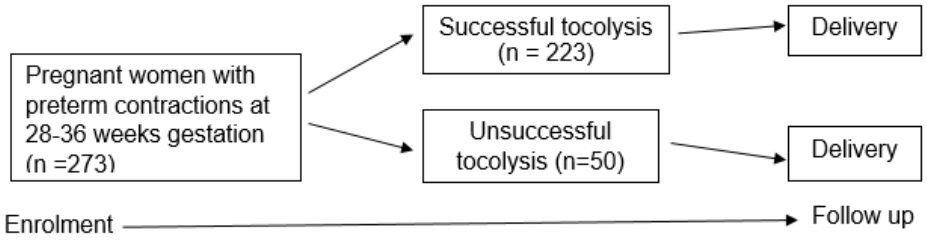

Figure 1: Cohort study flow diagram

No participant was lost to follow up.

the prevalence of preterm contractions at 68.1 per 1,000 obstetric admissions. The mean age of women with preterm contractions during the study period was 32.0 ± 4.6 years. The median parity was 1 (range 0-2). The mean gestational age at onset of preterm uterine contractions was 32.9 ± 2.9 weeks. The median number of admissions for preterm labour was 1 (Range 1 – 2). The mean duration of admission for preterm labour was 7.5 ± 2.2 days.

Nifedipine, a calcium channel blocker, was the commonest tocolytic agent used in our facility during the study period. The overall success rate of tocolysis for preterm uterine contraction inhibition with all agents was 81.7%. The highest success rate was found with the use of Atosiban (87.5%). There was a statistically significant difference in success rates when all tocolytic agents used during the study period were compared, p <0.001. *Table 2*.

The use of Atosiban is associated with a better fetal outcome as 96.9% of the mothers had delivery of live babies. There was a statistically significant difference in the fetal survival outcome with the use of various types of tocolytic agents as shown. *Table 3*.

Majority of parturient admitted for preterm uterine contractions had no previous admissions (84.6%) and made up 91.9% of the success rate of uterine inhibition. This was statistically significant.

The incidence of birth asphyxia was significantly more in women who were tocolyzed with Magnesium Sulphate compared to other tocolytic agents, with 62.5% of babies having birth asphyxia defined as APGAR score less than 7 at 5 minutes for this study. *Table 3*.

Atosiban had the best safety profile with fewer women, 3.1% undergoing tocolysis having side effects compared to women who used other drugs as shown in *Table 4*.

Incidence of nausea was significantly more in women who had magnesium sulphate for tocolysis, affecting 37.5% of women in this group. Vomiting occurred significantly more in women undergoing tocolysis with Salbutamol (22.9%) compared to use of other tocolytic agents. Headaches occurred most in women undergoing tocolysis with Nifedipine (20.5%). The association between various tocolytic agents used during study period and side effects was statistically significant for nausea (p = 0.001), vomiting (<0.001), and headaches (p = 0.003). *Table 5*.

Table 1: Baseline characteristics of women managed for preterm contractions in Lagos University Teaching Hospital between April 1, 2015 to March 31, 2020

Clinical characteristic	Frequency (%) (n = 273)
Age group (years)	
15 – 24	14 (5.1)
25 – 34	187 (68.5)
35 – 44	71 (26.0)
45 and above	1 (0.4)
Parity	
0	85 (31.1)
1	80 (29.3)
2 – 4	101 (37)
5 and above	7 (2.6)
Gestational age at diagnosis of preterm contractions (weeks)	
28 – 32	116 (42.5)
33 – 36	157 (57.5)
Gestational age at delivery (weeks)	
28 – 32	115 (42.1)
33 – 36	157 (57.5)
37 and above	1 (0.4)

Table 2: Success Rate of Preterm Uterine Contraction Inhibition With Various Tocolytic Agents

Type of Tocolytic	Success of Uterine Contractions Inhibition
Atosiban (n = 32)	28 (87.5%)
Magnesium Sulphate (n = 8)	2 (25.0%)
Nifedipine (n = 185)	154 (83.2%)
Salbutamol (n = 48)	39 (81.3%)
p = <0.001	
Number of admissions for preterm labour	**Success of uterine inhibition**
One	205 (91.9%)
Two	18 (8.1%)
Three	0 (0%)
p = <0.001	

*Some women who had failed tocolysis with one drug had another as an alternative

Table 3: Association Between Type of Tocolytic Used and Fetal Outcomes

Tocolytic agent	Frequency (%)	Fetal Survival		p-value
		Alive	Dead	
Atosiban	32 (11.7%)	31 (96.9%)	1 (3.1%)	
Magnesium Sulphate	8 (2.9%)	3 (37.5%)	5 (62.5%)	0.001
Nifedipine	185 (67.8%)	151 (81.6%)	34 (18.4%)	
Salbutamol	48 (17.6%)	36 (75%)	12 (25%)	
	n (%)	Apgar score at 5 minutes		
		<7	>7	
Atosiban	32 (11.7%)	4 (12.5%)	28 (87.5%)	
Magnesium Sulphate	8 (2.9%)	5 (62.5%)	3 (37.5%)	0.033
Nifedipine	185 (67.8%)	54 (29.2%)	131 (70.8%)	
Salbutamol	48 (17.6%)	13 (27.1%)	35 (72.9%)	

Table 4: Side Effect Profile of the Various Medications Used for Uterine Inhibition

Tocolytic agent	frequency (%)	Any side effects of medication	
	n = 273	Yes, n = 87	No, n = 186
Atosiban	32 (11.7%)	1 (3.1%)	31 (96.9%)
Magnesium Sulphate	8 (2.9%)	2 (25%)	6 (75%)
Nifedipine	185 (67.8%)	64 (34.6%)	121 (65.4%)
Salbutamol	48 (17.6%)	20 (41.7%)	28 (58.3%)
p = 0.002			

Table 5: Association Between Side Effects And Type Of Tocolytic

Side Effects	Atosiban (n = 32)	Magnesium Sulphate (n = 8)	Nifedipine (185)	Salbutamol (48)	p-value
Vomiting	1 (3.1%)	1 (12.5%)	0 (0%)	11 (22.9%)	**<0.001**
Diarrhea	1 (3.1%)	1 (12.5%)	6 (3.2%)	4 (8.3%)	0.292
Palpitations	0 (0%)	1 (12.5%)	21 (11.4%)	1 (2.1%)	0.053
Headaches	1 (3.1%)	1 (12.5%)	38 (20.5%)	1 (2.1%)	**0.003**
Dizziness	2 (6.3%)	1 (12.5%)	18 (9.7%)	3 (6.3%)	**0.805**
Nausea	3 (9.4%)	3 (37.5%)	3 (1.6%)	13 (27.1%)	**<0.001**

DISCUSSION

The mean age of parturients during the study period was 32 years which is higher than in a similar study where the mean age was 28 years.[9] The mean gestational age of onset of preterm uterine contractions of 33 weeks as found in this study is similar to findings in an earlier study where the mean gestational age was 33 weeks.[11] Unlike in an earlier study the mean frequency of re-admission for preterm contractions was lesser, being one in this study compared to two in a previous study.[12] This could be due to the differences in inclusion criteria as women with preterm contractions from 24 weeks gestational age were included in the previous study while only those at 28 weeks gestational age and above were included in this study.

The most used tocolytic was calcium channel blocker, specifically Nifedipine, and this was a similar pattern in an earlier study by Dias et al.[14] This may be so as Nifedipine is easily accessible, cheap, and easy to administer, compared to other tocolytic agents such as Magnesium Sulphate and Atosiban which are expensive and requires skilled personnel to administer and monitor the patient during administration.

The overall success rate of preterm uterine contraction inhibition with the various tocolytic agents was good, 81.7%. This finding is similar to the 86.4% success rate reported in an earlier study.[9] The high success rate buttresses the need to institute tocolysis of preterm contractions as the gain therein is much more than the risk of having preterm birth and its attendant consequences. The use of Atosiban was found in this study to be associated with the best success rate and fewer side effects in women undergoing tocolysis. In comparison to other tocolytic agents it is primarily uterus-specific without a significant influence on other systems. However, due to cost and availability it is not widely used in Nigeria. This is worsened by the fact that most people pay out-of-pocket in Nigeria compared to what obtains in developed countries where the national health insurance scheme is better developed. As a strategy to reduce perinatal deaths which commonest cause are complications associated with preterm birth, there is a need for the health insurance system in Nigeria to be developed.

Magnesium sulphate was found in this study to be associated with poorer foetal outcome in terms of foetal survival and incidence of birth asphyxia. To further explore its benefit in management of preterm contractions, a randomized control clinical trial will be necessary.

The commonest adverse drug event associated with the tocolytic agents used during the study period was nausea with the use of Magnesium Sulphate, vomiting with Salbutamol and headaches with the use of Nifedipine. The incidence of headaches associated

with the use of Nifedipine in this study was higher than in an earlier study.[11]

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