PERINATAL AND MATERNAL OUTCOMES OF HIGH DOSE VERSUS LOW DOSE OXYTOCIN REGIMEN FOR LABOR INDUCTION IN FOUR HOSPITALS OF ETHIOPIA

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JIMMA UNIVERSITY

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ABSTRACT

Background: Induction of labor is routine obstetric procedure. Oxytocin for the purposes of induction of labor is one of the most frequently used medications in obstetrics. Studies have estimated the relative efficacy and safety of high-dose versus low-dose oxytocin protocols for induction of labor. However, little is known regarding the optimal dose of oxytocin and maternal and perinatal outcomes**.**

Objective: To compare perinatal and maternal outcomes of high-dose compared with low-dose oxytocin regimen for labor induction among mothers who will give birth in four selected hospitals of Ethiopia.

Methodology: Facility based a comparative cross-sectional study design was used. The study was conducted in four selected Ethiopian hospitals. All pregnant women who undergo induction of labor at GA of ≥ 37 weeks in all the four selected facilities were included starting from October 1, 2017 till May 30, 2018. Code was given to questionnaire collected by face-to-face interview by structured questionnaire. Data was entered into Epidata version 3.1 and then exported to SPSS version 20 for cleaning and analysis. To explain the relationship of relevant variable; cross-tabulation between dependent and independent variables was conducted and simple relationship was checked. Bivariate and multivariate logistic regression was done to look for predictors of successful induction, factors associated with adverse maternal outcome and adverse neonatal outcome. The result is presented using 95% confidence interval (CI) of odds ratios (OR). P-value < 0.05 was used to declare statistical significance.

Result: A total of 216 laboring mothers are participated in the study in four hospitals. Overall mean age and gestational age at delivery for all participants were 26 years and 39.4 weeks respectively. Overall mean "oxytocin to delivery" time for study subjects is 5.9 hours and 6.3 hours for subjects of high dose group (HDG) and low dose group (LDG) respectively. Mean oxytocin concentration required till delivery is 77.6 mu/min and 22 mu/min for HDG and LDG respectively. Higher successful induction (72.2% versus 61.1%) and lower C/S rate (27.8% vs. 38.9) was observed among LDG as compared to HDG. Favourable bishop score [AOR=4.0, 95%CI: (1.9, 8.5)], elective induction[AOR=0.2,95%CI: (0.1,0.4)] , performing ARM [AOR=10.1,95%CI:(3.2, 32.2)], neonatal birth weight (NBW) of < 4Kg [AOR= 4.3, 95%CI: (1.6, 11.6)] and being parous [AOR=2.1, 95%CI: (1.1,4.0)] were found to be significantly associated with success of induction at P-Value < 0.05. While misoprostol use [AOR= 4.7, 95%CI: (1.6, 13.4)] and NBW ≥4 kg[AOR= 3.4, 95%CI: (1.1, 10.3)] are associated with adverse maternal outcome, Oxytocin regimen [AOR=2.4, 95%CI: 1.1, 5.5], caesarean delivery [AOR=9.3, 95% CI: 3.8, 22.5], instrumental delivery [AOR=7.7, 95% CI: 2.1, 27.8], APH as indication for induction [AOR=17.8,95% CI: (1.9,168.7)] are found to be associated with adverse neonatal outcome at P-value < 0.05.

Conclusion and recommendation: In the study high dose oxytocin regimen is significantly associated increased adverse perinatal outcome, slightly shorter oxytocin to delivery time, shorter duration of hospital stay. Favourable bishop score, emergent type of induction, performing ARM and delivery to neonate weighing < 4kg are positive predictors of successful induction. High dose oxytocin regimen, APH as indication of induction, caesarean delivery, and instrumental delivery are significantly associated with increased odds of adverse perinatal outcome while only misoprostol use and delivery to macrosomic neonate are associated with increased odds of adverse maternal outcome. The finding of the study favors the recommendation of low oxytocin regimen although more strong research that controls confounders is needed to come up with strong recommendation.

Key words: Induction, high dose, low dose, maternal outcome, perinatal outcome, successful induction, failed induction

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TABLE OF CONTENTS

ABSTRACT I
ACKNOWLEDGEMENTS II
TABLE OF CONTENTS III
LIST OF TABLES V
ACRONYMS AND ABBREVIATIONS VI
CHAPTER ONE: INTRODUCTION 1
1.1 Background 1
1.2 Statement of the problem 2
1.3 Significance of the study 4
CHAPTER TWO: LITERATURE REVIEW 5
2.1 LITERATURE REVIEW 5
2.2 CONCEPTUAL FRAME WORK 9
CHAPTER THREE: OBJECTIVE OF THE STUDY 10
3.1 General Objective 10
3.2 Specific Objectives 10
CHAPTER-FOUR: METHODS AND MATERIALS 11
4.1 Study area and period 11
4.2 Study design 11
4.3 Population 11
4.3.1 Source population 11
4.3.2 Study population 11
4.4 Inclusion and Exclusion criteria 11
4.5 Sample size determination and sampling technique 12
4.5.1 Sample size 12
4.5.2 Sampling technique 12
4.6 Data collection 12
4.7 Study Variables 13
4.7.1 Dependant variables 13
4.8 - Data Analysis 14
4. 9 Data quality control 14
4.10 Ethical clearance 14
4.11. Dissemination plan of the study findings 15
4.12 Operational definition and definition of terms 15
CHAPTER FIVE: RESULT 17
5.1 Socio-demographic, reproductive & obstetric Variables of study participants 17
5.2 Labor outcomes (oxytocin to delivery time, mean oxytocin concentration, rate of CS, Rate of instrumental delivery, induction success) 20
5.3 Factors affecting success of induction 21
5.4 Maternal outcomes & factors associated with adverse maternal outcome 22
5.5 Perinatal outcomes and factors associated with adverse perinatal outcome 25
CHAPTER SIX: DISCUSSION 29
6.1 Labor Outcomes 29
6.2. Mean Oxytocin to delivery time, & mean oxytocin level used 31

6.3 Adverse Maternal outcome and associated factors 32
6.4 Adverse Perinatal Outcomes and Associated Factors 33
Limitation of the study 34
CHAPTER SEVEN: CONCLUSION AND RECOMMENDATIONS 35
7.1 Conclusions 35
7.2 Recommendation 35
REFERENCES 36
ANNEXES 38
ANNEX I: QUESTIONNAIRE 38
ANNEX II: APPROVAL 43

LIST OF TABLES

Table 1: Socio-demographic characteristics of pregnant women undergoing IOL with high dose and low dose oxytocin regimen in JUMC, AGH, SGGH & KGH, during Oct1, 2017 to May30, 2018 ---------- 17
Table 2: Reproductive & Obstetric characteristics of pregnant women undergoing IOL with high dose and low dose oxytocin regimen in JUMC, AGH, SGGH & KGH, during Oct 1, 2017 to May 30, 2018. ---------- 19
Table 3: Multivariate Logistic Regression of factors associated with success of induction ---------- 21
Table 4: Cross-tabulation of maternal outcome variables with high dose and low dose oxytocin regimen in JUMC, AGH, SGGH & KGH, during Oct 1, 2017 to May30, 2018. ---------- 23
Table 5: Multivariate Logistic Regression of factors associated with adverse maternal outcomes ---------- 24
Table 6: Cross-tabulation of perinatal outcome with high dose and low dose oxytocin regimen in JUMC, AGH, SGGH & KGH, during Oct 1, 2017 to May30, 2018. ---------- 26
Table 7: Multivariate Logistic Regression of factors associated with adverse neonatal outcomes ---------- 28
Table 8: Protocol & schedule for escalating Oxytocin dosage for IOL among low dose & high dose groups. --------- 42
Table 9: Bishop Score Assessment ---------- 42

ACRONYMS AND ABBREVIATIONS

ACOG- American college of obstetrics and gynecology

AGH- Arbaminch general hospital

AJOG -American journal of obstetrics and gynecology

AOL - Augmentation Of Labor

AOR- Adjusted odds ratio

CPD - Cephalo Pelvic Disproportion

COR- Crude odds ratio

C/S - Caesarean Section

DPM – Drop Per Minute

EJHS – Ethiopian Journal of health science

HDG- High dose group

ICU - Intensive Care Unit

IESO- Integerated Emergency Surgical Officers

IOL - Induction of labor

IU – International Unit

JUMC - Jimma University Medical Centre

JUSH – Jimma University Specialized Hospital

KGH- Kuyu general hospital

LDG- Low dose group

LFSOL- latent first stage of labor

SDG – Sustainable Development Goal

MAS – Meconium aspiration syndrome

MSAF - Meconium Stained Amniotic Fluid

mu/min – Miliunit/minute

NICU - Neonatal Intensive Care Unit

NRFHRP: non reassuring fetal heart rate patterns

OJOG - Open Journal of Obstetrics and Gynecology

PPH – Post Partum Hemorrhage

PROM- Premature rupture of membrane

RR – Risk Ratio

SD – Standard Deviation

SGGH- Shanan Gibe general hospital

SPSS – Statistical Package for Social Scientists

SSOL – Second stage of labor

SVD - Spontaneous Vaginal Delivery

WHO – World Health Organization

CHAPTER ONE: INTRODUCTION

1.1 Background

Labor is the physiological process by which regular painful uterine contractions result in progressive effacement, dilatation of the cervix and ultimately leads to delivery of the fetus through the birth canal. Induction of labor (IOL) is a routine obstetric procedure which refers to the iatrogenic stimulation of uterine contractions before the onset of spontaneous labor with or without ruptured membranes to accomplish vaginal delivery (VD) **[1].** Induction of labor with the goal of achieving vaginal delivery prior to spontaneous onset of labor is recommended when the benefits of delivery out-weight the risk of continuing the pregnancy [**2**].

Oxytocin for the purposes of induction & augmentation of labor (AOL) is one of the most frequently used medications in obstetrics as it stimulates rhythmic contractions of uterine smooth muscle. This synthetic polypeptide hormone has been used to stimulate uterine contractions since 1950's after synthesized for the first time in 1953 by Vincent du Vigneaud (1901-1978) who was awarded the Nobel Prize for his discovery two years later [**2,3].**

Oxytocin protocols can be categorized as high-dose or low-dose protocols depending on the initial dose and the amount and rate of sequential increases in dose. The high-dose regimens varied across the trials; starting doses ranged from 4–10 mU/min, with increases in dose ranging from 4–7 mU/min and maximum rates ranging from 4–90 mU/min. Low-dose regimens commenced infusion at from 1-4 mU/min, with rate increases ranging from 1-2 mU/min and maximum rates ranging between 1–31.7mU/min [**4**].

Low-dose protocols mimic endogenous maternal physiology and are associated with lower rates of uterine tachysystole. Low-dose oxytocin is initiated at 0.5 to 1 mU and increased by 1 mU per minute at 40- to 60-minute intervals. Slightly higher doses beginning at 1 to 2 mU/min increased by 1 to 2 mU/min, with shorter incremental time intervals of 15 to 30 minutes, have also been recommended [**1]**.

1.2 Statement of the problem

Worldwide the incidence of delay in labor is not accurately known. But some studies showed the range to be between 10% to one-third of women in their first labors, and about 40% to 60% of these women have their labor augmented with oxytocin due to slow progress or other reasons in first stage of labor [**5**]. A major cause of failure to achieve spontaneous vaginal delivery (SVD) is delay in labor caused by presumed inefficient uterine action. Inadequate uterine activity has been described as the most frequent cause of dystocia which in turn is the leading indication for primary cesarean section (CS) [**4**].

IOL is associated with poorer maternal and perinatal outcomes when compared with spontaneous labor. There is a greater risk of CS, maternal complications including uterine hyper stimulation, hypotension, fever, water intoxication perineal lacerations, increased use of uterotonic agents and anesthetic/analgesic agents, hysterectomy, intensive care unit (ICU) admission, and hospital stay more than seven days. Neonatal & fetal complications include fetal heart rate decelerations, low 5-minute Apgar score, very low birth weight, admission to a neonatal intensive care unit (NICU) and delayed initiation of breastfeeding [**2,6**].

The rate of labor induction varies by location and institution, and is increasing. In Africa (average 4.4%), induction rates ranged from 1.4% in Niger to 6.8% in Algeria. Asian rates were generally higher (average 12.1%), ranging from 2.5% in Cambodia to 35.5% in Sri Lanka [**6**]. In study done at Kenya the rate of the CS following induction of labor was 38%, and a majority of the women took more than 24 hours to deliver after IOL. Outcome of IOL is influenced by age, type of employment, parity, and women being given information on the nature of the procedure [**7**].

Number of randomized clinical trials & systematic reviews have been done to estimate the relative efficacy and safety of high-dose versus low-dose oxytocin protocols for AOL and on indicators of maternal and neonatal morbidity. Despite the frequency with which oxytocin is used in clinical practice, there is little consensus regarding the optimal dose of oxytocin for labor augmentation [**4**].

Internationally although there are different guidelines and publications done to compare low and high dose oxytocin regimens, there is no agreement on a standardized oxytocin regimen nor is convincing evidence to show one oxytocin regimen superior to another. As a result there is no hard evidence to recommend a particular dosage of oxytocin for induction or augmentation of labor infusion regimens [**5, 8-9**]. However one meta-analysis done in 1998 supports use of a low-dose oxytocin infusion for IOL [**3**].

In Ethiopia both low & high dose oxytocin regimen protocols are used in different centers. The national guideline recommends low dose oxytocin regimen where 2 International Unit (IU) is added to 1000ml of normal saline(NS) & drop begin at 2mu/min & escalated every 30 minutes the maximum dose being 40mu/min [**10**]. However, the former Jimma university specialized hospital(JUSH)currently named Jimma university medical center (JUMC), is using high dose oxytocin regimen where 6IU of oxytocin in 1000ml of NS fluids, start at 6 mu/min & escalating every 20 minutes till a maximum of 92.7 mu/min [**11,12**].

Although IOL with oxytocin is a daily practice at public and private health institutions, there is limited data on prevalence of labor induction in Ethiopia. In one retrospective case-series from two teaching hospitals in Addis Ababa done in 2004, the prevalence of induction at term and post-term was 4% in both institutions [**13**]. Otherwise there is no comparative study done in Ethiopia to evaluate the effects of the two oxytocin regimens on pregnancy outcomes although different researches has done on determinant factors for failed induction at different centers including my study area[**12,14,15**].

The present study is, therefore aimed at determining & comparing the maternal and perinatal outcomes of the high dose oxytocin regimen as compared to low dose regimen and come up with finding that might help in recommending one regimen over the other based on the finding and context of the study area.

1.3 Significance of the study

Induction of labor is directly relevant to the health related sustainable development goals (SDGs). It has potentials for preventing maternal complications and improving perinatal outcome. Higher rate of IOL may also contribute to lowering CS rates without increasing other adverse pregnancy & perinatal outcomes. Minimizing CS rates without increasing other adverse pregnancy outcomes is a priority consideration in low income countries like Ethiopia where available resources need to be judiciously utilized. Efforts aimed at achieving the health related SDGs should focus on increasing access to effective interventions and on improving quality of health care, one of which is utilization of labor induction using different oxytocin regimens.

Worldwide, numerous amounts of randomized clinical trials & systematic reviews have done to assess the efficacy and safety of high-dose versus low-dose oxytocin protocols for AOL or IOL and to look for indicators of maternal and neonatal outcomes.

In Ethiopia both low dose & high dose oxytocin regimen protocols are being used. Ethiopia has a national guideline for IOL which is mainly of low dose oxytocin regimen which is being used throughout country. But some centers like JUMC follow high dose oxytocin regimen. However, as to the knowledge of principal investigator there is no study done in Ethiopia to compare high dose versus low dose oxytocin regimen despite utilization of both protocols. This initiates us to study on this area of interest to fill the information gap & to come up with better recommendation.

Hopefully this study has a valuable importance to address the effects & outcomes of the two regimens and will generate important findings that substantiate current knowledge, practice and fill the gap.

CHAPTER TWO: LITERATURE REVIEW

2.1 LITERATURE REVIEW

Limited number of studies are done in Ethiopia on the area of induction of labor. In study done in JUSH on outcome of induction and associated factors among term and post-term pregnancies, the top three indications for induction in the study were premature rupture of membrane (PROM) (36.6%), hypertensive disorders of pregnancy (34.3%) and post-term pregnancy (23.2%).Induction was successful in 65.7% while 21.4% of the mothers experienced failed induction. Only gravidity of the women and Bishop Score at admission persisted as independent predictors of outcome of induction with oxytocin in the multivariate model. Hence, primigravid, women who had unfavorable Bishop Score & those with intermediate bishop score were 2.3 times, 5.3 times & 4.3times more likely to have failed induction as compared to multigravida mothers & women with favorable Bishop score respectively [**12]**.

In another study done at Hawassa public hospitals of Ethiopia, predominant indications for induction of labor in the study area were PROM, Preeclampsia, Post term and Chorioamnionitis. Out of the total samples, 61.6% mothers ended with VD while others delivered by CS. The 1^{st} & 5^{th} Apgar scores of the newborns was >7 in 70.1% & 83.3% of cases respectively. Reasons for cesarean section among women were: CPD, fetal distress and failed induction. Prevalence of failed induction was 17.3%, and is 3.11 times more likely in primiparous mothers. Variables which increased the likelihood of failed induction were advanced maternal age, unfavorable bishop score, postdates delivery, PROM, mothers with age greater than 30 years and previous obstetric complications.[**15**].

In another Ethiopian study,the first three indications for induction were post term, term PROM and hypertension. SVD (46.4%), CS for failed induction (28.4%) and fetal distress (9.6%) were the top modes of delivery in both nulli-paras and multiparas. More than two-thirds of multiparous and half of nulliparous women achieved adequate uterine contractions with 20-mu/min and less oxytocin infusion among the total women (84.4%) who were diagnosed to have adequate uterine contractions. Although the starting, increment and maximum oxytocin regimen for nulliparas and multiparas were different but with parallel Bishop Score, the induction initiation to vaginal delivery time was almost comparable. Very high oxytocin dose for nulliparas wasn't superior to multiparas dose [**13**].

Bishop score was found to have an inverse relation with failed induction, and negative correlation with length of labor among VD. Although overall induction failure rate is 28.4%, 0-5 Bishop Score group

accounted for 67.5% of failed inductions. Failure to bring about cervical dilatation (45.2%) and unable to establish adequate uterine contractions (54.8%) were the two reasons for failed inductions. Although the range was wide (2:50 - 21:0), the mean length of induction in hours in both nulli-paras and multiparas prior to decision for failed induction was comparable (9:45 +/- 3:20 vs 9:25 +/- 2:55). The maximum oxytocin infused in mu/min for nulli-paras and multiparas was 73.4 and 36.7 respectively [**14**].

The other study done at Woliso St Luke hospital showed significant association between gestational age, presence of fetal heart beat abnormality, Bishop Score, membrane rupture and APGAR score to the outcomes of induced labor. Women with gestational age of <42 weeks , Bishop score >5 ,absence of fetal heart beat abnormality showed higher successful induction of 9 times, 4 times and 5times when compared to their post terms, bishop score of <5 and present of fetal heart beat abnormality counter parts respectively [**16**].

A systematic review published on American journal of obstetrics and gynecology (AJOG, 2010) found that high-dose oxytocin augmentation was associated with a moderate reduction in risk of CS (RR, 0.85; 95% CI: 0.75–0.97) & a significant shortening of labor duration (weighted mean difference: –1.54 hours;95% CI, –2.44 to –0.64). Although high-dose oxytocin was associated with a small but statistically significant increase in SVD (RR, 1.07; 95% CI, 1.02–1.12) & substantially increased risk of uterine hyper stimulation (RR,1.91; 95% CI, 1.49 –2.45) there was no evidence of an increase in adverse maternal or neonatal outcomes like PPH, maternal blood transfusion, uterine atony , uterine rupture, shoulder dystocia, chorio-amnionitis, fetal heart rate abnormalities, fetal distress, or neonatal morbidity indicators with this approach [**4**].

In another cohort study (2012) conducted to assess effects of two different protocols of oxytocin infusion for labor induction on obstetric outcomes they found that use of a high- dose oxytocin for labor induction at term is associated with similar rates of CS (27.3% vs 27%) and adverse neonatal outcome as a low-dose protocol, but with an average of 2.5 hours shorter duration of labor although significant association is not seen b/n rate of CS and type of oxytocin regimen [**8**]. In one Cochrane review (2016) a significant increase in uterine hyper stimulation without specifying fetal heart rate changes was found in the high-dose group (RR 1.86, 95% CI 1.55 to 2.25 [**9**].

However**,** one meta-analysis (1998) comparing low-dose to high-dose regimens showed, the potential shortening of induction to delivery time with the high-dose protocol occurs at the expense of higher rates

of excessive uterine activity, fewer SVD, a trend towards a higher Caesarean rate and an increased potential for maternal morbidity [**3**].

From Parkland Hospital, Satin and associates (1992) compared a low-dose (1-mU/min) with a high-dose (6-mU/min) oxytocin regimen. Uterine hyper-stimulation was more common (55 versus 42%) with the high-dose regimen, but no adverse fetal effects were observed. High-dose augmentation resulted in significantly fewer forceps deliveries (12 versus 16%), fewer CS rate for dystocia (9 versus 12%) & reduced rate of failed induction (14 versus 19%). Although the high-dose induction regimen was associated with a significantly increased cesarean incidence for fetal distress (6 versus 3%), the incidence of umbilical artery cord blood acidemia was not increased in this subset. Labor stimulation was more than 3 hours shorter with the high-dose oxytocin regimen and associated with a reduction in neonatal sepsis (0.2 versus 1.3%) [**17**].

Intervals to increase oxytocin doses vary from 15 to 60 minutes. Satin and colleagues (1994) used either 20- or 40-minute intervals. Uterine tachysystole was significantly more frequent with the 20-minute escalation regimen (40 versus 31%). Neonatal outcomes were unaffected by the dosage interval for both augmentation and induction [**18**]. Merrill and Zlatnik (1999) started with 4.5 mU/min, with increases every 30 minutes [**19**].Other investigators reported even more frequent incremental increases. Frigoletto (1995) and Xenakis (1995) and their coworkers gave oxytocin at 4 mU/min with increases as needed every 15 minutes [**20-21**]. López-Zeno and associates (1992) began at 6 mU/min with increases every 15 minutes [**22**].

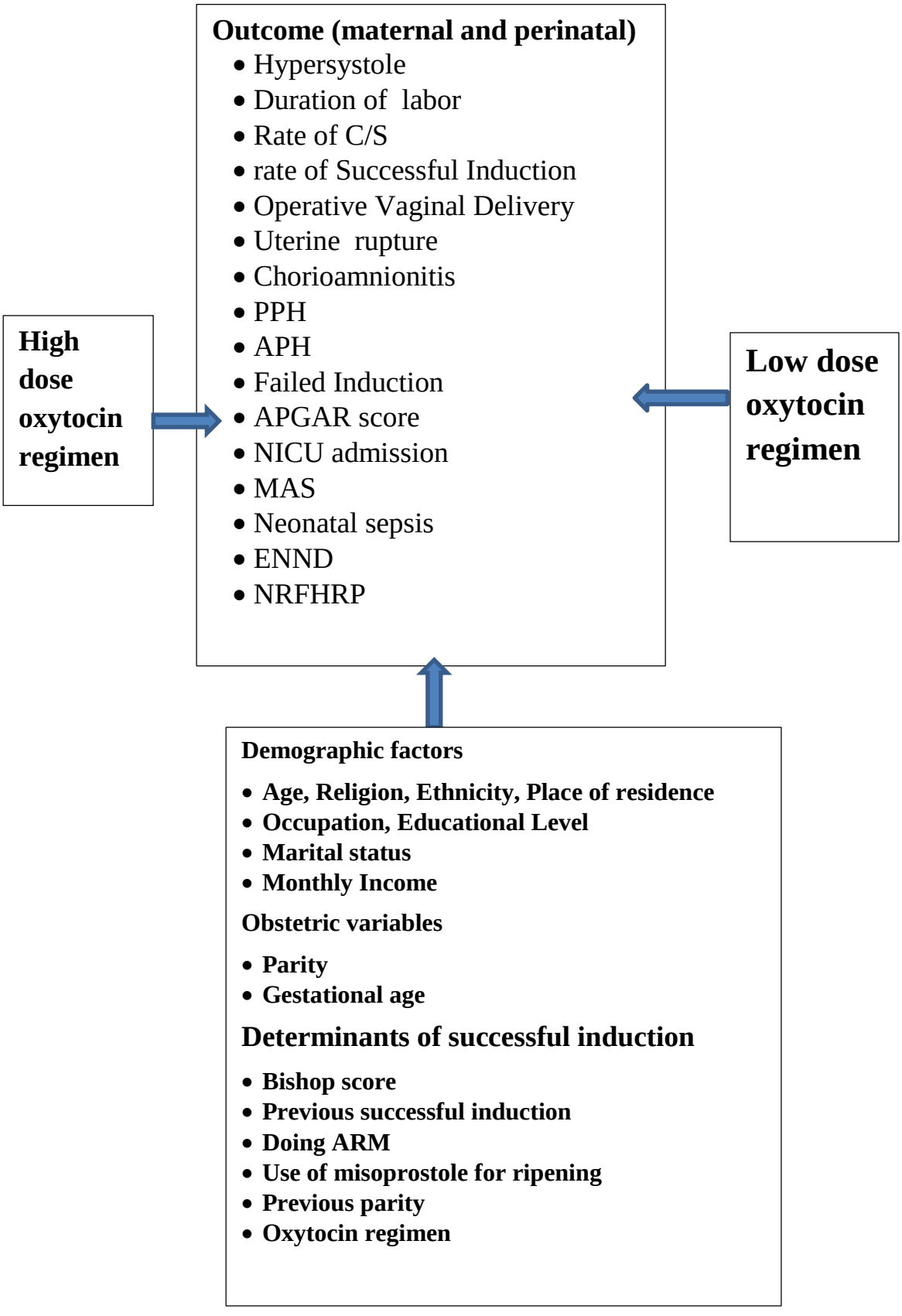
Satin AJ(1991) in other randomized trial the outcome of two protocols with similar initial dose of oxytocin of 2 mU/min but differing with incremental dose & interval was studied. Patients in protocol A received incremental doses of oxytocin of 1 mU/min at 30-minute intervals, while those in protocol B received incremental doses of 2 mU/min at 15-minute intervals. Induction failures were higher among patients on protocol A (31% vs 8%). Patients on protocol B had shorter times to delivery (mean = 10 hours 57 minutes vs 8 hours 3 minutes). The number of operative deliveries were similar regardless of protocol. There were no significant differences among the protocols in maternal and fetal complications, cesarean section rate, and uterine hyperstimulation [**23**].

In randomized, double-masked trials of high-dose(4.5 mu/min) compared with low-dose(1.5 mu/min) oxytocin for AOL and IOL with incremental dose similar to initial dose every 30 minute showed in the

group receiving oxytocin for induction, high-dose oxytocin was associated with a significant shortening of labor duration (oxytocin to delivery: 8.5 ± 0.3 hrs versus 10.5 ± 0.3 hrs),and reduced CS rate(11.3% Vs 15%).For nulliparous women undergoing induction, with high dose regimen rate of CS (11.7% vs 17.3%) & CPD(5.9% vs 11.9%) were lower as compared with low dose.When used for augmentation, high-dose oxytocin again was associated with a significant shortening of labor without a significant difference in CS rates. No differences in neonatal outcomes were noted between the groups for either augmentation or induction [**21**].Oxytocin during labor appears to be an independent risk factor for severe PPH, with a dose-related association [**24**].

In Ethiopia although limited number of studies are conducted on induction & augmentation of labor, neither of them has compared the effects of high dose versus low dose oxytocin regimen. Since 2010, Ethiopia is using both high dose & low dose oxytocin regimen but with no dosage difference between nulliparous & multiparous [**10-11**] even though some centers are still using half doses of induction for augmentation purpose.

2.2 CONCEPTUAL FRAME WORK



CHAPTER THREE: OBJECTIVE OF THE STUDY

3.1 General Objective

- To compare maternal and perinatal outcomes and determine factors associated with adverse maternal and perinatal outcomes among mothers undergoing IOL using high-dose and low-dose oxytocin regimen in JUMC, SGGH, AGH and KGH during October 1, 2017 to May 30, 2018.

3.2 Specific Objectives

1. To assess maternal, perinatal and labor outcomes among mothers undergoing IOL using high-dose and low-dose oxytocin regimen.
2. To compare maternal, perinatal and labor outcomes among high-dose as compared to low-dose oxytocin regimen used for labor induction
3. To determine factors associated with successful induction among mothers undergoing IOL using high-dose and low-dose oxytocin regimen.
4. To determine factors associated with adverse maternal outcomes among mothers undergoing IOL using high-dose and low-dose oxytocin regimen.
5. To determine factors associated with adverse perinatal outcomes among mothers undergoing IOL using high-dose and low-dose oxytocin regimen.

CHAPTER-FOUR: METHODS AND MATERIALS

4.1 Study area and period

The study was conducted in 4 facilities, JUMC, Shenen Gibe general hospital (SGGH) & Arbaminch general hospital (AGH) and Kuyu general hospital (KGH). JUMC & SGGH are located in Jimma town, which is about 352 km South-West of Addis-Ababa, a capital city of Ethiopia, while AGH and KGH are found at 550 km and 155 km away from Addis Ababa in South and North direction. JUMC is the specialized teaching referral hospital serving over fifteen million people in the southwest regions. It's maternity ward have 60 beds, while labor and delivery ward has 9 beds for first stage and five couches for second stage. In this hospital obstetric care is being provided by Midwifes, Medical Interns, Residents & Obstetricians. The center use high dose regimen for IOL. AGH, SGGH & KGH are general hospitals where obstetric care is being provided by obstetricians, midwifes, general practitioners & integrated emergency surgical officers (IESO). These three hospitals use low dose regimen for IOL. The research was conducted from October 1 to May 30.

4.2 Study design

Facility based cross-sectional comparative study design was employed.

4.3 Population

4.3.1 Source population

- Source populations were all pregnant women delivering in JUMC, SGGH, AGH and KGH during the study period.

4.3.2 Study population

- All pregnant women with singleton gestation who undergo induction of labor at GA of $\geq$ 37 weeks in all selected facilities during the study period

4.4 Inclusion and Exclusion criteria

- **Inclusion**: all post terms, medically indicated inductions at term & beyond. Gestational age precisely determined by LNMP or early US
- **Exclusion**: IUFD, critically ill mothers, pregnancy with gross fetal congenital anomaly, pregnancies complicated by cord prolapse , induced pregnancy for whom C/S done for non-obstetric indication like social reason

4.5 Sample size determination and sampling technique

4.5.1 Sample size

The required sample size was determined by using double population proportion formula. The outcome measure (proportion of C/S) among pregnant women undergoing augmentation of labor either by high dose or low dose oxytocin regimen found in the study done somewhere else [**21**] was used. In this study Proportion of C/S among high dose and low doses were 10.4% and 25.7% respectively. Considering 5% level of significance, 5% margin of error, 80% level of power and 10% non-response rate. Then Epi Info™ 7 software was used to calculate sample size.

p_0 = proportion of C/S done among high dose group = 10.4%

p_1 = proportion of C/S among low dose group = 25.7%

$q_0 = (1-p_0) = 1.0 - 0.104 = 0.89$, $q_1 = (1-p_1) = 1.0 - 0.257 = 0.74$

$z_{(1-a/2)}$ = 1.96 = value of the standard normal distribution corresponding to a significance level of a (1.96 for a one-sided test at the 0.05 level)

$z_{(1-b)}$ = 0.84 = value of the standard normal distribution corresponding to the desired level of power (0.84 for a power of 80%)

n1=n2=98

Considering the non-response rate of 10 % the sample size become 108. Taking equal proportion for both group total sizes of 216 was used for the study. Thus 108 pregnant women were taken from JUMC while the rest 108 were taken from AGH, KGH & SGGH with equal proportion. Thus 36 participants were taken from each three low dose centers.

4.5.2 Sampling technique

All pregnant women who undergo induction of labor during study period were recruited consecutively until the required sample size achieved.

4.6 Data collection

Data was collected by trained midwifes, 3rd year resident, third year IESO student (at AGH) and emergency surgical officers using pretested semi-structured questionnaire after verbal consent is obtained. Three data collectors and one supervisor at JUMC & 2 data collector & one supervisor at SGGH, KGH & AGH were recruited and given orientation on procedures, techniques and ways

of collecting the data. The questionnaire was developed and designed to meet all the objective of the study.

4.7 Study Variables

4.7.1 Dependant variables

- **Labor outcome variables**
  - Induction to delivery time
  - Mode of delivery (C/S, Instrumental & SVD)
  - Successful induction
  - Failed induction
- **Maternal outcome variables**
  - Composite adverse maternal outcome
  - PPH & uterine atony
  - Uterine Hyperstimulation
  - Uterine rupture
  - Chorioamnionitis
  - Purpureal sepsis
- **Perinatal outcome variables**
  - Composite adverse perinatal outcome
  - NRFHRP (Non reassuring fetal heart rate patterns)
  - APGAR scores
  - NICU admission
  - Still birth & ENND
  - Need of advanced neonatal resuscitation
- **Independent variables**
  - Socio - demographic variables (age, marital status, educational level, religion, ethinicity, occupation and place of residence ,income)
  - Parity
  - Gestational age
  - Oxytocin Regimen
  - Bishop scores

4.8 - Data Analysis

The completed questionnaire was checked for completeness and consistency by the principal investigator. Code was given to the completed questionnaire. Data was edited and entered into Epi data version 3.1 and then exported to SPSS version 20 for cleaning and analysis. Data was explored and cleaned (check for outliers, missing values and normality) using descriptive statistics. Cross-tabulation was conducted to compare the relationship of relevant variables with respect to the two oxytocin regimen using Chi-square test and Fisher's exact test for categorical variables. Bivariate logistic regression was done to look for association between 'successful induction and independent variables', 'maternal outcomes and independent variables', and 'perinatal outcome and independent variables.' Those variables having p value of < 0.25 on bivariate analysis was taken as a candidate for multivariate logistic model. Variables on multivariate logistic regression found to predict these outcomes were presented using 95% confidence interval (CI) of odds ratios (AOR). P-value < 0.05 was used to declare statistical significance.

4. 9 Data quality control

To assure the quality of the data properly designed data collection tool was prepared and training was given for data collectors and supervisors on how to gather the appropriate information, procedures of data collection techniques and the whole contents and subject matter of the questionnaire. The collected data was reviewed and checked for completeness and relevance by the supervisors and principal investigator for each questionnaire.

Twenty two questionnaires collected from other hospital outside study centers, which were not included in the main survey, were pre-tested prior to the actual data collection. Necessary modification was made for some gaps identified in on initial questionnaire after pre-test. Data was collected both from patient & patient's chart. A day to day supervision by the researcher & supervisors was being done during the whole period of data collection. At the end of each day, the questionnaire were reviewed and cross checked for completeness, accuracy and consistency by the supervisors and corrective discussion was under taken with all the data collectors. Data was cleaned and edited after it is entered in to the software.

4.10 Ethical clearance

Ethical clearance letter to conduct research given by IRB of Jimma University and official letter was obtained from Jimma University research and graduate studies coordinating office and was submitted to the responsible authorities of facilities to have permission for data collection. Verbal consent was taken from every study participant included in the study during data collection time

after explaining the objectives and benefits of the study. All the information collected from the study subjects were handled confidentially by omitting their personal identifiers and the data was used for the research purpose only. Subjects were told by the language they can that they have a right to participate or not in study as well as to interrupt at any time. Regarding the oxytocin regimen no new dosage protocol was employed for research purpose apart from the previously being used regimen for each of the study facilities.

4.11. Dissemination plan of the study findings

The final results of this study was submitted to the advisors, JU research, graduate studies and CBE coordinating office and to publishers for possible evaluation and publication of the paper. Recommendation was made based on the result.

4.12 Operational definition and definition of terms

- **Successful Induction**: if a woman delivered vaginally with or without aid of instrument after induction with oxytocin.
- **Failed induction**: if a woman deliver by C/S due to failure to acquire either adequate uterine contraction (≥3 contractions and duration lasting ≥40 seconds in ten minutes period) or failed to show favorable cervical changes (reach at least 4cm in dilatation and fully effaced) despite being on oxytocin drip for at least six to eight hours.
- **C/S for other indication:** if C/S is done for an indication other than failed induction.
- **Instrumental vaginal birth**: When vaginal delivery is effected by either vacuum or obstetric forceps.
- **Vaginal birth**: vaginal delivery without any assistance by instruments like vacuum or forceps
- **Adverse/unfavorable perinatal outcomes**: the sum total of each poor perinatal outcomes like low APGAR score ,admission to NICU, meconium at birth, need of advanced resuscitation, Neonatal sepsis, ENND and etc.
- **Adverse/ unfavorable maternal outcomes**: are any effects of oxytocin to the maternal condition & complications like PPH, uterine rupture, chorioamnionitis, uterine hypersystole & hyperstimulation.etc
- **Induction to delivery time**: the time it takes the mother from starting of oxytocin to delivery of the fetus either vaginally or abdominally.
- **NRFHRP (Non reassuring fetal heart rate patterns)** : fetal heart rate pattern of either fetal tachycardia or bradycardia leading to cesearean delivery.
- **Post partum hemorrhage (PPH)** : blood loss of >500ml following vaginal delivery, >1L following C/S,or any drop of postop or postpartum hematocrit of 10%.

- **Chorioamnionitis**: refers to infection of the amniotic fluid, membranes, placenta, and/or decidua as evidenced by maternal febrile morbidity in the peripartum period.
- **Tachysystole**: refers to > 5 contractions per 10-minute period averaged over 30 minutes.
- **Hypertonus** refers to excessive uterine contractions lasting > 120 seconds without FHR changes.
- **Hyperstimulation:** refers to excessive uterine contractions (tachysystole or hypertonus) with abnormal FHR changes.
- **Dystocia**: Abnormal labor resulting from abnormalities of "power, passenger, or passage" that results in slower than normal (protraction disorders) or complete cessation of progress (arrest disorders).
- **Low dose oxytocin regimen:** Initial dose of 2 mU/min increased by 2 mU/min every 30 minute up to a maximum of 40 mU/minute.
- **High dose oxytocin regimen:** Initial dose of 6 mU/min, increased by 6mU/min every 20 min up to a maximum dose of 92.8 mU/min.
- **Urban**: residence in towns & cities like Jimma, Arbaminch and Garba Guracha towns
- **Rular**: residence outside towns like Jimma, Arbaminch and Garba Guracha towns.
- **Bishop score** : It is a score used to assess cervical status and is a numeric value obtained from summation of the values given for each five cervical parameters like dilatation, station, consistency, position & cervical length or effacement.
- **Favorable bishop**: Those Bishop score having value of greater than six
- **Unfavorable bishop**: Those Bishop score having value of less or equal to six [**25**]

CHAPTER FIVE: RESULT

5.1 Socio-demographic, reproductive & obstetric Variables of study participants.

A total of 216 laboring mothers have participated in the study in four hospitals. Half of the participants are enrolled to high dose oxytocin regimen from JUMC while the remaining half is enrolled to low dose oxytocin regimen with equal proportion from AGH, SGGH and KGH. A total of 3162 mothers have delivered in JUMC during the study period of which 302 mothers undergo induction making prevalence of induction 9.5% at JUMC. Overall mean age of study participants is 26 years and it is also similar among the two study groups. Majority 138(64%) of the study participants are urban dwellers with comparable distribution to the two study groups. While 86(40%) of study participants are Orthodox followers, Muslim and Protestant followers accounts for 79 (36.6%0 & 43 (19.9%) respectively. More than half 116 (53.7%) of study participants are Oromo by ethnicity followed by Amhara 35 (16.2%), Gamo 23 (10.6%), Dawro 17 (8%) and Gurage 13(6%). Others account for only12 (5.6%) (**Table 1**).

Table 1: Socio-demographic characteristics of pregnant women undergoing IOL with high dose and low dose oxytocin regimen in JUMC, AGH, SGGH & KGH, during Oct1, 2017 to May30, 2018

Socio-demographic variables		Type of oxytocin regimen		Total No (%) N=216
		High dose (N=108)	Low dose (N=108)	
Age of respondent	Mean Age	26.1± 4.5	25.95±4.56	26.02 ± 4.526
	< = 19	4(3.7)	5(4.6)	9(4.2)
	20-29	76(70.4)	81(75.0)	157(72.7)
	≥30	28(25.9)	22(20.4)	50(33.1)
Ethnicity of respondents	Oromo	60(55.6)	56(51.9)	116(53.7)
	Amhara	27(25)	8(7.4)	35(16.2)
	Gamo	0(0)	23(21.3)	23(10.6)
	Dawro	5(4.6)	12(11.1)	17(7.9)
	Gurage	9(8.3)	4(3.7)	13(6.0)
	Others	7(6.5)	5(4.6)	12(5.6)

Religion	Muslim	50(46.3)	29(29.6)	79(36.6)
	Orthodox	44(40.7)	42(39.8)	86(39.8)
	Protestant	14(13)	29(19.9)	43(19.9)
	Others	0(0)	8(7.4)	8(3.8)
Occupation of respondent	House wife	66(61.1)	57(52.8)	123(57)
	Gov't employee	30(27.8)	25(23.1)	55(25.5)
	Merchant	7(6.5)	7(6.5)	14(6.5)
	Farmer	1(0.9)	9(8.3)	10(4.6)
	Student	2(1.9)	6(5.6)	8(3.7)
	Others	2(1.9)	4(3.7)	6(2.7)
Place residence	Urban	75(69.4)	63(58.3)	138(63.9)
	Rural	33(30.6)	45(41.7)	78(36.1)
Family income	Mean income	5068 ETB	4222 ETB	4645 ETB

A quarter of laboring mothers 57 (26.4%) have attended college and university while 40(18.5%) are illiterate. Occupation wise, 123(57%) are house wife while a quarter 55 (25.5%) are government employee. Overall mean income of laboring mothers for high dose group (HDG) and low dose group (LDG) are 5068 ETB and 4222 ETB respectively (**Table 1**).

Overall mean gestational age at delivery for all participants is 39.4 weeks which is also the same for the two study groups. Majority 176(82%) of the induction are undergone on emergency basis. Of all study subjects 88(41%) are nulliparous while the rest have at least given birth once in their life. However, distribution of the nulliparous among HDG & LDG is not equal as proportion of nulliparous among HDG & LDG is 52% and 30% respectively. The top three indications for IOL in this study in order are premature rupture of membrane (PROM) 128 (59.3%), hypertensive disorders of pregnancy (HDP) 49 (22.7%) and post-term pregnancy 27 (12.5%) while the others account for 12 (5.6%). This order is also the same among the two study groups as well. Majorities of the subjects enrolled in HDG 94(87%) have unfavorable bishop score at initiation of induction unlike those enrolled in LDG which is observed only in 43(40%) (**Table** 2)

Table 2: Reproductive & Obstetric characteristics of pregnant women undergoing IOL with high dose and low dose oxytocin regimen in JUMC, AGH, SGGH & KGH, during Oct 1, 2017 to May 30, 2018.

Variables	Catagories	Type of oxytocin regimen		
		High dose N_H=108	Low dose (N_L=108)	Total (N=216)
Parity	Nullipara	56(51.9)	32(29.6)	88(40.7)
	Parous	52(48.1)	76(70.4)	128(59.3)
Type of induction	Elective	22(20.4)	18(16.7)	40(18.5)
	Emergency	86(79.6)	90(83.3)	176(81.5)
Indication of Induction	POST TERM	12(11.1)	15(13.9)	27(12.5)
	PROM	69(63.9)	59(54.6)	128(59.3)
	HDP	23(21.3)	26(24.1)	49(22.7)
	Others	4(3.7)	8(7.4)	12(5.6)
Bishop score before induction	Unfavorable	94(87)	43(39.8)	137(63.4)
	Favorable	14(13)	65(60.2)	79(36.6)
GA at Delivery	Mean GA	39.34+1.8	39.36+1.7	39.35+1.8
Gestational Age category	Term	95(88)	94(87)	189(87.5)
	Post term	13(12)	14(13)	27(12.5)
Hx of previous successful induction	YES	5(4.6)	11(10.2)	16(7.4)
	NO	103(95.4)	97(89.8)	200(92.6)
Misoprostol use for Ripening	YES	40(37)	57(52.8)	97(44.9)
	NO	68(63)	51(47.2)	119(55.1)
ARM done	YES	27(25)	18(16.7)	45(20.8)
	NO	81(75)	90(83.3)	171(79.2)
Onset of Oxytocin to delivery time	Mean duration	5.9±1.8	6.27±2.74	6.07±2.32

Maximum Oxytocin conc. in mu/min	Mean concentration	77.6±24.5	22±12.5	49.8±33.9
Mode of delivery	**VD**	50(46.3)	73(67.6)	123(56.9)
	CS	42(38.9)	30(27.8)	72(33.3)
	• For failed Indn	19(45.2)	17(56.7)	36(50)
	• For NRFHRP	19(45.2)	6(20)	25(34.7)
	• For CPD	4(9.6)	7(23.3)	11(15.3)
	Instrumental delivery	16(14.8)	5(4.6)	21(9.7)
	• For Shortening SSOL	7(43.8)	4(80)	**11(52.4)**
	• For NRFHRP	7(43.8)	1(20)	8(36.4)
	• For Prolonged SSOL	2(12.5)	0(0)	2(11.2)
Reason for Failed induction	No cervical change	17(89.5)	12(70.6)	29(80.6)
	Poor Ux contraction	2(10.5)	5(29.4)	7(19.4)
ALOHS[1] in days	Mean ALOHS	2.0±1.5	2.7±1.5	2.4+1.6
Weight of newborn	Mean weight	3130gm+351	3390+499	3260+449
Weight of neonate in grams	2500-3999 (NBW)	103(95.4)	89(82.4)	192(88.9)
	≥ 4000 (Macrosomia)	5(4.6)	19(17.6)	24(11.1)
Sex of newborn	Male	61(56.5)	61(56.5)	122(56.5)
	Female	47(43.5)	47(43.5)	94(43.5)
Successful induction	Yes	66 (61.1)	78 (72.2)	144(66.7)
	No	42 (38.9)	30 (27.8)	72(33.3)

[1] ALOHS: Average length of hospital stay

5.2 Labor outcomes (**oxytocin to delivery time, mean oxytocin concentration, rate of CS, Rate of instrumental delivery, induction success**)

Overall mean "oxytocin to delivery" time is 5.9 hours and 6.3 hours for subjects of HDG and LDG respectively. Mean oxytocin concentration required till delivery for study subjects is 77.6 mu/min

(SD±24.5) and 22mu/min (SD±12.5) for HDG and LDG respectively. Induction was successful in 61.1% and 72.2 % of study subjects among HDG & LDG respectively while it is failed in 17.6 % and 15.7% of subjects in the two groups respectively. Mean duration of hospital stay was (2.0 days versus 2.7 days) for HDG and LDG respectively. (**Table 2**)

Rates of C/S are 38.8% and 27.8% while that of instrumental delivery are 14.8% & 4.6% among HDG and LDG respectively. Indications for C/S are failed induction 19 (45%), NRFHRP 19 (45%) and CPD 4 (10%) among HDG while failed induction 17(56.7%), CPD 7(23.3%) and NRFHRP 6(20%) are among LDG. NRFHRP as an indication of instrumental delivery is observed in 37.5% and 20% of subjects enrolled in HDG &LDG respectively. Inadequate uterine contraction as a reason for failed induction is observed in 10% & 30% of HDG & LDG while no cervical status change as a cause of failed induction share the remaining proportion (90% & 70%) respectively (**Table** 2).

5.3 Factors affecting success of induction

On Bivariate logistic regression analysis age, residence and family income of the respondent, previous history of successful induction, cervical ripening with misoprostol, type oxytocin regimen, gestational age at delivery and neonatal weight did not show any kind of association with successful induction of labor. However, previous parity [COR=2.1, 95%CI:(1.2,3.7)], bishop score at initiation of oxytocin [COR=3.4, 95%CI: (1.7, 6.7)], type of induction [COR= 0.4,95%CI:(0.2,0.7)] and performing ARM [COR=3.3,95%CI:(1.4, 7.9)] were found to be statistically significantly associated with successful IOL at P-Value < 0.05.(**Table 3**)

Table 3: Multivariate Logistic Regression of factors associated with success of induction

VARIABLES	RESPONSE	Successful Induction		COR(95%CI)	P – value	AOR (95%CI)	P-Value
		Yes	No				
Age of respondent	< = 19	4(2.8)	5(6.9)	1			
	20-29	103(71.5)	54(75)	2.4(0.6, 9.2)	.209		
	>30	37(25.7)	13(18.1)	3.6(0.8,15.3)	.088		
Residence	Urban	87(60.4)	51(70.8)	0.6(0.3, 1.2)	.134		
	Rural	57(39.6)	21(29.2)	1			

Oxytocin regimen	High dose	66(45.8)	42(58.3)	0.6(0.3, 1.1)	.084		
	Low dose	78(54.2)	30(41.7)	1			
Previous successful indn	YES	14(9.7)	2(2.8)	3.8(0.8, 17.1)	.085		
	NO	130(90.3)	70(97.2)	1			
GA at delivery	Term	129(89.6)	60(83.3)	1.7(0.8, 3.9)	.194		
	Postterm	15(10.4)	12(16.7)	1			
Ripening with misoprostol	YES	59(41)	38(52.8)	0.6(0.4, 1.1)	.101		
	NO	85(59)	34(47.2)	1			
Previous Parity	Paraus	94(65.3)	34(47.2)	2.1(1.2, 3.7)	.012	2.1(1.1,4.0)	.024
	Nulliparous	50(34.7)	38(52.8)	1		1	
Bishop score before indn	Favorable	65(45.1)	14(19.4)	3.4(1.7, 6.7)	.000	4.1(2.0, 8.8)	.00
	Unfavorable	79(54.9)	58(80.6)	1		1	
Type of induction	Elective	19(13.2)	21(29.2)	0.4(0.2,0.7)	.005	0.2(0.1,0.5)	.001
	Emergency	125(86.8)	51(70.8)	1		1	
ARM done	YES	38(26.4)	7(9.7)	3.3(1.4, 7.9)	.006	7.8(2.7, 22.6)	.00
	NO	106(73.6)	65(90.3)	1		1	
Neonatal weight in gm	< 4000	132(91.7)	60(83.3)	2.2(0.9, 5.2)	.071	4.3(1.6, 11.6)	.005
	≥4000	12(8.3)	12(16.7)	1		1	

On multivariable logistic regression analysis the variables remained in the model to predict success of induction are having favourable bishop score at initiation of oxytocin [AOR=4.0, 95%CI: (1.9, 8.5)], elective type of induction[AOR=0.2,95%CI: (0.1,0.4)] , performing ARM [AOR=10.1,95%CI:(3.2, 32.2)], neonatal weight of < 4000gm [AOR= 4.3, 95%CI: (1.6, 11.6)] and being parous [AOR=2.1, 95%CI: (1.1,4.0)] were found to be statistically significant at P-Value < 0.05 (**Table 3**).

5.4 Maternal outcomes & factors associated with adverse maternal outcome

Overall maternal outcome on discharge is favorable and no mother is discharged with severe complication or permanent sequel except one mother whose uterus ruptured and repaired after receiving high dose oxytocin regimen. Mean duration of hospital stay of study subjects is 2 days and 2.7 days for

HDG & LDG respectively (**Table** 2). Overall composite adverse maternal outcomes associated with oxytocin use were observed in 22(10.2%) of study subjects of which 13(6 %) are from LDG. Uterine hyper stimulation and uterine rupture has occurred only among HDG. Similarly, chorio-amnionitis diagnosed after initiation of oxytocin and puerperal sepsis, are adverse maternal outcomes solely occurred among LDG. The specific outcomes are detailed in table (**Table 4).**

On cross tabulation both successful induction and cesarean delivery has no significant relation with use of different oxytocin regimens. Of all maternal outcome variables like uterine hyper stimulation, uterine atony, postpartum hemorrhage, uterine rupture, pulmonary edema, puerperal sepsis and chorio-amnionitis, only puerperal sepsis, instrumental delivery and vaginal delivery are significantly related with use of different oxytocin regimens with P-value <0.05. Accordingly prevalence of puerperal sepsis are 5.6% and 0% (X^2=0.015, P= 0.029), rate of instrumental delivery are 4.6% and 14.8% (X^2=6.4, P= 0.012) and rate of vaginal delivery are 67.6 % and 46.3% (X^2 =9.9, P=0.002) among LDG and HDG respectively (**Table 4).**

On bivariate logistic regression age, residence, previous parity, oxytocin regimen, Bishop Score and indication of induction did not show any kind of association with adverse maternal outcome. However, misoprostol use [COR= 4.8, 95%CI: 1.7, 13.7], Caesarean delivery [COR=3.3, 95%CI: 1.2, 8.9] and neonatal birth weight ≥4000gm [COR=3.7, 95%CI: (1.3, 10.5)] has shown statistically significant association with adverse maternal outcome at P-Value < 0.05. On multivariate logistic regression analysis the only two variables remained in the model to predict association with adverse maternal outcome at P-Value < 0.05 are misoprostol use [AOR= 4.7, 95%CI: (1.6, 13.4)] and neonatal birth weight ≥4000gm [AOR= 3.4, 95%CI: (1.1, 10.3)] (**Table 5**).

Table 4: Cross-tabulation of maternal outcome variables with high dose and low dose oxytocin regimen in JUMC, AGH, SGGH & KGH, during Oct 1, 2017 to May30, 2018.

Maternal Outcome Variables	Response	Type Of Oxytocin Regimen		P- Value	Pearson X^2 VALUE
		High Dose N (%)	Low Dose N (%)		
Instrumental Vaginal Delivery	Yes	16 (14.8)	5(4.6)	0.012	6.4
	No	92 (85.2)	103(95.4)		
	Yes	50(46.3)	73(67.6)		

Vaginal delivery	No	58(53.7)	35(32.4)	0.002	9.9
C/S Delivery	Yes	42 (38.9)	30(27.8)	0.083	
	No	66 (61.1)	78(72.2)		
Composite Adverse Maternal outcome	Yes	9(8.3)	13(12)	0.368	
	No	99(91.7)	95(88)		
Puerperal Sepsis	Yes	0(0.0)	6(5.6)	0.029*	0.015
	No	108(100)	102(94.4)		
PPH Or Uterine Atony	Yes	3(2.8)	3(2.8)	1.00*	
	No	105(97.2)	105(97.2)		
Uterine Hyper Stimulation	Yes	4(3.7)	0(0)	0.122*	
	No	104(96.3)	108(100)		
Uterine Rupture	Yes	1(0.9)	0(0)	1.00*	
	No	107(99.1)	108(100)		
Chorio-Amnionitis Diagnosed After IOL	Yes	0(0)	3(2.8)	0.247*	
	No	108(100)	105(97.2)		
Pulmonary Edema	Yes	1(0.9)	1(0.9)	1.00*	
	No	107(99.1)	107(99.1)		

*Fisher's Exact Test is used

Table 5: Multivariate Logistic Regression of factors associated with adverse maternal outcomes

Variables	Response	**Adverse maternal outcomes**		COR (95%CI)	P – Value	AOR (95%CI)	P-Value
		YES No (%)	NO No (%)				
Residence	Rural	11(50)	67(34.5)	1.9(0.8,4.6)	0.157	1	
	Urban	11(50)	127(65.5)	1			

Oxytocin regimen	High dose	9(40.9)	99(51)	0.7(0.3, 1.6)	0.371*		
	Low dose	13(59.1)	95(49)	1		1	
Bishop score at induction	Unfavorable	17(77.3)	120(61.9)	2.1(0.7,5.9)	0.162	1	
	Favorable	5(22.5)	74(38.1)	1			
Misoprostol use	YES	17(77.3)	80(41.2)	4.8(1.7,13.7)	0.003	4.7(1.6,13.4)	0.004
	NO	5(22.7)	114(58.8)	1		1	
Delivery Mode	CS	12(54.5)	60(30.9)	3.3(1.2,8.9)	0.024		
	Instrumental	3(13.6)	18(9.3)	2.8(0.7,11.7)	0.349		
	SVD	7(31.8)	116(59.8)	1		1	
Neonatal weight	≥4000	6(27.3)	18(9.3)	3.7(1.3,10.5)	0.016	3.4(1.1, 10.3)	0.028
	< 4000(NBW)	16(72.7)	176(90.7)	1		1	

* Included b/c it is biologically plausible to the outcome variable and it is the main interest of the study.

NBW: Normal birth weight (neonatal weight of 2500g up to 3999.9g, we don't have weight <2500g)

5.5 Perinatal outcomes and factors associated with adverse perinatal outcome

Mean weight of newborns is 3260gm (SD±449). Surprisingly equal number of male and female neonates are delivered in both groups with male to female ratio of 1.3:1(**Table 2**).Of all 216 delivered, three neonates have complicated by early neonatal death (ENND); one from HDG and two from LDG. Overall composite adverse neonatal outcomes were observed in 47(21.8%) of study subjects, of which two third are from HDG, 32 (14.8 %). (**Table 6**).

The most common adverse neonatal outcomes were development of NRFHRP 33(15.3%) followed by need for advanced neonatal resuscitation, 20 (9.3%), presence of thick meconium at birth 19 (8.8%) and need of referral to NICU, 16(7.4%). The main reasons for neonatal resuscitation for those who required resuscitation are thick meconium at birth,14 (70%) followed by low APGAR score, 4 (20%) and respiratory distress, 2 (10%) while the main diagnosis at NICU for those who needs referral are meconium aspiration syndrome, 6 (37.5%) followed by perinatal asphyxia, 3(18.8%) (**Table 6**).

Cross-tabulation result showed occurrence of NRFHRP and composite adverse neonatal outcome has significantly related with use of different oxytocin regimens while other outcome variables like thick meconium at birth, need of advanced neonatal resuscitation, need of referral to NICU, first minute APGAR <5, Fifth minute APGAR <7, Neonatal life status on discharge showed no relation. Accordingly, prevalence of NRFHRP are 23.1% and 7.4% (X^2=10.33, P= 0.001), overall composite adverse outcome are 29.6% and 13.9% (X^2=7.86, P= 0.005) among HDG and LDG respectively (**Table 6**).

Table 6: Cross-tabulation of perinatal outcome with high dose and low dose oxytocin regimen in JUMC, AGH, SGGH & KGH, during Oct 1, 2017 to May30, 2018.

Perinatal Outcome Variables	**Response**	**Type Of Oxytocin Regimen**		**P-Value**	**Pearson X^2**
		High Dose (N=108) n (%)	Low Dose (N=108) n (%)		
Composite adverse neonatal outcome	Yes	32(29.6)	15(13.9)	0.005	7.86
	No	76(70.4)	93(86.1)		
NRFHRP	Yes	25(23.1)	8(7.4)	0.001	10.33
	No	83(76.9)	100(92.6)		
Grade 2 or 3 MSAF at delivery	Yes	12 (11.1)	7 (6.5)	0.230	
	No	96(88.9)	101 (93.5)		
Advanced neonatal resuscitation needed	Yes	14 (13)	6 (5.6)	0.06	
	No	94(87)	102(94.4		
Neonate referred to NICU	Yes	10(9.3)	6 (5.6)	0.299	
	No	98 (90.7)	102 (94.4)		
First minute APGAR	APGAR <5	1 (0.9)	2 (1.9)	1.000*	
	APGAR >=5	107 (99.1)	106 (98.1)		
Fifth minute APGAR	APGAR <7	1 (0.9)	4 (3.7)	.369*	
	APGAR >=7	107 (99.1)	104 (96.3)		

Outcome of neonate on discharge	Alive	107 (99.1)	106 (98.1)	1.00*	
	Dead(ENND)	1 (0.9)	2 (1.9)		

*Fisher's Exact Test is used

On bivariate logistic regression residence, previous parity, misoprostol use, and neonatal weight, uterine hyper stimulation did not show any kind of association with adverse perinatal outcome while maternal age $\leq$ 19 years [COR=4.4, 95%CI: 1.0,19.4], oxytocin regimen[COR=2.6, 95%CI: 1.3, 5.2], caesarean delivery[COR=9.0, 95% CI:4.0, 20.6], instrumental delivery[COR=7.8 95% CI: 2.6, 23.7], favorable Bishop score,[COR=0.2, 95% CI: (0.0,0.9)] presence of adverse maternal outcome[COR=2.8, 95% CI: 1.1, 7.1] and APH as indication[COR=8.8, 95%CI:(1.3, 57.0)] showed statistical significance with occurrence of adverse maternal outcome at P-Value < 0.05. (**Table 7**)

However, on multivariate model, Oxytocin regimen [AOR=2.4, 95%CI: 1.1, 5.5], caesarean delivery [AOR=9.3, 95% CI: 3.8, 22.5], instrumental delivery [AOR=7.7, 95% CI: 2.1, 27.8], APH as induction indication [AOR=17.8, 95% CI: (1.9, 168.7)] are found to be associated with adverse neonatal outcome at P-value < 0.05 (**Table 7**).

Table 7: Multivariate Logistic Regression of factors associated with adverse neonatal outcomes

Variables	Category	**Adverse neonatal outcomes**		COR(95%CI)	P – Value	AOR(95%CI)	P-Value
		Yes n(%)	No n (%)				
Oxytocin regimen	High dose	32(68.1)	76(45)	2.6(1.3, 5.2)	.006	2.4(1.0, 5.5)	.039
	Low dose	15(31.9)	93(55)	1		1	
Delivery Mode	CS	30(63.8)	42(24.9)	9.0(4.0, 20.6)	.000	9.4(3.8, 22.8)	.000
	Instrumental	8(17)	13(7.7)	7.8(2.6, 23.7)	.000	7.8(2.2, 28.3)	.002
	SVD	9(19.1)	114(67.5)	1		1	
Indication for induction	PROM	25(53.2)	103(60.9)	0.9(0.3, 2.3)	.751	1.0(0.3,3.2)	.943
	HDP	8(17)	41(24.3)	0.7(0.2, 2.2)	.527	0.6(0.1,2.0)	.373
	APH	5(10.6)	2(1.2)	8.8(1.3, 57.0)	.023	17.8(1.9,168.7)	.012
	Chorioamnionitis	3(6.4)	2(1.2)	5.3(0.7,39.0)	.105	9.0(0.8,97.0)	.071
	Post term	6(12.8)	21(12.4)	1		1	
Previous Parity	Nullipara	25(53.2)	63(37.3)	1.9(0.9,3.7)	.051		
	Multipara	22(46.8)	106(62.7)	1		1	
Bishop score	Unfavorable	38(80.9)	99(58.6)	3(1.3,6.6)	.007		
	Favorable	9(19.1)	70(41.4)				
Maternal Age in years	< = 19	5(10.6)	4(2.4)	4.4(1.0,19.4)	.048		
	20-29	31(66)	126(74.6)	0.9(0.4,1.9)	.730		
	> = 30	11(23.4)	39(23.1)	1		1	
maternal complxn	Yes	9(19.1)	13(7.7)	2.8(1.1, 7.1)	.026		
	No	38(80.9)	156(92.3)	1		1	
Uterine hyperstimulation	Yes	5(10.6)	5(3.0)	3.7(0.5, 27.1)	.196		
	No	42(89.4)	164(97)	1		1	

CHAPTER SIX: DISCUSSION

6.1 Labor Outcomes

Being parous, having favorable Bishops score at initiation of oxytocin and performing ARM are significantly associated with increased success of induction by 2 times, 4 times and 10 times compared to nulliparous, unfavorable Bishop score and not performing ARM respectively. This is in line with other study reports from Ethiopia [**12, 14, 15, 16**]. This is because it is a well-established science that being parous, favorable cervical status and elective amniotomy or ARM are good predictors of successful induction of labor. Performing ARM strengthen the cascade of uterine contraction thus hastens labor and increase successful vaginal delivery. It is found that nulliparity has increased risk of failed induction by 1.5-3 times in other studies as well [**12, 15**, **26, 27**].

Similarly delivering to normal birth weight neonate compared to macrosomic neonate increase success by 4 times. This might be justified by the fact that macrosomia is associated with labor dystocia and cephalo-pelvic disproportion thus ending in cesarean delivery than successful vaginal delivery. But our finding is not consistent with different literatures of the similar settings in Ethiopia that showed no association between neonatal birth weight outcome and induction success [**12, 15, 16**].

However, induction on elective basis compared to emergency induction reduces the induction success by 80%. This doesn't show association with failed induction in study conducted by Woubishet et al [**l2**]. We expect successful induction with elective induction than emergency induction. Because with elective induction one can buy time to ripen cervix till it gets favorable before initiating oxytocin thus increasing the success rate. But the finding of our study is opposite to this logic. This might be explained by the fact that majority of study participants (82%) are induced on emergency basis. On other hand, of all remaining elective inductions, 68% are induced for post term pregnancy. Post term is associated with decreased induction success as seen in different literatures [**15, 16**].

Success of induction is lower among HDG compared to LDG (61.1% vs. 72.2%). The Success of induction among the three low dose setting ranges from 69.4% to 75% all of which are higher than the high dose setting. This tells us whatever the level of the facility, those enrolled in LDG are having higher successful induction compared to HDG. The rate of successful induction in HDG is slightly lower than previous study (65.7%) done in the same center that use same protocol[**12**] while having almost the same success rate (61.5%) to other study from Ethiopia [**15**]. Rate of C/S is higher among HDG compared to LDG (38.8% versus 27.8%). This is consistent with one meta-analysis that showed higher C/S rate among

HDG [**3**] and one cohort study done at Inova Alexandria Hospital (28% versus 27%)[**8**]. However, the finding of our study is in contrary to one Cochrane review (18.8 versus 19.8) [**9**], one double masked randomized oxytocin trial (11.3% versus 15%) [**19**] and other two studies (9% versus 12%)[**17]** and (10.4% versus 25.8%) [**21**] showing higher C/S rate among LDG.

When we see indication of C/S, although C/S for failed induction occurred less frequently with the high-dose regimen (45.2% versus 56.7%), C/S for NRFHRP was performed more frequently (45.2% versus 20%) as compared to LDG. This is in line with one study where lower rate of failed induction among high-dose compared with low-dose oxytocin (14% versus 19%) and significantly increased cesarean incidence for fetal distress (6% versus 3%) was found [**17**]. Rate of instrumental delivery is higher among HDG than in LDG (14.8% versus 4.6%). This finding is consistent with one meta-analysis and one recent (2016) Cochrane review [**3**, **9**]. The occurrence of NRFHRP requiring either instrumental or cesarean delivery observed in HDG is increased by four times that of LDG (24.1 versus 6.4%) in this study. Thus the likelihood of developing NRFHRP is higher with mothers receiving high oxytocin regimen. This higher utilization of instrument for delivery and higher development of NRFHRP with high dose as compared to LDG is found to be statistically significant as it is seen in table 4&6 above.

In this study higher successful induction and lower C/S rate among LDG is observed compared to HDG. We can raise many possible explanations why these occur unlike other studies. Firstly, 60% of subjects in LDG have favorable Bishop Score compared to HDG (only 13%) predicting higher successful induction and lower c/s rate. Secondly, high dose oxytocin has statistically significant relation with NRFHRP in this study and mere occurrence of NRFHRP necessitating C/S during labor may reduce the possible number of successful vaginal deliveries if labor is to be continued. The fact that the number of mothers undergoing C/S for NRFHRP among HDG is higher by 2.3 times than among the LDG (45% versus 20%) may explain higher C/S & lower successful induction observed among HDG.

Thirdly, although not statistically significant in this study, higher utilization of misoprostol for cervical priming among LDG (52.3% versus 37%), presence of higher proportion of mothers with previous history of successful induction (10.2% versus 4.6%) and significantly lower proportion of nulliparous women in LDG (29.6% versus 51.9%) compared to HDG might have contributed to higher successful induction rate among LDG in our study. Because misoprostol use is standard of management and is a known fact that it increases success of induction. Lastly, the fact that centers with low oxytocin regimen use oral misoprostol for cervical priming before oxytocin induction in contrary to high dose center which initiate

direct oxytocin induction for prolonged PROM, and PROM being major indication of induction (60%), might have contributed to higher induction success rate and thus lower C/S rate among LDG .

Rate of failed induction is nearly the same among HDG (17.6%) and LDG (15.7%).This similarity in rate among the two groups is also seen in one cohort study comparing the two oxytocin regimen (4.3% & 5.1 %) [**8**] and in other double masked randomized oxytocin trial (6.0% & 6.1%)[**19**]. However, rate of failed induction is generally higher in our study compared to those studies. This might be due to the fact that the studies are following different protocols in relation to total duration of hours waited to diagnose failed induction. In this study failure to acquire either adequate uterine contraction (≥3 contractions and duration lasting ≥40 seconds in ten minutes period) or failed to show favorable cervical changes (reach at least 4cm in dilatation and with full effacement) despite being on oxytocin drip for six to eight hours is used to diagnose failed induction.

But other centers in literatures used to give more time ranging from 12 to 24 hours as latent phase can usually be prolonged but ended in vaginal delivery [1]. In one recent large cohort study conducted on 10,677 laboring mothers in USA majority (96.4%) of women entered active phase by 15 hours and the authors concluded that cesarean delivery should not be undertaken during the latent phase prior to at least 15 hours after oxytocin and rupture of membranes have occurred leaving the decision to continue labor beyond this point to be individualized [**28**]. In one other large study (18,142 mothers) at time points from 6 to 18 hours of oxytocin and ROM, the rates of nulliparous women remaining in the latent phase declined (35.9% to 1.4%) and they finally recommend at least 12 hours of oxytocin and rupture of membranes in nulliparous and 15 hours in multiparous women is reasonable before considering an induction to have failed [**29**]. Thus early decision to diagnose failed induction in our protocol might have contributed to the higher rate of failed induction in our study as compared to other literatures used for comparison.

6.2. Mean Oxytocin to delivery time, & mean oxytocin level used

Overall mean "oxytocin to delivery" time for study subjects is 6.1 hours. Oxytocin to delivery time is 5.9 hours and 6.3 hours for subjects of HDG and LDG respectively. This shows that mothers receiving high dose oxytocin regimen will have slightly shorter duration of labor. This finding is similar to many literatures although majority of them showed significant shortening (2-3 hours) of induction to delivery time as compared to our study [**3, 8, 17, 19, 20, 23**]. Similar effect was also seen in studies using oxytocin for augmentation [**4, 5**].

Mean time elapsed from initiation of oxytocin to vaginal delivery and till diagnosis of failed induction were 5.1 hours and 8 hours among HDG respectively compared with their LDG counterparts (6 hours & 8.3 hours) and other study conducted at the same center (JUMC) 8 years back which is 6.2 and 9.9 hours respectively [**12**]. Although duration of labor before diagnosing failed induction is nearly the same for the reason both centers using similar protocol to diagnose failed induction, shorter duration for oxytocin to vaginal delivery among HDG shows that high dose regimen is associated with significant shortening of labor duration as it is also true in different literatures that showed a 2 hours difference [**19, 22**]

Mean maximum oxytocin level at which oxytocin infusion maintained is 22 mu/min and 77.6 mu/min among LDG and HDG respectively. Mean maximum oxytocin levels used until vaginal delivery and at time of diagnosis of failed induction were 68.4 mu/min and 92.8 mu/min respectively among HDG. The respective required oxytocin level in HDG is by far higher than the one required by subjects of LDG (20.5mu/min & 28.4 mu/min respectively) and the one reported from the same center which is 55mu/min and 89.7 mu/min respectively [**12**].

6.3 Adverse Maternal outcome and associated factors

The study generally showed lower adverse maternal outcomes (8.3% versus 12%) with HDG compared to LDG. Puerperal sepsis and chorio-amnionitis after IOL are seen among women receiving low dose regimen only. On other hand, uterine tachysystole and one uterine rupture are observed only in women receiving high dose regimen. This is because low-dose protocols mimic endogenous maternal physiology and are associated with lower rates of uterine tachysystole [**1, 3**]. The higher uterine tachysystole with HDG is consistent with other studies [**4, 9, 17, 18]**. However, no difference is observed on development of post partum hemorrhage (PPH) and pulmonary edema in both groups as it holds true in one systematic review published on American journal of obstetrics and gynecology in 2010[**4**]. But one study showed increased risk of PPH with increasing oxytocin dose [**24**].

Composite adverse maternal outcome has no significant association with different oxytocin regimen. This is in line with many literatures [**4, 9, 18, 21, 23**]. However, puerperal sepsis has got statistical significance with regard to oxytocin regimen used (x^2=0.029). Misoprostol use and delivery to macrosomic baby are significantly associated with adverse maternal outcome. Accordingly, use of misoprostol for cervical ripening and delivery to macrosomic baby increases odds of adverse maternal outcomes by 4.7 times and 3.4 times as compared to not using misoprostol and delivery to non macrosomic baby respectively. We didn't get study with similar outcome variables to compare with our study.

Association of misoprostol use to adverse maternal outcome seen in this study is difficult to justify thus it needs further study to see if there is true association. Macrosomic fetus is associated with uterine atony, labor dystocia and cephalo-pelvic disproportion that may require cesarean delivery which in turn is associated with adverse maternal outcome like PPH, uterine atony, endomyometritis, anesthesia complications. Vaginal delivery of macrosomic delivery is also associated with birth trauma which might have contributed to adverse maternal outcome.

6.4 Adverse Perinatal Outcomes and Associated Factors

The study generally showed higher adverse perinatal outcomes with HDG compared to LDG (36% versus 25%). Adverse perinatal outcomes like non reassuring fetal heart rate patterns (NRFHRP), need for advanced resuscitation, thick meconium at birth, and referral to NICU were observed in higher proportion in HDG than in LDG. But early neonatal death, first minute APGAR <5, fifth minutes APGAR < 7 were found more commonly among LDG as compared to HDG. In this study high dose oxytocin regimen, antepartum hemorrhage(APH) as indication of induction, caesarean delivery, and instrumental delivery are found to be associated with adverse neonatal outcome with P-value of < 0.05. Accordingly, use of high dose oxytocin regimen is associated with 2.5 times increased odds of developing adverse perinatal outcome as compared to low dose oxytocin regimen. This is inconsistent with other studies that showed no significant difference on perinatal outcome with regard to oxytocin regimen [**8, 17, 19, 21, 23**]. The association observed in this study can be explained by the fact that high dose oxytocin is associated with uterine hyper-systole and NRFHRP thus increasing composite adverse neonatal outcome.

Similarly APH as indication of induction are associated with 18 times increased odds of developing adverse perinatal outcome as compared to post term. Similarly caesarean delivery & instrumental delivery are associated with 9 times and 8 times increased odds of developing adverse perinatal outcome compared to vaginal delivery. It is known that APH, specifically abruptio placenta, causes severe perinatal morbidity like intra-partal NRFHRP, severe neonatal acidemia, cerebral palsy and also cause severe maternal morbidity which may lead to bad perinatal outcome [**1**]. On other hands, although delivery by C/S and instrumental deliveries are not a cause for adverse perinatal outcome, the indication to do C/S or to apply instrument, mainly NRFHRP might have contributed for this increased risk. Because nearly half of C/S and half of instrumental deliveries are performed for NRFHRP and contribution of NRFHRP for composite adverse perinatal outcome is 70%.

Limitation of the study

The selected facilities are of teaching & public in their type and the available experts in the field of obstetrics, & the facility they have for obstetric care are different. Additionally there is some difference in protocol for induction, specifically utilization of oral misoprostol with mothers presented with PROM in low dose setting while direct induction with oxytocin among high dose center irrespective of Bishop score. These might have affected the finding of the study.

CHAPTER SEVEN: CONCLUSION AND RECOMMENDATIONS

7.1 Conclusions

- In the study high dose oxytocin regimen is significantly associated with increased adverse perinatal outcome, slightly shorter oxytocin to delivery time, shorter duration of hospital stay. However, oxytocin regimen didn't show any statistically significant association with maternal outcome and induction success.
- Favourable bishop score, emergent type of induction, performing ARM and delivery to neonate weighing < 4kg are positive predictors of successful induction.
- High dose oxytocin regimen, APH as indication of induction, caesarean delivery, and instrumental delivery are significantly associated with increased odds of adverse perinatal outcome while only misoprostol use and delivery to macrosomic neonate are associated with increased odds of adverse maternal outcome
- High dose oxytocin regimen is significantly associated with higher utilization of instrument for delivery and higher development of NRFHRP.
- Rate of failed induction is generally high in this study at both setting.

7.2 Recommendation

- The fact that higher successful induction, lower C/S rate, decreased risk of adverse perinatal outcome but with no significant d/c in adverse maternal outcome found in low dose oxytocin regimen compared to high dose oxytocin regimen favors the recommendation of low oxytocin regimen
- However, more strong research that controls confounders is needed to come up with strong recommendation.

- Thus, I would like to recommend the following stake holders:
    - **Ethiopian FMOH & JU**: to use our study as a base line to initiate further stronger studies related to effect of different oxytocin regimen.
    - **Researchers**: control known confounding factors associated with successful or failed induction to look the true effect of different oxytocin regimen and use larger sample size & multicenter approach but of similar setting.
    - **Funding organizations** (government and/or NGO's) to allocate adequate budget for researchers to undergo research.
    - **JU oby/gne dep't**: take initiative to revise protocol related with IOL

REFERENCES

1. Deborah A. Wing and Lili Sheibani. Abnormal Labor and Induction of Labor. In: Steven G. Gabbe, Jennifer R. Niebyl, Joe Leigh Simpson et al. Obstetrics: Normal and Problem Pregnancies, 7th edition.China: Philadelphia, PA: Elsevier, 2017: 276-283
2. ACOG Practice Bulletin.Induction Of Labor. Number 107, August 2009
3. Joan M.G. Crane, David C. Young. Meta-Analysis Of Low—Dose Versus High—Dose Oxytocin For Labour Induction. J SOC OBSTET GYNAECOL CAN 1998;20(13):1215-23
4. Shu-QinWei, Zhong-Cheng Luo, Hui-Ping Qi, Hairong Xu, William D. Fraser. High-dose vs low-dose oxytocin for labor augmentation: a systematic review. American journal of obstetrics and gynecology · May 2010. 203(4): 296-304 DOI: 10.1016/j.ajog.2010.03.007 · Source: PubMed
5. Mori R, Tokumasu H, Pledge D, Kenyon S. High dose versus low dose oxytocin for augmentation of delayed labour.*Cochrane Database of Systematic Reviews* 2011, Issue 10. Art. No.: CD007201.DOI: 10.1002/14651858.CD007201. pub2
6. Vogel JP, Souza JP, Gulmezoglu AM (2013). Patterns and Outcomes of Induction of Labour in Africa and Asia: A Secondary Analysis of the WHO Global Survey on Maternal and Neonatal Health. PLoS ONE 8(6): e65612. doi:10.1371/journal.pone.0065612.
7. Evalyne J. Masan, Blasio O. Omuga and Miriam C.A. Wagoro. Outcomes of Induction of Labor among Women giving birth at a National Hospital in Kenya. Kenyan Journal of Nursing & Midwifery, 2016; 1:1, 40-50.
8. Alessandro Ghidini, Diann Wohlleb, Victoria Korker, John C. Pezzullo, Sarah H. Poggi. Effects of two different protocols of oxytocin infusion for labor induction on obstetric outcomes:A cohort study. OJOG 2012, 2, 106-111 http://dx.doi.org/10.4236/ojog.2012.22020
9. Budden A, Chen LJY, Henry A. High-dose versus low-dose oxytocin infusion regimens for induction of labour at term.Cochrane Database of Systematic Reviews 2014, Issue 10. Art.No.:CD009701.DOI: 10.1002/14651858.CD009701.pub2.
10. Management Protocol on Selected Obstetric Topics: Federal Democratic Republic Of Ethiopia, Ministry Of Health. January 2010
11. Segni H, Niguse D. et al. Obstetrics management guideline in JUSH Jimma University.September 2010 First edition Volume one
12. Woubishet Girma,Fitsum Tseadu, Mirkuzie Wolde.Outcome of Induction and Associated Factors among Term and Post-Term Mothers Managed at Jimma University Specialized Hospital: A Two Years' Retrospective Analysis. EJHS Vol. 26, No. 2 March 2016. ***DOI:*** http://dx.doi.org/10.4314/ejhs.v26i2.6
13. Berhan Y, Dwivedi AD. Currently used oxytocin regimen outcome measures at term & postterm: Outcome indicators in relation to parity & indication for induction. Ethiop Med J. 2007 Jul;45 (3):235-42.
14. Berhan Y, Dwivedi AD . Currently used oxytocin regimen outcome measures at term & postterm. II: Outcome indicators in relation to Bishop Score & other covariates. Ethiop Med J. 2007 Jul;45(3):243-50
15. Bekana Fekecha Hurissa, Mathewos Geta and Tefera Belachew. Prevalence of Failed Induction of Labor and Associated Factors Among Women Delivered in Hawassa Public Health Facilities, Ethiopia, 2015. available at http://dx.doi.org/10.4172/2167-0420.1000253

16. Abdulkadir Y, Dejene A, Geremew MA, Dechasa B (2017) Induction of Labor Prevalence and Associated Factors for Its Outcome at Wolliso St. Luke, Catholic Hospital, South West Shewa, Oromia. Intern Med 7: 255. doi:10.4172/2165-8048.1000255
17. Satin AJ, Leveno KJ, Sherman ML, Brewster DS, Cunningham FG. High- versus low-dose oxytocin for labor stimulation. Obstet Gynecol 80:111, 1992. Date accessed 18/2/217.
18. Satin AJ, Leveno KJ, Sherman ML, McIntire D. High-dose oxytocin: 20 versus 40-minute dosage interval. Obstet Gynecol. 1994 Feb 83 (2):234-238. Date accessed 18/2/217
19. Merrill DC, Zlatnik FJ. Randomized, doublemasked comparison of oxytocin dosage in induction and augmentation of labor. Obstet Gynecol 1999;94:455-63.
20. Frigoletto FD , Lieberman E, Lang JM, Cohen A, Barss V, Ringer S, Datta S. A clinical trial of active management of labor.N Engl J Med. 1995 Sep 21;333(12):745-50. Date accessed 18/2/217.
21. Xenakis EM, Langer O, Piper JM, Conway D, Berkus MD. Low-dose versus high-dose oxytocin augmentation of labor–a randomized trial. Am J Obstet Gynecol 1995;173:1874-78.
22. Lopez-Zeno JA, Peaceman AM, Adashek JA, Socol ML. A controlled trial of a program for the active management of labor. N Engl J Med 1992;326:450-4.
23. Satin, AJ, Hankins, GDV, and Yeomans, ER. A prospective study of two dosing regimens of oxytocin for the induction of labor in patients with unfavorable cervices. Am J Obstet Gynecol. 1991; 165: 980–984.Date accessed 18/2/2017.
24. Belghiti J, Kayem G,Dupont C, et al. Oxytocin during labour and risk of severe postpartum haemorrhage:a population-based cohort-nested case-control study. BMJ Open 2011;1:e000514. doi:10.1136/bmjopen-2011-000514
25. Pimentel VM, Arabkhazaeli M, Moon, J-Y, et al. Induction of labor using one dose vs multiple doses of misoprostol: a randomized controlled trial. Am J Obstet Gynecol 2018;218:614.e1-8.
26. Dina Delvin Anggriani, Lilik Herawati, Ernawati. Parity as failure determinants of labor induction in Bangka Belitung. Majalah Obstetri & Ginekologi, Vol. 24(3) September - December 2016 : 79 – 83
27. Ghadeer K. Al-Shaikh, Hayfaa A. Wahabi, Amel A. Fayed, Samia A. Esmaeil, Ghada A. Al-Malki. Factors associated with successful induction of labor. Saudi Med J 2012; Vol. 33 (3).
28. William A. Grobman ; Jennifer Bailit ; Yinglei Lai et al. Defining failed induction of labor. Jan, 2018 American Journal of Obstetrics & Gynecology 122.e8
29. Tetsuya Kawakita, Uma M. Reddy et al. Duration of oxytocin and rupture of the membranes before diagnosing a failed induction of labor. Obstet Gynecol. 2016 August ; 128(2): 373–380. doi:10.1097/AOG.0000000000001527.

ANNEXES

ANNEX I: QUESTIONNAIRE

JIMMA UNIVERSITY INSTITUTE OF HEALTH, POST GRADUATE SCHOOL, DEPARTMENT OF GYNAECOLOGY & OBSTETRICS QUESTIONNAIRE FOR HEALTH FACILITY RELATED INFORMATION

Informed Consent For Participant

Hello! My name is_____. I am working in research team of jimma university. We are doing our research on "perinatal and maternal outcomes of high dose versus low dose oxytocin regimen for labor induction. This is a study to be conducted with objective of comparing effects of high dose vs low dose oxytocin regimen for labor induction on maternal & perinatal outcomes in different hospitals with different protocols. I would like to inform you that the responses that you provide are very essential, not only, for the successful accomplishment of the study but also for producing relevant information which will be helpful in addressing and choosing the better option of induction regimen being practiced in Ethiopia.

Your privacy will be kept secret and you have the right to not to participate in the study or can stop your participation at the middle of interview if you feel uncomfortable to continue.

Are you willing to participate? Yes ---------- No ----------

Guca Walii Galtee Hirmaattota Qorannichaa

Nagaa jirtuu?

Akkam Jirtu? Maqaan koo_____jedhama. Ani miseensa garee qo'annoo fi qorannoo yuuniversiitii Jimmaati. Qorannoo keenya haadholii hospitaalota garaagaraa keessatti qorichaa ciniinsuu(miixuu) fidu fudhatanii dahaan irratti gaggeessaa jirra. Ijoon qorannoo keenyaa garaagarummaa qorichi miixuu fidu oksiitosinii jedhamu hammi isaa guddaa fi xiqqaa tahee miixuu fi ulficha ykn daa'iima dhalatu irratti qabu qorachuu taha.

Kanaaf eyyamamaa yoo taatan ragaan isin nuuf laattan kun qorannicha raawwachuuf barbaachisaa ta'uu bira darbee bu'aan qorannaa kanaa fulduratti hangi qorichaa kum akka wayyu biyya keenyaaf filachuuf illee murteessaadha. Odeeffnnoon dhuunfaa keessan iccitiin isaa kan eegamu waadaa isiinif gala. Mirgi hirmaachuu dhiisuu ykn immoo gidduutti adda kuutuu keessan kan eegamedha.

Qorannoo kana irratti hirmaachuuf fedhii qabduu? Eeyyee_____Lakkii_____

Checklist code number _____

Name of interviewer---------- Sign ---------- Date of interview----------

Name of the supervisor ---------- Sign ---------- Date of interview----------

I. Socio-Demographic & Economic Characteristics Of Respondents		
Code	**Questions**	**Response and coding category**
101	Which oxytocin regimen is used?	1. High dose_____2. Low dose_____
102	How old are you?	_____ years
103	Where is your residence?	1. Urban 2. Rular
104	What is your religion?	1. Muslim 4. Catholic 2. Orthodox 5. Waqefata 3. Protestant 6. Others(specify)_____
105	What is your ethnicity?	1. Oromo_____ 4. Gurage_____ 2. Amhara_____5. Tigre _____ 3. Dawro _____6. kafa ____ 7.Others (specify)_____
106	What is your current marital status?	1. Married 2. Unmarried
107	What is highest education level you have attained?	1. Can't read and write 2. Primary school (1-8) 3. High school & preparatory (9-12) 4. College or university
108	What is your occupation?	1. House wife_____5. Housemaid_____ 2. Farmer_____6. NGO employee_____ 3. Gov't employee_____ 7. Student _____ 4. Merchant_____8.Others(specify)_____
109	Family's monthly income in birr?	_____ birr/ a month
II. Reproductive history		
201	Total No of parity (Delivery experience)	G___P____
202	GA on date of induction (use LNMP, Early U/S,)	_____wks
203	Type of induction	1. Elective (planned) 2. Emergency induction
204	What is Indication for induction?	1. Post term 4.APH 2. PROM 5. Chorioamnionitis 3. HDP 6.Others(specify) _____
205	Was there previous history of successful induction	1. Yes 2. No
206	Bishop score before induction	_____/13
207	Was Cervical ripening with misoprostol done for unfavorable bishops?	1. Yes 2. No

208	Was Artificial rupture of membranes (ARM) done?	1. Yes 2. No
III. Labor & Maternal outcome measures		
301	What was the total duration in hours from initiation of oxytocin to delivery?	_____hrs
302	At what oxytocin infusion rate she attained adequate Ux contraction or it is maintained?	_____mu/min Or Phase ___Dpm_____
303	What was Mode of delivery?	1. SVD 2. C/S 3. Instrumental delivery(Vacuum or Forceps)
304	If 2 for Q 303 above what is the indication for C/S?	1. Failed induction 2. CPD 3. Non Reassuring Fetal status 4. Failed instrumentation 5. Poor maternal effort 6. Other specify_____
305	If 3 for Q 303 above what is the indication for instrumentation?	1. Shorten second stage of labor 2. NRFHRP 3. Prolonged second stage of labor 4. Poor maternal effort
306	If induction failed how was it diagnosed?	1. Failure to bring about cervical dilatation or change 2. Unable to establish adequate uterine contractions
307	Which of the following complication (s) has occurred? (Possible to choose more than once)	1. Uterine hyperstimulation 2. Uterine rupture 3. Post Partum Hemorrhage 4. Chorioamnionitis (if diagnosed after IOL) 5. Pulmonary edema 6. PURPUREAL SEPSIS 7. Others specify_____ 8. No complication _____
308	Outcomes of mother with complication	1. Discharged improved 2. Discharged with complications 3. Dead
309	If the mother is discharged with complications, specify	_____
310	What is the total duration of hospital stay in days	_____days
IV . Perinatal outcome measures		

401	Delivery Outcome (sex & weight)	Sex _____ Wt _____ gms
402	What was the 1st minute Apgar score?	_____
403	What was the 5th minute Apgar score?	_____
404	Grade II or III meconium-stained amniotic fluid present at delivery	1. Yes 2. No
405	Was there a need for advanced neonatal resuscitation?	1. Yes 2. No
406	If yes to Q 405, what are the reasons	1.Thick meconium 2. low APGAR score 3. respiratory distress 4. Others(specify)_____
407	Was the neonate referred to NICU?	1. Yes 2. No
408	What is the diagnosis at NICU?	1.Perinatal Asphyxia 2.Meconium Aspiration Syndrome 3.Transient Tachypnea of newborn 4.Neonatal Sepsis 5. Others(specify)_____
409	What is the Duration of NICU stay in days OR hours	_____Hrs /Days
410	Neonatal outcome at discharge	1. Cured, alive 2. Dead 3. Left against medical advice 4. Discharged with complications (sequale)
411	If discharged with complications (sequale) specify	_____

Table 8: Protocol & schedule for escalating Oxytocin dosage for IOL among low dose & high dose groups.

High Dose protocol				**Low Dose protocol**			
Phase	Amount Added & Oxytocin concentration	Oxytocin dpm	Oxytocin Mu/min	Phase	Amount Added Oxytocin conc.	Oxytocin dpm	Oxytocin mu/min
I	6IU Into 1L of NS (6mu/ml)	20	6	I	2IU Into 1L of NS (2mu/ml)	20	2
		40	12			40	4
		60	18			60	6
		80	24			80	8
II	6IU into remaining fluid (13.5mu/ml)	40	27	II	2IU into remaining fluid (4.86mu/ml)	50	12
		60	40.5			60	15
		80	54			80	20
III	6IU into remaining fluid(23.2mu/ml)	60	69.6	III	2IU into remaining fluid (9.6mu/ml)	50	24
		80	92.8			60	30
		>>	>>			80	40
The drop is escalated every 20 minute till adequate uterine contraction is achieved and maintained with the same concentration.				The drop is escalated every 30 min till adequate uterine contraction is achieved and maintained with the same concentration			

Table 9: Bishop Score Assessment

Cervical Parameter	**0**	**1**	**2**	**3**
Dilatation (cm)	Closed	1–2	3–4	5 or more
Effacement (%)	0–30	40–50	60–70	80 or more
Station	-3	-2	-1 or 0	+1 or +2
Consistency	Firm	Medium	Soft	
Cervical Position	Posterior	Mid-position	Anterior	

ANNEX II: APPROVAL

ASSURANCE OF PRINCIPAL INVESTIGATOR

The undersigned agrees to accept responsibility for the scientific ethical and technical conduct of the research project and for provision of required progress reports as per terms and conditions of the college of health and medical science in effect at the time of grant is forwarded as the result of this application.

Name of the student: _____

Date._____

Signature _____

APPROVAL OF THE FIRST ADVISOR

Name of the first advisor: _____

Date._____

Signature _____

APPROVAL OF THE SECOND ADVISOR

Name of the second advisor: _____

Date._____

Signature _____