Meeting WHO's Conditions For Labor Augmentation: A Narrative Literature Review on South Asia and A linked Analysis Using DHS 2016 and SPA 2015 Surveys in Nepal

by

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Abstract

Background:

Labor augmentation using oxytocin is commonly used throughout the world, but certain precautions need to be taken, and certain conditions need to be met; otherwise, complications are possible for both mothers and babies.

Method:

We conducted a narrative literature review study to gather evidence on the administration of oxytocin during labor, its resulting adverse effects on mothers and babies, and the circumstances where the WHO's conditions for such practice are met or not met in both homebirth and hospital birth settings in South Asia. In addition, we conducted a cross-sectional study utilizing Nepal Demographic Health Survey (DHS) 2016 data and Nepal Service Provision Assessment (SPA) Survey 2015 data to assess the extent of labor augmentation practice without following the WHO recommended conditions in case of hospital births in Nepal (excluding the primary level hospitals). By geographically linking the Nepal DHS 2016 birth dataset and Nepal SPA 2015 Inventory dataset, the closest hospital (secondary or tertiary level) to each DHS cluster was identified; and those hospitals were categorized into 'apparently ready' (all 4 of the following criteria met: surgeon and anesthetist available, blood available, and cesarean deliveries done over the preceding 3 months), 'possibly ready' (cesarean deliveries done over the preceding 3 months but not all of the 4 criteria for "apparently ready" were met) and 'definitely not ready' (no cesarean deliveries over the preceding 3 months or cesarean deliveries are usually not offered in that hospital) [according to SPA data] to manage complications for labor augmentation. Bivariate analyses, including proportions of birth received oxytocin during labor disaggregated by different types of place of delivery, types of residences (urban/rural), and different provinces in Nepal, were conducted depending on data availability; the significance of differences was reported using a chi-square test. In addition, a multinomial logistic regression model was utilized to assess the association of women's socio-economic factors with labor

augmentation received in 'possibly ready' and 'definitely not ready' hospitals compared to 'apparently ready' hospitals.

Result:

Our literature review findings suggest that using oxytocin during labor without following the WHO's labor augmentation recommendations is common in both home and hospital births in South Asia. The common adverse outcomes of such injudicious practice include uterine rupture, birth asphyxia, and stillbirth. Our quantitative analyses reported that, based on the DHS 2016 data, 66.9% (95%CI: 56.7%, 75.7%) of mothers who delivered at home, attended by a health worker, and responded to the labor augmentation specific survey question received oxytocin during labor; for hospital births, these proportions were- 64.3%(95% CI: 59.1%, 69.1%) and 52.9% (95% CI: 49.1%, 56.8%) in private hospitals and public hospitals, respectively. The geographically linked analysis reported that 50.4% (95% CI: 45.7%, 55.2%) of DHS reported government hospitals births for which the closest government hospital is categorized as 'apparently ready-for labor augmentation' received oxytocin during labor, 57.5% (95% CI: 48.4%, 66.1%) of DHS reported government hospital births for which the closest hospital is categorized as 'possibly ready-for labor augmentation' received oxytocin during labor, and 55.0% (95% CI: 47.5%, 62.7%) of DHS reported government hospital births for which the closest hospital is categorized as 'definitely not ready-for labor augmentation' received oxytocin during labor; for private hospital births, these proportions are 69.7% (95% CI: 60.9%, 77.4%), 52.5% (95% CI: 37.4%, 67.1%) and 62.5% (95% CI: 55.9%, 68.7%), respectively. In view of these proportions, we can say that the practice of labor augmentation in every level of healthcare delivery is considerably high, including settings without adequate readiness to manage its complications. Besides, our multinomial logistic regression model reported that, for the DHS reported private hospital births, women's socio-economic factors have a significant association with receiving labor augmentation in a 'definitely not ready' hospital compared to 'apparently ready' hospital- women with secondary level education compared to no education [RRR: 2.56,

(95% CI 1.12, 5.82)], women with higher education compared to no education [RRR: 3.72, (95%CI: 1.20, 11.47)], women in richest wealth index compared to poorest wealth index [RRR: 0.04, (95% CI: <0.01, 0.38)] (adjusted by women's parity and age). However, for the govt. hospital births, women's socio-economic factors did not seem to influence the facts of receiving labor augmentation in hospitals with adequate readiness to manage its complications.

Preface

This thesis received research ethics approval from the University of Alberta Research Ethics Board, Project Name "Meeting WHO's conditions for labor augmentation: A cross-sectional study using two nationally representative surveys in Nepal," No. Pro00112662, July 23, 2021. Chapter 1, chapter 3 (including the data analysis), and chapter 4 are my original work. Chapter 2 of this thesis was developed by myself, with the assistance of Sandra Campbell, Librarian (Health Science), University of Alberta, to design the method for the systematic literature review, develop the search terms and retrieve the identified studies for literature review. No part of this thesis has been previously published.

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List of Abbreviations

ACOG	American College of Obstetricians and Gynecologists
AHW	Auxiliary Health Worker
AMTSL	Active Management of Third Stage Labor
ANM	Auxiliary Nurse Midwife
APGAR	Appearance, Pulse, Grimace, Activity, Respiration
ARR	Adjusted relative risk
CEmONC	Comprehensive Emergency Obstetric and Newborn Care
CI	Confidence Interval
CS	Cesarean Section
DHS	Demographic Health Survey
EAS	External Anal Sphincter
HA	Health Assistant
HTC	HIV testing and Counselling sites
IM	Intramuscular
IPR-NE	Intrapartum related Neonatal Encephalopathy
IPR-NRD	Intrapartum related Neonatal Respiratory Depression
IV	Intravenous
MCHW	Maternal and Child Health Worker
MoH	Ministry of Health
MSL	Meconium Stained Liquor
NDHS	Nepal Demographic Health Survey
OBGYN	Obstetrics and Gynecology
OR	Odds ratio

PHCC	Primary Health Care Center
PSU	Primary sampling unit
RR	Relative risk
RRR	Relative risk ratio
SPA	Service Provision Assessment
TBA	Traditional Birth Attendant
UHC	Urban Health Center
VHW	Village Health Worker
WHO	World Health Organization

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CHAPTER 1. INTRODUCTION

1.1 BACKGROUND

Administering uterotonics, commonly oxytocin, to increase the intensity, frequency, and duration of contraction after the onset of spontaneous labor is a method that has been used across the low, middle, and high-income settings since the late 1950s (Nucci, M. 2018). Oxytocin is a hormone physiologically released into the bloodstream in response to stimulus, like labor (Gimpl, G. 2001). Since increased uterine contractions help speed up the birthing process and hasten the delivery of the baby, synthetic oxytocins are used by health professionals from different levels to stimulate labor during delivery in hospital births, even in home births in some contexts (Magon, N. 2011). However, without due care, oxytocin use can cause uterine rupture and reduced placental perfusion by hyper-stimulating the uterus, thereby reducing oxygen supply to the fetus. Hence, on the premise of ensuring safety for both mothers and babies, in 2014, World Health Organization (WHO) published guidelines for using oxytocin as a method of labor augmentation, including specifying conditions for safe use- those are context-specific (WHO 2014).

There are three significant uses of oxytocin in labor and delivery care-

Labor induction

Labor induction stimulates the uterine contractions or initiates the uterine contractions before the labor begins by using uterotonics like oxytocin or other methods (ACOG 2009). Induction of labor using oxytocin means helping the mother get labor started (Kim, HI. 2019).

Labor augmentation

Labor augmentation is the process of stimulating the uterus to increase the frequency, duration, and intensity of uterine contractions by using uterotonics (e.g., oxytocin) and other methods after the onset of spontaneous labor (WHO 2014). Augmentation of labor using oxytocin helps

speed up the slow labor that had already started (Kim, HI. 2019). This process facilitates faster labor to readily achieve a vaginal delivery (Son, M. 2020; Kernberg, A. 2017).

As a part of active management of third stage labor

Active management of third-stage labor (AMTSL) is a strategy to reduce the chances of excessive blood loss after the baby's delivery. AMTSL consists of administration of uterotonic to increase uterine tone and contractions and gentle cord traction to facilitate delivery of the placenta (Salati, JA. 2019). As a part of this strategy, oxytocin is commonly administered to increase uterine tone and contractions following the delivery of the baby's shoulder (Salati, JA. 2019).

In the thesis, we are mainly focusing on the use of oxytocin for augmentation of labor. Normal labor is hard for every woman to varying levels of extent, and for first-time mothers, the pain might feel extreme. As the labor continues, the pain worsens. Therefore, any medication that would speed up the delivery process for the mothers enduring the pain is unquestionably appreciated. However, the benefits of administering medicine, including oxytocin, for easing the delivery process for the mothers do not always outweigh the risk. In some contexts, the injudicious use of oxytocin may bring regrettable consequences for both mothers and babies.

Why is oxytocin administration before the baby's delivery is a matter of concern?

It is well documented that administering oxytocin for labor induction and augmentation poses risks of adverse effects for mothers and babies. Uterotonics, including oxytocin, cause increasing intensity, frequency, and duration of uterine contractions. At the extreme, this condition is known as uterine hyperstimulation. If not detected early and not appropriately managed, uterine hyperstimulation can have important consequences for both mothers and babies. When contractions happen in normal labor, this results in compression of the uterine blood vessel, intermittently decreasing blood flow to the intervillous space, to where the umbilical veins carry fresh oxygenated blood, allowing gas exchange with the baby's systemic circulation (Wang, Y.

2010). In the normal physiological birth process, healthy fetuses can tolerate normal labor contractions without complications (Simpson, KR. 2009). But with uterine hyperstimulation caused by oxytocin administration before the delivery of the baby, there is a risk of fetal oxygen desaturation: fetal oxygen decreases progressively until the normal uterine activity is restored (Simpson, KR. 2009). This reduced fetal oxygenation eventually results in important negative consequences, including fetal distress, birth asphyxia, and subsequent brain damage due to lack of oxygen and blood flow to the baby's brain (Simpson, KR. 2009). A study conducted in Sweden analyzing all malpractice claims against physicians and midwives during the period 1996-2003 reported that oxytocin was administered in 90% of cases, and in 68.5% cases it was determined that injudicious use of oxytocin was practiced (Jonsson, M. 2007).

For mothers, oxytocin administration during labor is no less critical than for fetuses. Several adverse maternal events are associated with intrapartum oxytocin administration, including placental abruption, uterine rupture, and unnecessary cesarean section. Labor induction and augmentation are important contributors to uterine rupture in women, particularly those with previous cesarean sections. Further complications associated with uterine rupture include severe maternal hemorrhage, perinatal mortality, and hysterectomy (Guise, JM. 2004). A retrospective analysis of uterine rupture cases in a tertiary hospital in Nepal (n=216) indicated that intrapartum (during labor) oxytocin use was one of the commonest causes of uterine rupture (44%) in mothers with a previous cesarean section (Chuni, N. 2006). Considering the significant medical risks labor augmentation carries for both mothers and babies, increasing numbers of critiques raised a red flag against this practice; the Institute for Safe Medication Practices added 'Oxytocin' to the high alert medication list in 2007 (Simpson, KR. 2009). High alert medications are drugs that have an increased risk of patient harm if the drugs are not used with careful consideration (Simpson, KR. 2009). Administration of high alert medications generally requires a precise protocol to eliminate variation in doses and other indications,

thereby reducing the chances of unintentional errors causing potential grim consequences (Clark, SL. 2009). Therefore, it is recommended that oxytocin be administered with a clear clinical indication that the benefit would outweigh the risk. Several other imperative prerequisites should not be ignored at any cost, including (WHO 2014)-

- Augmentation of labor with oxytocin should only be performed after conducting a clinical assessment to exclude cephalopelvic disproportion and abnormal fetal presentation,
- Augmentation of labor with oxytocin should only be conducted among women with pregnancies in cephalic presentation and unscarred uterus (i.e., no prior cesarean deliveries),
- Augmentation with oxytocin should not be given intramuscularly or by an intravenous (IV) bolus dose; instead should be given through controlled intravenous drip infusion started at a relatively low infusion rate.
- The IV infusion rate for oxytocin should be titrated depending on the frequency of uterine contractions, labor progress, and fetal heart rate. Therefore, the facilities where labor is augmented should have the capacity to closely and regularly monitor fetal heart rate and uterine contraction patterns.
- Augmentation of labor should be carried out in facilities with the capacity to manage its potential consequences, including the capacity of conducting emergency cesarean sections and managing any adverse effects in mothers and babies.
- "The mothers undergoing labor augmentation, particularly with oxytocin, should never be left unattended."
- The condition of the mother and fetus and the status of labor should be reassessed at least every 30 minutes.

The above prerequisites are the WHO recommended conditions for labor augmentation using oxytocin (WHO 2014). Unfortunately, many facilities in developing countries are not able to

reliably meet all of these WHO's conditions for safe use of oxytocin. This makes the use of oxytocin in lower-income countries more questionable. According to Nepal Demographic Health Survey (DHS) 2016 data, 57% of all births during the five years preceding the survey happened in health facilities in Nepal. The same survey found that nearly 50% of mothers who were attended by a skilled birth attendant, including doctor, nurses/midwives, health assistants (HAs), auxiliary health workers (AHWs), maternal and child health workers (MCHWs) and village health workers (VHWs), were given injections or any medicine through IV drip before the baby was born (Ministry of Health - MOH/Nepal 2017). As expected, similar to other low-income countries, not all district and tertiary level hospitals in Nepal where births are occurring are reliably able to meet the WHO's labor augmentation recommendation. Since complications might happen in mothers and babies in case of uterotonic administration before delivery of the baby, the facilities practicing labor induction/ augmentation should be prepared to manage the complications at a comprehensive level- such as conducting timely cesarean sections when it is necessary.

If we consider the condition related to surgical capacity, which is a prime condition to ensure safety during labor augmentation as recommended by WHO, Nepal's situation is not near satisfactory. According to the Nepal Health Facility survey 2015, only 18.4% of all district-level hospitals carried out at least one cesarean section and at least one blood transfusion in an obstetric context, and all other seven Comprehensive Emergency Obstetric and Newborn Care services (CEmONC) signal functions at least once within the three months before the survey (Ministry of Health/Nepal 2017). In Bangladesh, the situation is even more distressing: only 5% (6% excluding Community Clinics) of all facilities had performed all nine CEmONC signal functions in the past three months of the Bangladesh Health Facility Survey conducted in 2017 (National Institute of Population Research and Training - NIPORT 2020). There are nine CEmONC signal functions; for a facility to be considered a CEmONC-capable facility, those

functions should be performed over the last three months preceding the health facility survey (Roy, L. 2017). Performing cesarean (CS) delivery and availability of blood transfusion services for 24 hours a day on seven days a week are two of the nine CEmONC signal functions more specific to ensuring a hospital's surgical capacity (Roy, L. 2017). Facilities in resource-constrained settings, even those which by definition should be equipped to provide all nine signal functions, often fall behind in the capacity to perform cesarean section deliveries (Kruk, ME. 2016). Hence, the overuse of oxytocin is more hazardous in low-income contexts than in high-income contexts. After all, low-income settings do not always have the capacity to manage emergencies caused by overmedicalization of childbirth, such as unnecessary labor augmentation, which is less of an issue in most high-income settings.

Labor augmentation is often considered a relatively benign procedure in high-income country settings, but not always in low-income settings- Why?

Despite posing substantial risks to mothers and fetuses, under circumstances where frequent monitoring of mothers and fetuses is possible and prompt action can be taken if complications arise, the use of oxytocin in labor augmentation and induction is comparatively low-risk. Induction is indicated when better outcomes can be expected for the mother and/or the baby than prolonging the pregnancy (Kim, HI. 2019). Similarly, augmentation is justified if shortening labor can be expected to yield better outcomes (Kim, HI. 2019). There are several indications and contraindications for using intrapartum oxytocin. It is the health worker's responsibility to determine if using intrapartum (during labor) oxytocin for induction or augmentation of labor is indicated and if the risk to the mother and the fetus of continuing normal labor without any such intervention exceeds the associated risks of labor induction or labor augmentation. Likewise, the common contraindications for labor augmentation using oxytocin infusion include previous cesarean section, any previous uterine surgery, abnormal fetal presentation, and mothers' pelvic structure abnormality (Alberta Health Service. 2021).

However, identifying these indications and contraindications in low-income countries is challenging since not all births are not attended by skilled health workers and happen in a CEmONC level hospital.

According to Nepal DHS 2016, approximately 41% of all births in the five years preceding the survey occurred at home setting; out of 43% of deliveries that reported to take place in a government health facility, 12.8% of births took place in a primary level health facility. Even in facility births, nurses and midwives are not trained enough to identify indications and assess the benefit vs. risk of using such interventions. Studies conducted in low resource settings, including Bangladesh and India, reported the use of oxytocin by unqualified providers (Egbe, TO. 2016; Jeffery, P. 2007). These providers have limited training from unregulated training institutions, mostly focused on common illnesses; do not include training on comprehensive care during labor and delivery (Egbe, TO. 2016; Jeffery, P. 2007). Intramuscular injection of oxytocin to augment labor was also found common in low-income settings due to a lack of knowledge of indications and contraindications of labor augmentation (Jeffery, P. 2007).

It is recommended to administer oxytocin for labor augmentation using a controlled infusion pump, starting at a rate of 1-2 milliunits per minute and then increasing the infusion rate by one to two milliunits every thirty units until an adequate uterine response is obtained (Alberta Health Service 2021; Institute of Obstetricians and Gynaecologists 2019). Therefore, frequent maternal and fetal status monitoring is the prime principle of using oxytocin to augment labor. Usually, it is ideal for assessing mothers' blood pressure and pulse and fetal heart rate, and status of labor with each increase in the oxytocin unit and measuring the frequency of uterine contractions every 10 to 15 minutes (Alberta Health Service 2021; Institute of Obstetricians and Gynaecologists 2019). These major evidence-based requirements have been recommended to identify and prevent possible complications in mothers and babies, thereby taking timely actions

so that both the mother and the baby stay safe. However, the evidence-based guidelines and the WHO labor augmentation recommendations are often neglected by healthcare providers in a low-resource setting. Such negligence calls into question the safety and appropriateness of practicing labor augmentation in low-resource settings, including countries in South Asia. Oxytocin is widely available in local pharmacies in South Asia, contributing to the widespread injudicious use of oxytocin to induce and augment labor (Jeffery, P. 2007). Even local health care providers, including dais (traditional birth attendants) and family members, can easily purchase oxytocin from pharmacies, often even without a prescription.

As low-income countries are saddled with challenges to ensure the WHO's labor augmentation recommendations/conditions, documenting evidence on the extent to which the labor augmentation conditions are met in various settings in resources-constrained areas and what are the related fetal and maternal outcomes is crucial. Hence, this thesis includes a narrative literature review on using uterotonics during labor in South Asia. The primary purpose is to marshal the available evidence on actual conditions for labor augmentation and maternal and fetal outcomes of such injudicious practice in South Asia. In addition, the analytic component of this thesis has utilized two nationally representative surveys of Nepal - Nepal Demographic Health Survey (DHS) 2016 and Nepal Service Provision Assessment (SPA) Survey 2015; by triangulating and cross-validating these two surveys, this thesis investigated the extent to which labor is augmented for hospital births following the conditions for safe labor augmentation in regard to the availability of cesarean section capacity in Nepal. The findings from this analysis call for the scientific bodies and policymakers to conduct further prospective studies that characterize adherence to safe labor augmentation guidelines in lower-income settings.

1.2 RESEARCH OBJECTIVES

The objectives of the systematic review (Chapter 2) are to determine:

1) How common is labor augmentation in South Asia?
2) In the circumstances in which labor is augmented in this region, how frequently are the WHO labor augmentation conditions actually met, and
3) What are the effects of labor augmentation on maternal and fetal outcomes?

The objectives of the quantitative analysis (Chapter 3), based on the data available in the 2016 Nepal Demographic Health Survey (DHS) (limited within the births that occurred during the three years prior to the survey) and the 2015 Nepal Service Provision Assessment Survey (SPA), are :

1) To determine the proportion of births where using of Inj./IV medicine during labor was reported in the DHS survey disaggregated by place of delivery,
2) By linking the SPA post-partum client Interview dataset with the SPA Inventory dataset,
    - ✓ To determine the proportion of births received oxytocin during labor reported in the Postpartum client interviews in the SPA survey, disaggregated by type of facilities,
    - ✓ To determine the proportion of births received oxytocin during labor reported in the Postpartum client interviews in the SPA survey, disaggregated by Government (Secondary and tertiary level) hospitals and Private hospitals that are categorized into 'Apparently ready,' 'Possibly ready' and 'Definitely not ready' to manage complications due to labor augmentation in regards to cesarean capacity.
3) By geographically linking the DHS with the SPA survey datasets,
    - ✓ To determine the proportion of births augmented among the women reported giving birth in clusters (in DHS) for which the closest hospital is categorized as 'Apparently ready' to manage complications due to labor augmentation,

- ✓ To determine the proportion of births augmented among the women reported giving birth in clusters (in DHS) for which the closest hospital is categorized as 'Possibly ready' to manage complications due to labor augmentation,
- ✓ To determine the proportion of births augmented among the women reported giving birth in clusters (in DHS) for which the closest hospital is categorized as 'Definitely not ready' to manage complications due to labor augmentation,
- ✓ To assess the influence of women's socio-economic factors (reported in DHS) on their risks of receiving labor augmentation in hospitals 'Possibly ready' compared to hospitals 'Apparently ready,' and in hospitals 'Definitely not ready' compared to hospitals 'Apparently ready' to manage complications [by utilizing a multinomial logistic regression method]

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CHAPTER 2. LITERATURE REVIEW

2.1 INTRODUCTION

Oxytocin, the most commonly used uterotonic, is widely available in South Asia. However, given its known effectiveness in enhancing labor contractions, this drug is often administered without following the clinical guideline. Therefore, in many cases, particularly in low-income countries such as in South Asia, administering oxytocin to speed up the labor may cause inadvertent grim consequences, including uterine hyperstimulation and fetal distress (Jonsson, M. 2008). These outcomes, in turn, increase the likelihood of subsequent invasive interventions for which low-resource facilities are not always ready. Hence, in 2007, the Institutes of Medicine declared this medicine a high alert drug, requiring special caution (Hidalgo-Lopezosa, P. 2016).

Increased risk of harm in using oxytocin before the delivery of a baby arises from administration in incorrect doses or without any clear medical indication or in a context that does not have the capacity to manage potential adverse effects. Furthermore, there is growing concern that indications and contraindications for augmenting labor are not carefully evaluated in many circumstances. For example, augmentation using oxytocin should be performed when lack of adequate contraction is the primary cause of abnormally slow labor progress, and the expected benefit of augmentation outweighs the potential harm. In addition, it is recommended to exclude cephalopelvic disproportion before proceeding with augmenting labor using oxytocin (WHO 2014). However, identifying the primary cause of slow progress of labor is often challenging, particularly where mothers rely mostly on untrained health workers for delivery, and the facilities are not adhering to these rules.

Inappropriate use of oxytocin for labor augmentation and its detrimental effects on maternal and fetal outcomes is documented in numerous studies. A study conducted in Sweden evaluating the obstetric factors during the last two hours of delivery in the neonates born with

acidemia reported that increased uterine contractions due to oxytocin-stimulated labor was the leading cause for fetal compromise (Jonsson, M. 2008). In addition, deviation from the labor ward department's oxytocin use guideline was also demonstrated in the same study: fetal heart rate monitoring was inadequate in 11% of cases, and there was no monitoring of uterine activity in 22% of patients (Jonsson, M. 2008). When oxytocin is used in labor augmentation, monitoring uterine activity is indispensable because of the increased risk of uterine hyperstimulation and subsequent uterine rupture. However, it is challenging to ensure adequate frequent monitoring of the mothers and the fetuses in low-income countries context in many cases. Recent publications from South Asia indicated concerns over intrapartum use of oxytocin, given its role as an intrapartum risk factor for birth asphyxia, increased risk of neonatal resuscitation, low APGAR score, and neonatal death in low-income context (Shah, S. 2016) (Day, LT. 2016; Brahmawar Mohan, S. 2020).

A narrative literature review allows us to determine how widespread the practice of labor augmentation is in health facilities and home birth settings in South Asia and the resulting effects on mothers and babies. This chapter presents results of a broader search of the existing literature documenting the prevalence of labor induction or augmentation, particularly lack of adherence to the WHO's conditions for labor augmentation, and the effects of such practice on adverse feto-maternal outcomes.

2.2 METHODS

A search was executed on the following databases: PROSPERO, OVID Medline, OVID EMBASE, OVID Global Health, Cochrane Library (CDSR and Central), EBSCO CINAHL, Proquest Dissertations and Theses Global and SCOPUS. Controlled vocabulary (e.g., MeSH, Emtree, etc.) and keywords representing the concepts "oxytocin"; and "birth and maternal outcomes"; and "South Asia" were used to identify relevant articles. Databases were searched from inception to

March 12, 2021. Broad search term was developed using- Oxytocin, Pitocin, Syntocinon, Oxytocics, Uterotonic, labor induction, labor augmentation, still birth, low APGAR, low PH, unsafe/adverse, outcome/ effect, resuscitation, hypoxia, unsafe/ risky/ judicious/ injudicious/ misuse /safety, cesarean section, uterine hyperstimulation, uterine tachysystole, neonatal encephalopathy, neonatal/ perinatal/ fetal/ fetus/ foetal/ foetus/ birth/ maternal/ newborn, mortality/ death/ distress/ injury/ damage/ result, asphyxia/ acidosis/ acidemia, ischemia/ischemic, uterus /uterine, rupture/ ruptured, unmonitored intrapartum oxytocin, Afghanistan, "sri lanka/ srilanka/ ceylon, Nepal, Bhutan, Maldives, Pakistan, Bangladesh, Indian subcontinent, South Asia. Articles were included if they were published in English or with English translation.

This review considered several types of study, including descriptive analysis, case-control study, cohort study, cross-sectional study, qualitative studies, mixed-method studies, and descriptive case series study. This review did not include review articles or randomized controlled trials where the effects of oxytocin are compared with other drugs. Since the purpose of this review is to understand the widespread practice of using uterotonics during labor in both home and hospital births, not to characterize the benefits or harms of administering oxytocin during labor in comparison with another drug, such studies were excluded. However, studies conducting secondary analysis of randomized controlled trial or field trials that did not define using oxytocin during labor as an intervention or an exposure factor in a controlled environment instead presented information related to oxytocin exposure during labor as maternal characteristic or a component of usual maternal healthcare delivery practice in any setting are included in this review. Besides, no editorial, commentary, and any piece of writing published on websites or blog pages are included in this review. Scientific studies with a specific methodology that provided evidence of using oxytocin to augment or induce labor in the South Asian context were included, irrespective of place of delivery and effect on mothers and fetuses.

A study was relevant, thereby was included, if it fulfilled the following criteria:

- The population of focus is on any countries in South Asia, AND
- Oxytocin was administered before the delivery of the baby either to induce labor or to augment labor, AND
- The study provides evidence of: administering either injudicious use of oxytocin or any other medical uterotonics or assessing a possible association between inappropriate use of oxytocin before the delivery of the baby and adverse outcomes in mothers or babies

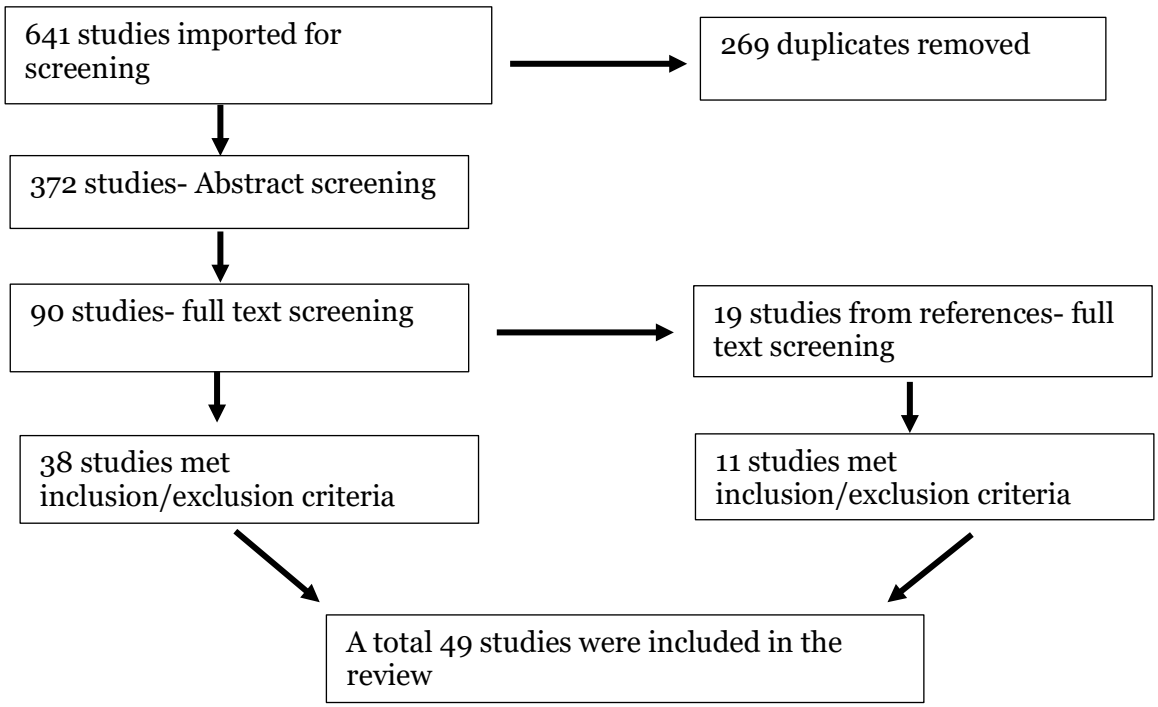

Figure 1: Literature searches and inclusion of studies

2.3 RESULTS

This literature search used the COVIDENCE Systematic Review application for screening the articles. After conducting the database search, a total of 641 articles were imported to

COVIDENCE for screening; then, after removing 269 duplicates, there were 372 studies for abstract screening (Figure 1). Of these 372 studies, 90 were selected for full-text screening. Of the 90 studies selected for full-text review, 38 fulfilled the inclusion and exclusion criteria. An additional 11 articles were identified from references in the 90 identified articles that met the inclusion /exclusion criteria, resulting in a total of 49 studies included in this review: 10 from Nepal, 17 from India, 15 from Pakistan, one from Sri Lanka, and six from Bangladesh (one poster presentation was identified from the selected studies in this review; and for two studies, only abstracts were available) (Table 1). No articles on the topic of interest of this review were identified from Bhutan, Maldives, or Afghanistan.

Evidence on the frequency of labor augmentation in South Asian settings and the extent it is failing to fully meet the WHO's conditions for labor augmentation:

Using oxytocin during labor in home births or outside of a CEmONC hospital settings

From the evidence gathered from included literature in this review, using uterotonic during labor at home birth and a setting outside of a CEmONC hospital was identified as a prevalent practice in the context of South Asia. Multiple studies (a total of 16 studies out of 49) conducted in several countries in South Asia reported findings regarding such risky use of oxytocin during labor. Table 2 provides information on the frequency of uterotonic use in case of home births and out of CEmONC level hospital settings; Table 3 provides information on the frequency of uterotonic use in case of hospital settings (most likely in a CEmONC level hospital setting). In many cases, the proportion of using oxytocin during labor at home was higher than 40%. Moran et al. (2010) conducted a cross-sectional survey to investigate the use of oxytocin for labor augmentation during home delivery among 463 women living in an urban slum in Dhaka, Bangladesh. Out of 463 women, 43.6% (n=202) reported using medicine or treatments to

augment labor and accelerate delivery; of these, 65.5% explicitly reported that the drug used was oxytocin (Moran, AC. 2010).

Fronczak et al. (2007) conducted a community-based prospective study among 1506 women living in slum areas in Dhaka, Bangladesh; this study reported using labor augmenting medicine among 19% of women who delivered at home. Evidence of injudicious use of oxytocin before delivery of the baby outside of hospital settings is commonly reported in other studies in the context of Bangladesh. A descriptive cross-sectional study documented that 66.7% of the ruptured uterus patients admitted to a tertiary hospital setting in Bangladesh were exposed to injudicious use of oxytocin before delivery of the baby prior to admission to the facility (Roy, N. 2017). Day et al. (2016) also conducted a cross-sectional study using seven years of hospital record data in a low-income setting in rural Bangladesh, reported that 5.6 % of the women out of 22,426 singleton term births had a history of using a uterotonic during labor before arriving at the CEmONC facility. Singh et al. (2012) conducted a cross-sectional study to assess the role of the Traditional Birth Attendants (TBAs) in the provision of antenatal and perinatal care at home among the urban poor in India (Singh, S. 2012). Interviews were conducted with 29 TBAs in this study; of whom 17 reported administering medicine to the mother in labor at home to augment labor (Singh, S. 2012).

Another similar study was conducted in India by Sharan et al. (2005) to examine the factors associated with using oxytocin among women delivered at home. In this study, 23% out of 527 women who delivered at home received oxytocin injections during labor. Another study, in South India, found that 76.4% of women delivered at home received oxytocin for labor augmentation, primarily administered by Auxiliary Nurse Midwives (ANMs) (Karachiwala, B. 2012). Matthews et al. (2005) also conducted a prospective study among women in rural Karnataka in Southern India, reported oxytocin use during labor in case of home deliveries- 2%

by laypersons, 7% by traditional dais, and 51% by ANM or Nurse. A study analyzing retrospective medical record data in a tertiary hospital in India reported 253 cases of uterine rupture during a ten-year study period from January 1995 to December 2004; 3.2% of ruptured uterus cases received oxytocin to induce labor outside of the hospital (Latika, S. 2006). Neogi et al. (2018) conducted a case-control study in two districts (Gaya and Purnea) of the Bihar state in India to investigate risk factors for stillbirths and reported oxytocic exposure during labor before reaching the facilities among 36.3% cases and 26.1% controls; cases (a total of 400) were identified as stillbirths ("any baby born dead after the 24th week of pregnancy), and for each identified case, two controls (a total of 800) were determined ("two live-born babies from the same village/ward as the case") in the study. The primary exposure in Neogi S. et al. (2018) study was "administration of two or more doses of oxytocin during labor" before arriving the health facilities for delivery.

Administration of oxytocin during labor in case of home births was also reported in another case-control study conducted in Haryana in India by Mohan et al. (2020). The study was a population-based case-control study nested in a previously completed cluster-randomized trial conducted to estimate the association of stillbirth and deaths on day 1, day 2, day 3, day 4-7 with uterotonic administration during labor (Brahmawar Mohan, S. 2020). In the study, the cases were babies who experienced early deaths, which was defined as "the intrapartum stillbirths and live-born babies who died within 24 hours of delivery, and the controls were babies who experienced a late neonatal death which was defined as "the neonates who died after day 7 (8–28 days)" (Brahmawar Mohan, S. 2020). The study identified 2076 cases and 532 controls and reported oxytocin administration during labor among 71% of 1997 cases (missing data on 79 cases) and 60% of 517 controls (missing data on 15 controls). The reported proportions for oxytocin administration during labor in home births in the study were - 64% of mothers who delivered at home among the cases and 49% of mothers who delivered at home among the

controls (Brahmawar Mohan, S. 2020). Using oxytocin to quicken labor in case of home deliveries was also documented in an experimental study on home-based neonatal care conducted in rural settings in India; the study identified the practice of using oxytocic to accelerate labor in home births by unqualified village doctors in 23.1% of births (from 1995 to 1996) and in 21.2% of births (from 1996 to 2003) (Bang, AT. 2005).

Among the studies providing evidence of uterotonic use during labor conducted in Pakistan, a limited number of studies explicitly reported the use of uterotonic during labor outside of hospitals. A prospective study conducted among patients admitted with a ruptured uterus in a hospital in Pakistan reported injections administered intramuscularly by "dais" (traditional birth attendants) to augment labor outside of hospitals among 47.8% of patients with a ruptured uterus (Munim, T. 2002). A cohort study, conducted to describe the exposure to labor-inducing medication and its possible risks among a vulnerable population living in the Timurgara district in Pakistan, reported 9.5% of (607 out of 6379) of women with a history of exposure to the labor-inducing medication before arriving the facility for delivery; of these, 87% received the medication during labor from an unauthorized staff (Shah, S. 2016).

Uterotonic use during labor outside of a hospital is also commonly reported in the studies conducted in Nepal. Mullany et al. (2013) conducted a study among 22,352 live-born infants delivered in peripheral health facilities and home deliveries in Sarlahi District in Nepal using data collected during a community-based cluster-randomized trial related to neonatal and maternal morbidity interventions. This study was conducted to understand the association between any type of injection received by the mothers during labor and neonatal outcomes; and reported administering oxytocin during labor in 31.8% of mothers; receipt of injections during labor among uncomplicated deliveries at home was reported in 22.8% of cases (Mullany, LC. 2013). In addition, Manandhar et al. (2010) conducted a prospective study utilizing a verbal

autopsy interview method in the Dhanusha district in Nepal to classify and review the causes of stillbirths and neonatal deaths. The interviews with households of 601 stillbirths and 671 neonatal deaths reported a home delivery rate of 65%; of these, 59% were assisted by untrained persons, and 50% received an injection (presumably an oxytocic drug) during home delivery for labor augmentation.

Controlled infusion rather than IM or IV bolus

We found 14 studies that reported information related to the route of administration of oxytocin used during labor (Table 4). Evidence of uterotonic administration at high doses as an IM injection or IV bolus rather than through an IV drip were reported in multiple studies. Batra et al. (2016) conducted prospective study in a tertiary hospital in New Delhi in India, reported uterotonic use during labor in 2.1% (three cases) of patients with a ruptured uterus. These authors documented evidence of an uncontrolled high dose of oxytocin administration by intravenous or intramuscular routes in all three cases. Stanton et al. (2014) conducted a descriptive study to describe intrapartum (during labor) uterotonic drug use and related behaviors in public health facility-based deliveries in Uttar Pradesh and Karnataka, India. By conducting direct observation of deliveries at public health facilities, the authors reported labor augmentation rates ranged from 53.5% to 93.0% of deliveries across four districts (the Hassan and Bagalkot districts in Karnataka, and the Agra and Gorakhpur districts in Uttar Pradesh).

Administration of multiple drugs for labor augmentation was also documented in their study- the proportions of women who received two or more drugs for augmentation were 20.8% and 55.5% among the women whose labor was augmented in Gorakhpur and Hassan districts, respectively (Stanton, CK. 2014). In addition, the authors reported the variation in the proportions for different routes of oxytocin administration (either intramuscular injection or by intravenous push) during labor across districts: 6.0% women in Hassan and 62.5% women in

Agra received the drug for labor augmentation via intramuscular injection and 7.6% women in Hassan and 19.0% women in Agra received the drug for labor augmentation via intravenous push (Stanton, CK. 2014). Singh et al. (2012) conducted interviews with 29 Traditional Birth Attendants (TBAs) in their study to assess the role of TBAs in the provision of antenatal and perinatal care for urban poor in India, documented a widespread practice of administering oxytocin intramuscularly for labor augmentation- 23 out of 29 TBA (79.3%) reported to administer oxytocin through intramuscular injections for augmenting labor. Moreover, the TBAs reported of not conducting any assessment for clinical indications for labor augmentation before administering oxytocin using IM injection for labor augmentation (Singh, S. 2012). Considerably high proportions of intramuscular oxytocin administration during labor in both home and hospital births were documented in Karachiwala et al.'s (2012) study on assessing the use of oxytocin in South India- 76.4% of women received oxytocin during labor at home, and most of them received the drug through an intramuscular injection; 23% women who delivered at healthcare institutions also received oxytocin during labor through intramuscular injections.

Day et al.'s (2016) study on uterotonic use during labor prior to arriving at a facility in Bangladesh reported that 3.4% and 4.4% of mothers with a history of labor lasting for less than twelve hours received uterotonics through injections and through IV drips, respectively. Besides, among the mothers having labor lasting for at least 12 hours- 11.6% of mothers reported receiving uterotonics through injections specifically and 13.0% through an IV drip specifically. Moran et al.'s (2010) cross-sectional study on exploring the use of oxytocin to augment labor during home births in an urban slum in Dhaka in Bangladesh reported receiving multiple doses of oxytocin administration for labor augmentation in many cases- 84% of the labor augmented women received one dose of oxytocin; 13.7% of the labor augmented women in the study received two doses of oxytocin. In addition, 20.6% reported receiving the labor augmenting drug through an intramuscular injection.

Ellis et al. (2000) conducted an unmatched case-control study to determine the risk factors for neonatal encephalopathy among term infants; maternal characteristics were also reported in the study. The study was conducted in a tertiary hospital in Nepal among 131 infants (gestational age more than 37 weeks) with neonatal encephalopathy as cases, and 635 infants who met all inclusion criteria (except for not being encephalopathic) as controls (Ellis, M. 2000). The authors reported 39% of cases and 22.4% of controls with exposure to labor augmentation with oxytocin for hospital births. In addition, Ellis et al. (2000) documented that oxytocin for labor induction or augmentation was given through a controlled IV infusion in dosages of 2 mU per minute titrated up to 15 mU per minute. However, the practice of administering oxytocin through an injection instead of the recommended method of a controlled infusion was reported in a study conducted among women in the Southeastern region of Nepal (Manandhar, SR. 2010). Injections during labor by informal health providers were also frequently reported in a study conducted by Mullany et al. (2013); the study was conducted to determine the association between injections during labor in a home-setting and intrapartum related neonatal mortality and morbidity among home births in Sarlahi District in Nepal.

Commonly practiced routes for administration of oxytocin for labor induction or augmentation were also reported in several studies conducted in the context of Pakistan. Rizwan et al. (2009) reported a 38.8% rate of labor augmentation with oxytocin among 90 patients diagnosed with a retained placenta in their study conducted in a tertiary hospital in Pakistan; the authors also documented labor augmentation by intramuscular injections by untrained birth attendants in their study. Shah et al. (2016), in their cohort study conducted in the Timurgara District Hospital in Pakistan, reported that 87.0% (528 out of 607) of the population who received labor-inducing medication prior to reaching the facility received unregulated (oral or IV or IM labor-inducing drugs by unauthorized health workers) medicines; of these, 8% of the population received IM injections (presumably, oxytocin). Among the rest of the 13% population

(79 out of 607) who received regulated labor-inducing medication (non-oral, administered by authorized provider) prior to reaching the hospital, 15.2% reported receiving an IM oxytocin injection (presumably oxytocin) (Shah S. 2016).

Adequate frequency of reassessment

We found 9 studies (Table 5), included in this review, that provided explicit information regarding the frequency of fetal and maternal assessment when uterotonics are used during labor. A lack of monitoring of uterine contractions and fetal heart rate in mothers who received oxytocin during labor was reported in 5 studies (three studies were conducted in India, one in Nepal, and one in Bangladesh).

Chowdhury (2015) conducted a hospital-based study on incidence, etiology, and management of obstructed labor in a rural area based comprehensive facility in Jharkhand in India. The author documented evidence of injudicious oxytocin use without labor monitoring in 84% of mothers with obstructed labor (Chowdhury, G. 2015). Administration of oxytocin during labor by TBAs without considering the mothers' status of progress of labor or monitoring the mothers for effects of oxytocin were reported in Singh et al.'s cross-sectional study in two urban colonies in northeast Delhi in India (Singh, S. 2012). Batra et al. (2016) also reported evidence of oxytocin administration during labor without frequent monitoring for uterine contractions in their hospital-based study to understand the etiology of the ruptured uterus in mothers with an unscarred uterus in New Delhi in India.

Nahar et al. (2004) conducted a cross-sectional study in a tertiary level hospital in Khulna in Bangladesh to determine the safety and effectiveness of misoprostol in cervical ripening and labor induction among mothers with eclampsia and preeclampsia with inadequate cervical ripening. The study was a prospective observational study, conducted among patients with

severe preeclampsia and eclampsia with an unripe cervix who went through labor induction with misoprostol; 29.3% of preeclampsia patients and 35% of eclampsia patients also received labor augmentation with oxytocin. The authors documented adequately frequent monitoring of fetal heart rate to identify any abnormal fetal heart rate and of uterine activity to identify uterine tachysystole among the mothers who received misoprostol for labor induction and oxytocin for labor augmentation (Nahar, S. 2004). A cross-sectional survey conducted in a home-birth setting with mothers living in an urban slum in Dhaka in Bangladesh reported monitoring of fetal heart rate among 1.9% of mothers who received oxytocin for labor augmentation (Moran, AC. 2010).

Ruling out contra-indications for using oxytocin during labor

A total of 14 studies provided clear information regarding administering oxytocin during labor without assessing for contraindications. Using oxytocin during labor is indicated only among women with pregnancies in cephalic presentation and unscarred uterus (i.e., no prior cesarean deliveries). Other specific contraindications to using oxytocin during labor include mothers with complete placenta previa, invasive cervical cancer, active genital herpes infection, vasa previa, and prolapse or presentation of the umbilical cord) (Osilla EV. 2021). Multiple studies conducted in the South Asian context included in this review reported using oxytocin during labor with one or more specific contra-indication. In addition, administering oxytocin during labor is contra-indicated in mothers with cephalopelvic disproportion (women with pelvises not large enough to allow a baby to pass through her birth canal) and in mothers with abnormal fetus position, including transverse lie.

Cephalopelvic disproportion (CPD), which is a contra-indication for using oxytocin during labor, is the major cause for developing obstructed labor. Yet, several studies included in this review reported evidence of administering oxytocin during labor among mothers with obstructed labor.

Qazi et al. (2012) documented evidence of obstructed labor and injudicious use of oxytocin during labor in 15.6% of cases of uterine rupture in their prospective observational study in a hospital setting in Pakistan. Khan et al. (2003) conducted a prospective study on patients with ruptured uterus in a tertiary level hospital in Abbottabad in Pakistan from July 2001 to June 2002. The study documented 32.4% (11) of cases of using oxytocin during labor by traditional birth attendants among 34 uterine rupture cases; of these, 18.2% (2 out of 11) in mothers with previous scar. Hassan et al. (2009) also documented evidence of administering oxytocin during labor among mothers with a previous uterine scar in 34.1% of cases and administering Prostaglandin E2 for labor induction among mothers with a previous uterine scar in 2.4% cases. Besides, the authors reported 85.8% (73) of all ruptured cases received oxytocin during labor, and 42.3% of all ruptured uterus cases had obstructed labor. Aziz et al. (2015) reported 54.1% (33) of ruptured uterus cases with a history of labor augmentation in their study conducted in a tertiary level hospital in Pakistan; of these, 34.4% cases of labor augmentation using oxytocin were reported in mothers with scarred uterus. Hameed et al. (2017), in their prospective observational study on ruptured uterus, indicated scarred uterus with augmentation with oxytocin as a risk factor for uterine rupture. The study was conducted in a hospital setting in Baluchistan in Pakistan, reported 17.6% of cases with previous cesarean scar received oxytocin for labor augmentation.

Agha et al. (2019) conducted a cross-sectional observational study on Maternal and Newborn Health (MNH) care in selected facilities in the Sindh province in Pakistan, reporting a labor augmentation rate of 67.2% among 293 mothers; evidence on the assessment during labor was documented 49.6% of mothers for checking fetal presentation. Hassan et al. (1993) conducted a study on 251 uterine rupture cases in a tertiary hospital in Pakistan, indicated evidence of a previous uterine scar, administration of oxytocin during labor, and presence of obstructed labor in 37.7% of cases, 53.7% of cases, and 65.0% of cases, respectively. Ara et al. (2010) reported

93% of cases with oxytocin exposure during labor in their study conducted among a total of 30 ruptured uterus cases admitted to a tertiary level hospital in Pakistan; in addition, a previous cesarean section was reported in 86.7% of cases, and the presence of CPD was reported in 23.3% of cases in their study. A similar finding in the context of Pakistan was also reported in Munim et al.'s (2002) study; they conducted an observational study on 23 uterine rupture patients admitted to a presumably tertiary level hospital in Karachi in Pakistan. The authors recorded 60.9% of cases with a history of injudicious use of oxytocin during labor and with evidence of obstructed labor, and 39.1% of cases with a previous cesarean scar.

Evidence related to the administration of oxytocin during labor among mothers with cephalopelvic disproportion and previous cesarean sections was also demonstrated in studies conducted in India. Trivedi et al. (1968) reported 23.2% (41 cases) cases of oxytocin use during labor in their study on ruptured uterus (178 cases) conducted in a hospital setting in India. The authors reported that among the mothers who received oxytocin during labor, 19.5% of mothers had babies in transverse lie position, 2.4% of mothers had a previous cesarean scar, and 4.9% mothers had disproportion. A similar study on patients with a ruptured uterus (28 cases) was conducted by Rajora et al. (2018) in a tertiary level hospital in India. Using the case records documented in a tertiary level hospital in Punjab in India, the authors reported that 35.7% of all ruptured uterus cases received uterotonic during labor, and 75.0% of uterine rupture cases had a previous uterine scar. Chowdhury et al. (2015) reported evidence of using oxytocin during labor in 84.0% (687 cases) of cases among 818 obstructed labor cases included in their study on obstructed labor conducted in a tertiary level hospital setting in India. Veena et al. (2012) conducted a retrospective study utilizing data on ruptured uterus cases in a tertiary level hospital in Pondicherry in India. The authors reported 72 cases of uterine rupture with a previous uterine scar in their study, and of these, 26.3% of cases had labor induction presumably with oxytocin.

Presence of labor companion

According to the WHO recommendation for labor augmentation, a mother receiving uterotonics for labor augmentation should never be left unattended. We found only one study that provided information on having a companion or attendant during labor augmentation. Cederfeldt et al. (2016) conducted a cross-sectional study to assess the quality of intra-partum care provided to women expecting to have a normal birth in a tertiary level hospital in Nepal. The authors utilized a self-administered questionnaire to collect data from 164 women in their study that consists of four sections- maternal characteristics, outcomes of previous pregnancies and births, current pregnancy, and current labor and birth. The current labor and birth section of the questionnaire included questions related to Bologna score- an instrument by WHO to evaluate the management of care in normal birth. Five variables under the Bologna score are- Presence of labor companion during labor and birth, absence of labor augmentation and use of partograph, non-supine position, and skin-to-skin contact of mother and child for more than 30 minutes. 70.7% of mothers received labor augmentation and a labor companion was present in only 1.8% of mothers.

Effects of labor augmentation on adverse maternal and fetal outcomes:

Administering uterotonics, including oxytocin, during labor was one of the commonly reported risk factors for all the outcomes identified from the studies included in this review (Table 7).

Maternal outcomes

Aziz et al. (2015) indicated the injudicious use of oxytocin during labor as the most important etiologic and predisposing factors for ruptured uterus in their study conducted in a teaching hospital in Pakistan; in this study, 54.1% of ruptured uterus cases were attributed to the administration of oxytocin during labor. In addition, the authors reported that 23.0% of

ruptured uterus cases admitted to the facility during the study period (January 1st to December 31st of 2012) required hysterectomy as a management modality of uterine rupture. Padhey (2005) also reported oxytocin infusion during labor as a contributory factor for uterine rupture in their study conducted among ruptured uterus patients (251 cases) admitted to a tertiary level health facility in Nepal. The study documented 11% cases of oxytocin infusion during labor among the cases of uterine rupture. Chuni (2006) conducted a descriptive study on 126 cases of uterine rupture presented in a tertiary level hospital in Nepal; this study documented 15.9% of ruptured uterus cases with a history of using oxytocin during labor. A similar study conducted by Mishra et al. (2006) among 52 cases of ruptured uterus admitted to a tertiary level hospital in Nepal reported 61.5% of cases with a ruptured uterus due to oxytocin use during labor.

Qazi et al. (2012) documented 51.6% of uterine rupture cases due to exposure to oxytocin during labor in their study on evaluating risk factors, management, maternal and fetal outcomes of ruptured uterus cases at a teaching hospital in Pakistan. Hassan et al. (2009) reported 85.8% of uterine rupture due to oxytocin exposure in their study conducted in a tertiary level hospital in Pakistan. A study conducted in a tertiary level hospital in India reported that oxytocin exposure during labor contributed to 5.5% of ruptured uterus cases in the study (Latika, S. 2006). Incidence of uterine rupture due to oxytocin exposure during labor was indicated in several other studies conducted in countries in South Asia- 35.7% (Rajora, P. 2018)[India], 33.3% (Veena, P. 2012)[India], 26.5% (Hameed, H. 2017) [Pakistan], 53.7% (Hassan, TJ. 1993) [Pakistan]. As cause of uterine rupture, Munim et al. (2002) documented 60.9% of ruptured uterus cases due to oxytocin administration during labor in their study conducted in a hospital setting in Pakistan; besides bleeding per vagina and shock were reported as major complications in 86.8% and 65.2% of ruptured uterus cases, respectively.

Shah et al. (2016) conducted a cohort study to describe the exposure to unregulated labor-inducing medication (any oral medication, IM/IV by unauthorized staff) and its possible adverse outcomes in women living in Timurgara district in Pakistan. The study compared the outcomes of unregulated labor-inducing drugs (oral/IV/IM and administered by unauthorized staff) with regulated labor-inducing drugs (non-oral, administered by authorized staff) among 607 women who received labor-inducing medication prior to reaching the facility. These women were furthers subdivided into four obstetric risks subgroups (based on registered complications in the hospital MCH database) as follows: women with prolonged/obstructed labor, women with post-partum hemorrhage, women with antepartum hemorrhage and women with no registered complication. By conducting multivariable analysis, the authors indicated a significant association of unregulated oxytocin exposure with risks of uterine rupture among the women in the prolonged labor/obstructed labor subgroup. Among the prolonged/obstructed labor subgroup women who received unregulated labor-inducing drug during labor were reported to have 4.1 times risk of developing uterine rupture compared to those who did not receive unregulated oxytocin during labor [RR: 4.1, 95% CI: 1.7-9.9]. A similar association was reported for developing cervical tear; among the prolonged/obstructed labor subgroup women who received unregulated oxytocin during labor were reported to have 1.5 times the risk of developing cervical tear compared to those who did not receive unregulated oxytocin during labor [RR: 1.5, 95% CI: 0.7-3.0]; however, this association was not significant.

A community based prospective study conducted among 1506 women living in an urban slum in Bangladesh reported that a considerably high proportion of women who received labor augmentation experienced postpartum morbidity- 76% (among the women who received labor augmenting medicine at home and delivered at home), 71% (among the women who received labor augmenting medicine at a facility and delivered at a facility), and 73% (among the women who began the labor at home but transferred to a health facility for delivery (emergency transfer

to a facility) and received labor augmenting medicine most likely at home) (Fronczak, N. 2007). The included conditions under postpartum morbidity mentioned in Fronczak et al.'s study are: perineal tears, pelvic infection, weakness or pain in the leg, urinary tract infection, vaginal tract infection, uterine prolapse, fistula, secondary postpartum bleeding, and/or feeling poorly with no specific morbid condition.

A prospective study evaluating obstetric anal sphincter injuries (OASI) among 97 primigravida women in a tertiary level hospital in Sri Lanka reported that women who received oxytocin for labor induction/augmentation were 30 times more likely to have external anal sphincter defect (EAS) compared to women who did not receive oxytocin for labor induction or augmentation (Wickramasinghe, DP. 2016).

A prospective observational study conducted by Brohi et al. (2012) in a hospital setting in Pakistan reported a significant association between perineal tear and the use of oxytocin for either induction or augmentation of labor. The study was conducted to determine the frequency and severity of perineal tears during vaginal delivery; thereby, only mothers (women with a full-term singleton pregnancy, primigravida, or multigravida, in active labor, were observed) with perineal injuries were included in the study. Out of 147 mothers with perineal injuries included in the study, 62.6% reported receiving oxytocin for labor induction or augmentation.

Khaskheli et al. (2014) conducted an observational cross-sectional study to identify iatrogenic risk factors among 51 pregnant women who required intensive care admission during labor or immediately after delivery in a tertiary level hospital in Pakistan and misuse of oxytocin was identified as a medical management-related risk factor among 31.4% of mothers.

Fetal outcomes

(Table 8) presents data on fetal outcomes in the event of using oxytocin during labor from the identified studies conducted in South Asia.

A hospital-based prospective study conducted in Nepal to identify the risk factors of cesarean section among mothers with indications for labor induction at terms reported increased risk of cesarean section among the mothers who received oxytocin for labor augmentation compared to who did not receive oxytocin during labor; overall, fetal distress and meconium stained liquor were reported as an indications for cesarean section in 46.0% and 15.5% of cases, respectively (Rijal, P. 2014). Rijal et al. (2014) noted that the mothers included in the study were at full terms with indications of labor induction aged from 18-35 years old, none had any other risk factors that might increase the chance of cesarean delivery independently.

Fetal distress was also reported to be a common reason for a cesarean section in Acharya et al.'s (2017) study among a sample population who are induced after admission for delivery in a tertiary hospital in Nepal. They documented fetal distress in 64.3% of mothers who received only oxytocin for labor induction and in 20% of mothers who received oxytocin for labor induction only after failure with misoprostol. The study population included in Acharya et al.'s study was mothers with singleton pregnancy, cephalic presentation, and gestational age of 37 weeks and above; mothers with grand multiparity, previous lower segment cesarean section, antepartum hemorrhage, and premature rupture of membrane were excluded from the study. The authors reported several other adverse fetal outcomes identified in the study population, including irregular fetal heart rate, meconium-stained liquor, oxygen resuscitation required and baby unit admission required. Incidence of irregular fetal heart rate was reported in 5.7% of cases who received only oxytocin for labor induction in the study. Incidence of Meconium Stained Liquor (MSL) was documented in 45.7% of cases who received only oxytocin for labor

induction and 66.7% of cases who received oxytocin for labor induction only after failure with misoprostol in the study. They documented 25.7% and 11.1% of babies who required oxygen resuscitation among the mothers who received only oxytocin for labor induction and who received oxytocin for labor induction after failure with misoprostol, respectively.

Shah et al. (2016) reported a statistically significant association of severe birth asphyxia with unregulated (oral/IV/IM administration of oxytocin by unauthorizes staff) oxytocin exposure among the obstructed or prolonged labor subgroup of women in their cohort study conducted in Pakistan (adjusting for potential confounders, including patient origin, referral source, parity, gestational age, multiple pregnancies). Among the prolonged/obstructed labor subgroup women who received unregulated oxytocin during labor were reported to have 3.9 times risk of developing severe birth asphyxia compared to those who did not receive unregulated oxytocin during labor in the study [RR: 3.9, 95% CI: 2.5–6.1].

A study targeting home births conducted in an urban slum in Bangladesh reported trouble breathing after birth in 4.6% cases among the mother who received oxytocin to augment labor compared to 3% cases among mothers without any history of labor augmentation with oxytocin (Moran, AC. 2010).

Mullany et al. (2013) conducted a secondary analysis of a cluster-randomized trial assessing the association between injections (any type of injections including oxytocin) received during labor by mothers and intrapartum-related neonatal mortality and morbidity among home births in Nepal; the study demonstrated a significant association of neonatal respiratory depression and neonatal encephalopathy with mothers' injection receipt status during labor. By conducting multivariable adjusted analyses (restricted to home births and excluding any maternal labor complications), Mullany et al. reported that the infants born to mothers with a history of

exposure to injections during labor were 2.35 times as likely to develop Neonatal respiratory depression (NRD) compared to children born to unexposed mothers [RR 2.35; 95% CI 2.18–2.53]. The risk of developing moderate to severe neonatal encephalopathy was also reported to be 1.34 times as likely increased among the children born to mothers who were exposed to injections compared to children born to unexposed mothers in the study [RR 1.34; 95% CI, 1.02–1.76] (multivariate analysis; restricted to homebirths and without any maternal complications). Furthermore, they reported that children born to mothers with a history of injection during labor were more than twice as likely to experience Intrapartum related Neonatal Respiratory Depression (IPR-NRD) [RR 2.52; 95% CI, 2.29–2.78]; and Intrapartum related moderate to severe Neonatal Encephalopathy (IPR-NE) [RR 3.48; 95% CI, 2.46–4.93] in multivariable analysis (restricted to homebirths and without any maternal complications). In the study, IPR-NRD was defined as "presence of NRD among full-term infants (at least 37 weeks), and excluding those with a major congenital malformation", and IPR-NE was defined as "an IPR-NRD case resulting in death or developing seizures and two of the following: lethargy, poor suck, or a respiratory rate less than 40 breaths per minute, observed anytime during the first 7 days after birth among full-term infants". Similar findings were reported regarding the association between injection receipt status during labor among mothers with IPR-NRD and IPR-NE related case fatality rates among babies. The IPR-NRD specific mortality rate was reported to be 3.7 times higher among the babies born to mothers with exposure to injections during labor than mothers without any such exposure [RR 3.78; 95% CI, 2.53–5.66] (multivariable analysis; restricted to homebirths and without any maternal complications). Similarly, The IPR-NE specific mortality was reported to be 4.47 times higher among the babies born to mothers with exposure to injections during labor compared to mothers without any such exposures [RR 4.47; 95% CI, 2.78–7.19] (multivariable analysis; restricted to homebirths and without any maternal complications).

In an unmatched case-control study conducted in a tertiary-level hospital in Nepal, Ellis et al. (2000) reported similar findings concerning neonatal encephalopathy and other adverse outcomes in mothers with labor augmentation. The authors reported that 39.0% in the encephalopathic group had a history of labor augmentation with oxytocin compared to 22.4% in the non-encephalopathic group with an adjusted odds ratio of 3.51 [OR 3.51, 95% CI 2.04 to 6.07] (adjusted for maternal antenatal confounders and history of preeclampsia).

By conducting verbal autopsy interviews with families of 601 stillbirths and 671 neonatal deaths in 60 village development committees in Dhanusha district in Nepal, Manandhar et al. (2010) documented 50% of cases among 1272 stillbirth and neonatal death cases had a history of injection given during labor, and the injection was most likely an oxytocin injection. Besides, the authors reported birth asphyxia (44%) as the most common cause of perinatal death in the study.

An association of early neonatal deaths (intrapartum stillbirths and live born babies who died within 24 hours of delivery) with the administration of oxytocin during labor was reported in Brahmawar Mohan et al.'s (2020) population-based case-control study in Haryana in India. By conducting multivariable logistic regression (adjusted for presence of skilled birth attendants), the authors reported that the odds of oxytocin exposure during labor among the cases of early death was 1.9 times higher compared to late deaths (neonates who died after day 7 (8-28)) in case of homebirths [adjusted OR 1.9, 95% CI 1.5- 2.4]. For births in private health facilities, the odds of oxytocin exposure during labor among the cases of early death was 1.8 times higher among the births compared to late deaths [adjusted OR 1.8, 95% CI 1.2-2.5]. Besides, increased odds of exposure to oxytocin during labor was found still associated with cases of early deaths compared to late deaths considering only the babies who did not have any conditions other than the administration of oxytocics during labor [OR 1.7, 95% CI 1.4-2.1].

Day et al. (2016) also conducted a cross-sectional study using seven years of hospital record data in low income setting in rural Bangladesh, demonstrated significant associations of fresh stillbirth, early neonatal death, birth asphyxia, and all perinatal death with uterotonics received during labor outside of a CEmONC facility; the analysis was adjusted for prolonged labor, pre-eclampsia, eclampsia, hospital administration of uterotonics, and Cesarian section. By conducting multivariable regression analysis, Day et al. reported that a higher odds of exposure to an outside CEmONC facility uterotonic among the mothers with births outcomes- stillbirth [adjusted OR 4.0, 95% CI 3.0-5.3], early neonatal death [adjusted OR 2.9, 95% CI 2.1-4.0], birth asphyxia [adjusted OR 3.1, 95% CI 2.2-4.5)] and perinatal death [adjusted OR 3.0, 95% CI 2.4-3.7](compared to mothers who did not have such birth outcomes).

Litorp et al.'s (2021) study on labor augmentation with oxytocin and delivery outcomes found a higher risk among the women who received labor augmentation with oxytocin for:

- newborn requiring bag-and-mask ventilation (aRR 2.10, 95% CI 1.80-2.50)
- APGAR score <7 at 5 minutes (aRR 1.65, 95% CI 1.49-1.86), and
- neonatal death before discharge (aRR 1.93, 95% CI 1.46-2.56).

Krishnan et al. (2016) conducted a case-control study in a tertiary level hospital in Tamilnadu in India to determine the incidence and risk factors of birth asphyxia among babies exposed to intrapartum risk factors, including administration of oxytocin during labor. The intrapartum risk factors as reported in the study are abnormal presentation, cord prolapse, premature rupture of membrane, induction, and acceleration of labor with oxytocin and with cerviprime (Prostaglandin E2), and meconium-stained amniotic fluid. Regarding the association between birth asphyxia and oxytocin infusion to accelerate labor, the authors reported that the babies born to mothers who received oxytocin for labor augmentation were 3.35 times as likely to

develop birth asphyxia compared to the babies born to mothers who did not receive oxytocin for labor augmentation [RR 3.35 (unadjusted), 95% CI: 1.41-1.82].

Shireen et al. (2010) conducted a case-control study in a tertiary level hospital in Bangladesh to determine the maternal and fetal risk factors contributing to developing birth asphyxia and the short-term outcomes of birth asphyxia in babies. The babies admitted to the hospital from October 2003 to March 2004 for birth asphyxia were cases, and the babies admitted to the hospital during the same period for causes other than birth asphyxia were considered controls in this study. The authors documented evidence of oxytocin use during labor as one of the risk factors for developing perinatal asphyxia; 16% of babies among the cases were born to mothers who received oxytocin during labor compared to 0% among the controls.

2.4 DISCUSSION

A total of 49 studies were included in this review, most conducted in India, followed by Pakistan and Nepal. Very few studies were conducted in Bangladesh. We found only one study conducted in Sri Lanka with limited data on uterotonic uses during labor and its effect on maternal and fetal outcomes. None were found from Maldives, Bhutan, and Afghanistan. The most commonly used uterotonic reported in the selected studies is oxytocin.

We found home use or outside of a hospital setting use of oxytocin during labor as a frequent practice in several countries in South Asia (Bangladesh- 4 studies, India- 8 studies, Pakistan- 2 studies, Nepal - 2 studies) [Table 2]. A systematic literature review on oxytocin use in low-income countries also reported similar findings for oxytocin administration to accelerate labor in case of home-deliveries for the countries in South Asia (Flandermeyer, D. 2010). A narrative review on using oxytocin during home deliveries in Uttar Pradesh, India, demonstrated evidence

of the widespread use of oxytocin for labor augmentation in home deliveries, 48.2% to 74.7% (Jeffery, P. 2007).

Administering oxytocin during labor using an IM injection or IV bolus increases the risk of adverse effects of oxytocin in both mothers and fetuses. Hence, oxytocin during labor is recommended using ideally a controlled infusion pump or at least using the IV drip infusion method. However, we found evidence of administering oxytocin using IM injections/IV bolus injections in 12 studies. These IM/IV injections of oxytocin were administered during labor most commonly by untrained birth attendants, unqualified medical practitioners, traditional birth attendants in both home and hospital birth settings, and in some cases by authorized medical providers and Auxilliary Nurse Midwives (ANMs) (Karachiwala, B. 2012; Agha, S. 2019) in a hospital setting. Administering oxytocin during labor without assessing for a previous cesarean section and the presence of cephalopelvic disproportion was a common finding in most of the ruptured uterus related studies (11 studies) that we retrieved from South Asia; noncompliance with this WHO recommendations for labor augmentation contributed a significant proportion of ruptured uterus among mothers. Ruptured uterus among mothers is the extreme adverse outcome that develops due to uterine hyperstimulation resulting from the practice of using oxytocin during labor, particularly when the augmented mother is left unattended and unmonitored.

Uterine hyperstimulation in the mothers also leads to reduced fetal oxygen level, thereby developing fetal distress, birth asphyxia, neonatal respiratory depression, and neonatal encephalopathy. In extreme cases, it may cause stillbirth and early neonatal death. All these deadly consequences are preventable if adequate monitoring of augmented mothers for uterine contractions and fetal heart rate at least every thirty minutes can be ensured; this is also a recommendation for ensuring safety during labor augmentation using oxytocin by WHO. A five-

year retrospective study conducted among 40 patients from 2003-2007 in a teaching hospital in Nigeria indicated injudicious use of oxytocics to be a contributory factor for uterus rupture in mothers with a previous cesarean section (Nyengidiki, TK. 2011). In addition, this study strongly supported the importance of continuous monitoring of mothers during labor augmentation and advocated for strict regulation against the use of oxytocic by unskilled health workers (Nyengidiki, TK. 2011).

We searched for evidence documented in the related studies in South Asia in regard to WHO's frequent assessment of mothers and fetuses and presence of labor attended condition. The findings we gathered are limited, not clear, and did not provide any satisfactory impression about the situation in South Asia, specifically regarding the frequency of assessment and ensuring a continuous presence of a labor companion. Only four studies that were conducted among mothers with complications and with indications for labor induction reported careful monitoring of mother's uterine contractions and fetal heart rate, and all of these studies were conducted in an equipped tertiary level healthcare setting (Rijal, P. 2014; Acharya, T. 2017; Litorp, H. 20021; Nahar, S. 2004).

We also investigated the possible potential outcomes related to oxytocin administration during labor among the studies conducted in the context of South Asia. The most common reported maternal outcome due to injudicious administration of oxytocin during labor is uterine rupture. All 19 ruptured uterus studies indicated oxytocin administration during labor as the primary risk factor for developing a ruptured uterus. Another important observation from these studies is that most of these studies were conducted among the patients admitted to a hospital with already developed uterine rupture, and patients gave a history of oxytocin exposure during labor in almost all uterine rupture related studies. In most instances, these women might have received oxytocin during labor either at home or at a lower-level facility. Unavailability of blood

transfusion services and delay in management due to long distance from a tertiary level facility with surgical capacity were reported as contributing factors to maternal mortality in the uterine rupture related studies (Chuni, N. 2006; Qazi, Q. 2012). Since there were other risk factors as well contributing to ruptured uterus, we could not attribute these outcomes solely to oxytocin administration during labor. Other reported adverse maternal outcomes of using oxytocin during labor are- emergency cesarean section (Cederfeldt, J. 2016), increased risk of cesarean section among the mothers with an indication for labor induction (Rijal, P. 2014; Acharya, T. 2017), perineal tear (Fronczak, N. 2007; Brohi, ZP. 2012), cervical tear among the women in the prolonged/obstructed labor subgroup (Shah, S. 2016), external anal sphincter injury (Wickramasinghe, DP. 2016), and requiring intensive care admission (Khaskheli, MN. 2014).

With respect to fetal outcomes due to exposure to oxytocin during labor, 'still birth' was commonly documented in almost all studies related to uterine rupture that indicated administration of oxytocin during labor as the prime risk factor contributing to a ruptured uterus. An increased risk of neonatal respiratory depression and neonatal encephalopathy among the babies born to mothers with exposure to injections during labor compared to without such exposure was found in a study conducted among home-based deliveries in Nepal (Mullany, LC. 2013; Ellis, M. 2000). A recently published systematic review and meta-analysis on the effect of oxytocin during labor on neonatal encephalopathy in low-income countries also demonstrated similar findings (Burgod, C. 2021). The other identified fetal outcomes due to oxytocin exposure during labor in the studies in South Asia are- fetal distress and meconium stained liquor among the mothers with indications for labor induction (Rijal, P. 2014; Acharya, T. 2017; Sarvanan, N. 2017), birth asphyxia (Manandhar, SR. 2010; Shah, S. 2016; Krishnan, M. 2016), early neonatal death (Brahmawar Mohan, S. 2020), Apgar score <7 at 5 minutes and bag-and-mask ventilation (Litorp, H. 2021). All these findings underscore the importance of ensuring the safe labor augmentation conditions; labor augmentation using oxytocin should not

be done in any setting without adequate monitoring capacity and surgical capacity.

This is the first review investigating the widespread use of oxytocin during labor before the baby's delivery and its potential adverse effects on mothers and babies in South Asian countries. Unsafe use of oxytocin during labor has important potential adverse consequences for both mothers and fetuses. Understandably, labor augmentation is not recommended for home-births and birth in primary level care facilities. Furthermore, ensuring adequate monitoring of uterine contractions and fetal heart rate when oxytocin is used during labor is critical to prevent any of its complications in mothers and babies. Additionally, to minimize the deadly consequence of resulting adverse effects in both mothers and babies, it is crucial to initiate prompt definitive management in instances of such adverse effects. However, any management modality requiring surgeries is impossible to conduct in a context without surgical capacity and blood transfusion services (e.g., conducting emergency cesarean delivery if there are potential indications for fetal distress due to uterine hyperstimulation attributed to oxytocin administration during labor). Moreover, if a baby develops neonatal respiratory depression and requires immediate intensive care unit admission to manage the complication, that is also only possible in a tertiary care facility. Hence, considering the evidence presented in this review indicating the widespread use of uterotonics not complying with the WHO's conditions for labor augmentation, it is desperately important to acknowledge this issue as a public health problem in lower-income settings, particularly South Asia.

Table 1: List of studies included in the review

Study title	**Author, Year**	**Country**	**Type of study**
Outcome of misoprostol and oxytocin in induction of labour	Acharya, T. 2017	Nepal	Observational study
Quality of labor and birth care in Sindh Province, Pakistan: Findings from direct observations at health facilities	Agha, S. 2019	Pakistan	Cross-sectional study
Uterine Rupture: A Catastrophic Complication	Ara, J. 2010	Pakistan	Prospective Observational Study
Analysis of uterine rupture at university teaching hospital Pakistan	Aziz, N. 2015	Pakistan	Descriptive study
Management of Birth Asphyxia in Home Deliveries in Rural Gadchiroli: The Effect of Two Types of Birth Attendants and of Resuscitating with Mouth-to-Mouth, Tube-Mask or Bag–Mask	Bang, AT. 2005	India	Field trial (Mixed-method)
Determinants of rupture of the unscarred uterus and the related feto-maternal outcome: current scenario in a low-income country	Batra, K. 2016	India	Descriptive study
Antenatal Uterotonics as a Risk Factor for Intrapartum Stillbirth and First-day Death in Haryana, India	Brahmawar Mohan, S. 2020	India	Case-control study
Frequency and severity of perineal tears in Countess Lady Dufferin Fund Hospital, Hyderabad	Brohi, ZP. 2012	Pakistan	Prospective observational study
Uterine rupture: a study of its frequency and etiology at military hospital Rawalpindi	Butt, MH. 2005	Pakistan	Descriptive study
Quality of intrapartum care at a university hospital in Nepal: A prospective cross-sectional survey	Cederfeldt, J. 2016	Nepal	Prospective cross-sectional study
Obstructed Labour (OL): A Major Failure of Obstetric Care **[Abstract]**	Chowdhury, G. 2015	India	Descriptive study
Analysis of uterine rupture in a tertiary center in Eastern Nepal: Lessons for obstetric care	Chuni, N. 2006	Nepal	Descriptive study
Perinatal mortality associated with the use of uterotonics outside of Comprehensive Emergency Obstetric and Neonatal Care: a cross-sectional study	Day, LT. 2016	Bangladesh	Cross-sectional Study
Risk factors for neonatal encephalopathy in Kathmandu, Nepal, a developing country: unmatched case-control study	Ellis, M. 2000	Nepal	Unmatched Case-control study
Delivery Practices of Traditional Birth Attendants in Dhaka Slums, Bangladesh	Fronczak, N. 2007	Bangladesh	Prospective study (mixed-method)

Audit of Ruptured Uterus in Bolan Medical Complex Hospital Quetta	Hameed, H. 2017	Pakistan	Prospective Observational Study
Uterine Rupture at LUMHS: A Review of 85 Cases	Hassan, N. 2009	Pakistan	Prospective Observational Study
Rupture of the Uterus in Full-Term Pregnancy	Hassan, TJ. 1993	Pakistan	Descriptive study
Frequency of Postpartum Haemorrhage in induced Versus Spontaneous Labour	Hussain, SS. 2014	Pakistan	Cross-sectional Comparative Study
The use and misuse of oxytocin: a study in rural Karnataka, India **[Poster presentation]**	Karachiwala, B. 2012	India	Prospective study
Uterine rupture: a review of 34 cases at Ayub teaching hospital Abbottabad	Khan, S. 2003	Pakistan	Descriptive study
Iatrogenic risks and maternal health: Issues and outcomes	Khaskheli, MN. 2014	Pakistan	Cross-sectional study
To study the Incidence of Uterine Ruptures in Kashmiri Population	Khurshid, R. 2010	India	Descriptive study
A Prospective Study on Intrapartum Risk Factors for Birth Asphyxia	Krishnan, M. 2016	India	Case-control study
A 10-year analysis of uterine rupture at a teaching institution	Latika, S. 2006	India	Descriptive study
Augmentation of labor with oxytocin and its association with delivery outcomes: A large-scale cohort study in 12 public hospitals in Nepal	Litorp, H. 2021	Nepal	Cohort Study
Causes of stillbirths and neonatal deaths in Dhanusha district, Nepal: A verbal autopsy study	Manandhar, SR. 2010	Nepal	Prospective study (mixed-method)
Birth rights and rituals in rural South India: care seeking in the Intrapartum period	Matthews, Z. 2005	India	Prospective study (mixed-method)
Uterine rupture: Preventable obstetric tragedies?	Mishra, SK. 2006	Nepal	Descriptive study
Oxytocin to augment labour during home births: an exploratory study in the urban slums of Dhaka, Bangladesh	Moran, AC. 2010	Bangladesh	Cross-sectional study
Injections during labor and intrapartum-related hypoxic injury and mortality in rural southern Nepal	Mullany, LC. 2013	Nepal	Secondary analysis of a cluster randomized trial
Ruptured uterus: A 3-year study	Munim, T. 2002	Pakistan	Prospective Observational Study
Utility of misoprostol for labor induction in severe pre-eclampsia and eclampsia	Nahar, S. 2004	Bangladesh	Observational study
Risk factors for stillbirths: how much can a responsive health system prevent?	Neogi, SB. 2018	India	Case-Control Study (Mixed-method)
Rupture of the pregnant uterus – A 20-year review	Padhye, SM. 2005	Nepal	Descriptive study
Woman Health; Uterus Rupture, Its Complications, and Management in	Qazi, Q. 2012	Pakistan	Prospective observational study

Teaching Hospital Bannu, Pakistan			
A 3 Year Review of Uterine Rupture in Tertiary Hospital: Lessons for Obstetric Care	Rajora, P. 2018	India	Descriptive study
Identification of Risk Factors for Cesarean Delivery Following Induction of Labour	Rijal, P. 2014	Nepal	Observational study
Retained Placenta still a continuing cause of maternal morbidity and mortality	Rizwan, N. 2009	Pakistan	Descriptive case series
Socio-demographic background in perinatal Outcome of rupture uterus cases **[Abstract]**	Roy, N. 2017	Bangladesh	Cross-sectional study
Feto-maternal Outcome in Medically Indicated Induction of Labour at Term Gestation	Sarvanan, N. 2017	India	Observational study
Unregulated usage of labor-inducing medication in a region of Pakistan with poor drug regulatory control: characteristics and risk patterns	Shah, S. 2016	Pakistan	Cohort Study
Intrapartum oxytocin use for labor acceleration in rural India	Sharan, M. 2005	India	Mixed-method (Quantitative analysis of survey data and Qualitative interviews)
Risk Factors and Short-Term Outcome of Birth Asphyxiated Babies in Dhaka Medical College Hospital	Shireen, N. 2010	Bangladesh	Observational study
Role of Traditional Birth Attendants (TBAs) in Provision of Antenatal and Perinatal Care at Home Amongst the Urban Poor in Delhi, India	Singh, S. 2012	India	Cross-sectional study (Qualitative)
Direct observation of uterotonic drug use at public health facility-based deliveries in four districts in India	Stanton, CK. 2014	India	Descriptive study
Rupture of the uterus: A clinical study of 181 cases	Trivedi, RR. 1968	India	Descriptive study
A review of 93 cases of ruptured uterus over a period of 2 years in a tertiary care hospital in South India	Veena, P. 2012	India	Descriptive study
Effect of vaginal delivery on anal sphincter function in Asian primigravida: a prospective study	Wickramasinghe, DP. 2016	Sri Lanka	Cohort study

Table 2: Frequency of Uterotonic use in home births or outside of a CEmONC Hospital setting

Author, Year	**Country**	**Type of study**	**Frequency of uterotonic use during labor**
Bang, AT. 2005	India	Field trial (Mixed-method)	**23.1%** (from 1995 to 1996), **21.2%** (from 1996 to 2003)
Brahmawar Mohan, S. 2020	India	Case-control study	**64%** of cases who delivered at home and **49%** of controls who delivered at home
Day, LT. 2016	Bangladesh	Cross-sectional Study	**5.6%** [Prior to arriving at a CEmONC facility]
Fronczak, N. 2007	Bangladesh	Prospective study (mixed-method)	**19 %** [among 1238 women who delivered at home], **69%** [among 88 women who started delivery at home and then experienced emergency transfer to a facility]
Karachiwala, B. 2012 [Poster Presentation]	India	Prospective study	**76.4%** (out of 99 women who delivered at home)
Latika, S. 2006	India	Descriptive study	**3.16%** received oxytocin during labor outside of a hospital setting
Manandhar, SR. 2010	Nepal	Prospective study (mixed-method)	**50%** of women who delivered at home reported receiving injections during labor
Matthews, Z. 2005	India	Prospective study (mixed-method)	**21%** overall, 2% of home deliveries by laypersons, 7% of home deliveries by traditional dais, and 51% of home deliveries by ANM or Nurse
Moran, AC. 2010	Bangladesh	Cross-sectional study	**46.3%** [drug use for labor augmentation at home]
Mullany, LC. 2013	Nepal	Secondary analysis of a cluster randomized trial	**31.8%**of mothers reported receiving injections during labor in case of deliveries in home and peripheral health facilities
Munim, T. 2002	Pakistan	Prospective Observational Study	**47.83%** of patients with a ruptured uterus received labor augmenting drugs outside of a hospital setting
Neogi, SB. 2018	India	Case-Control Study (Mixed-method)	Administration of two or more doses of medicines to augment labour before arriving in the health facility in **36.3%** of cases and **26.1%** of controls
Roy, N. 2017 [Only abstract available]	Bangladesh	Cross-sectional study	**66.67%** [outside of a hospital setting]
Shah, S. 2016	Pakistan	Cohort Study	**9.5%** received labour-inducing medication prior to reaching the hospital
Sharan, M. 2005	India	Mixed-method (Quantitative analysis of	**23%** of women who delivered at home received

		survey data and Qualitative interviews)	oxytocin injections during labor.
Singh, S. 2012	India	Cross-sectional study (Qualitative)	58.6% of 29 TBAs interviewed [reported using oxytocin during labor at home]

Table 3: Frequency of Uterotonic use in hospital settings (most likely a CEmONC level hospital)

Author, Year	Country	Type of study	Frequency of uterotonic use during labor
Acharya, T. 2017	Nepal	Observational study	138 (67.3%) women were induced with misoprostol, 50 (24.4%) were induced with oxytocin. In total, 17 (8.3%) were induced with oxytocin only after failure of misoprostol which is placed in 'other' group
Agha, S. 2019	Pakistan	Cross-sectional study	67% (out of 300 births in 162 facilities)
Ara, J. 2010	Pakistan	Prospective Observational Study	80% (out of 30 cases of ruptured uterus)
Aziz, N. 2015	Pakistan	Descriptive study	54.09% of cases received oxytocin during labor (Out of 61 cases of ruptured uterus, 33 have a history of intrapartum use of oxytocin)
Batra, K. 2016	India	Descriptive study	16.67% of ruptured uterus cases received oxytocin during labor(among the 18 cases with unscarred uterus)
Brohi, ZP. 2012	Pakistan	Prospective observational study	62.58%% (92 out of 147 with perineal tears women had labor augmented with oxytocin in hospital)
Butt, MH. 2005	Pakistan	Descriptive study	12.50% of ruptured uterus cases received oxytocin during labor (out of 32 cases of ruptured uterus)
Cederfeldt, J. 2016	Nepal	Prospective cross-sectional study	53% (87 out of 164 women of low risk who expected to have a normal birth)
Chowdhury, G. 2015 (abstract, oral presentation)	India	Descriptive study	84% (Out of 818 obstructed labor cases, 687 with history of injudicious Oxytocin use)
Chuni, N. 2006	Nepal	Descriptive study	15. 87% of cases received oxytocin during labor (Out of 126 cases of ruptured uterus 20 patients have a history of intrapartum using of oxytocic/ prostaglandin)
Ellis, M. 2000	Nepal	Unmatched Case-control study	Induction with oxytocin- 5.3% (41 out of 766 was induced with oxytocin); Augmentation with oxytocin- 24.67% (189 out of 766 were augmented with oxytocin).
Fronczak, N. 2007	Bangladesh	Prospective study (mixed-method)	40 % [among 180 women who delivered at an elective facility]
Hameed, H. 2017	Pakistan	Prospective Observational Study	26.47% (out of 68 cases of ruptured uterus)
Hassan, N. 2009	Pakistan	Prospective Observational	85.8% of ruptured uterus cases received oxytocin during labor (out of 85 cases of

		Study	ruptured uterus)
Hassan, TJ. 1993	Pakistan	Descriptive study	53.7% (out of 257 cases of ruptured uterus, 138 had history of intrapartum use of oxytocin)
Hussain, SS. 2014	Pakistan	Cross-sectional Comparative Study	Induction with Prostaglandin- 9.09%, Induction with oxytocin- 14.28%; (Analysis included data on 88 patients with term pregnancies, 44 patients were recruited who had spontaneous onset of labour and 44 patients with induced labour either with ARM, oxytocin or prostaglandin E2)
Karachiwala, B. 2012 [Poster Presentation]	India	Prospective study	23% (out of 501 women who delivered in a health facility)
Khan, S. 2003	Pakistan	Descriptive study	32.35% of ruptured uterus cases received uterotonic during labor (out of 34 cases of ruptured uterus)
Khaskheli, MN. 2014	Pakistan	Cross-sectional study	31.37% out of 51 women (Analysis of hospital based data from delivered or undelivered women who needed intensive care unit (ICU) admission due to management related life threatening complication referred from periphery or within this hospital; 76.47% of patients were referred from periphery)
Khurshid, R. 2009	India	Descriptive study	27% (out of 100 cases of ruptured uterus)
Krishnan, M. 2016	India	Case-control study	19% (oxytocin infusion and/ or cerviprime insertion was practiced to accelerate labor)
Litorp, H. 2021	Nepal	Cohort Study	37% [28,915 out of 78,931 women (37%) had labor augmented with oxytocin]
Mishra, SK. 2006	Nepal	Descriptive study	61.5% (out of 52 cases of ruptured uterus)
Nahar, S. 2004	Bangladesh	Observational study	Oxytocin augmentation was required in 29.3 and 35% of cases in severe pe-eclampsia and eclampsia group, respectively.
Padhye, SM. 2005	Nepal	Descriptive study	11% (out of 251 cases of ruptured uterus)
Qazi, Q. 2012	Pakistan	Prospective observational study	51.6% (out of 64 ruptured uterus patients had a history of oxytocin exposure during labor)
Rajora, P. 2018	India	Descriptive study	35.71% (out of 28 cases of ruptured uterus)
Rijal, P. 2014	Nepal	Observational study	Augmentation with oxytocin- among vaginal delivered women: 41.37% (out of 174), among cesarean delivered women: 75.28% (out of 174).
Rizwan, N. 2009	Pakistan	Descriptive case	38.8% (out of 90 patients with retained

		series	placenta)
Sarvanan, N. 2017	India	Observational study	Augmentation with oxytocin was required in 17.09% of patients, all patients had indications for labor induction
Shireen, N. 2010	Bangladesh	Observational study	Analysis of data collected in a hospital setting. 16% out of 100 cases of birth asphyxia
Stanton, CK. 2014	India	Descriptive study	Out of 366 study sample, labor augmentation rates ranged from53.5%–93.0% of deliveries across districts (the Hassan and Bagalkot districts in Karnataka, and the Agra and Gorakhpur districts in Uttar Pradesh)
Trivedi, RR. 1968	India	Descriptive study	23.16% (out of 178 cases of ruptured uterus)
Veena, P. 2012	India	Descriptive study	Induced labor- 33.3% (unscarred uterus), 26.3% (scarred uterus) [out of 93 cases of RU]
Wickramasinghe, DP. 2016	Sri Lanka	Cohort study	Patients were followed up 6 weeks and 6 months after delivery. 13.40% (13 out of 97) required oxytocin

Table 4: Using Uterotonics for labor induction and augmentation with safety (Controlled Infusion rather than IM/IV bolus)

Author, Year	Country	Type of study	Controlled infusion rather than IM or IV bolus
Acharya, T. 2017	Nepal	Observational study	Reported evidence of administering oxytocin (24.4% of study sample) in a hospital setting through IV drip infusion for labor induction
Batra, K. 2016	India	Descriptive study	Three cases of ruptured uterus due to uncontrolled high dose of oxytocin administration by intravenous or intramuscular dose
Day, LT. 2016	Bangladesh	Cross-sectional Study	Prior to arriving at a facility- 3.4% (injections) and 4.4% (IV drip). Among the mothers having labor lasting at least for at least 12 hours- 11.6% (injections specifically) and 13.0% (an IV drip specifically)
Ellis, M. 2000	Nepal	Unmatched Case-control study	Oxytocin for labor induction or augmentation was given through a controlled IV infusion in dosages of 2 mU per minute titrated up to 15 mU per minute
Fronczak, N. 2007	Bangladesh	Prospective study (mixed-method)	Provided evidence of administering injectable oxytocic medications to augment labor (home birth).
Karachiwala, B. 2012 [Poster Presentation]	India	Prospective study	76.4% of women received labor augmentation at home; most of these women received via an intramuscular injections 23% women who delivered in hospitals received oxytocin – mainly via intramuscular Injection during labor.
Manandhar, SR. 2010	Nepal	Prospective study (mixed-method)	Oxytocin was administered using an injection.
Moran, AC. 2010	Bangladesh	Cross-sectional study	Received oxytocin using an intramuscular injection during labor- 20.6%
Mullany, LC. 2013	Nepal	Secondary analysis of a cluster randomized trial	Reported evidence of administering oxytocin during labor via injections by unqualified village doctors
Munim, T. 2002	Pakistan	Prospective Observational Study	Administering oxytocin via intramuscular injections by "dais" (traditional birth attendants) for labor augmentation at home birth- 11 out of 14 cases (78.57%)
Rizwan, N. 2009	Pakistan	Descriptive case series	Reported evidence of administering oxytocin for labor augmentation via

(Pakistan)			intra-muscular injections by untrained birth attendants.
Shah, S. 2016	Pakistan	Cohort Study	Labor inducing medication (presumably oxytocin) administered by unauthorized providers- IM: 8%. Labor inducing medicine by authorized provider: IM injection:15.2%
Singh, S. 2012	India	Cross-sectional study (Qualitative)	Reported practice of administering IM oxytocin injection for labor augmentation by TBAs (29 TBAs were interviewed regarding their practice)
Stanton, CK. 2014	India	Descriptive study	Labor augmentation by IM injection: : 6.0% women in Hassan district and 62.5% women in Agra district IV push: 7.6% women in Hassan district and 19.0% women in Agra district

Table 5: Using Uterotonics for labor induction and augmentation with safety (Adequate frequency of reassessment)

Author, Year	Country	Type of study	Adequate frequency of reassessment
Acharya, T. 2017	Nepal	Observational study	Uterine contractions (for 10 min) was monitored Hourly. Fetal heart rate was monitored every 30 min.
Batra, K. 2016	India	Descriptive study	Documented evidence of administration of oxytocin during labor without frequent monitoring for uterine contractions in a health center.
Chowdhury, G. 2015	India	Descriptive study	Documented evidence of injudicious oxytocin use during labor without labor monitoring in 84% among the mothers with obstructed labor
Ellis, M. 2000	Nepal	Unmatched Case-control study	A lack of monitoring of uterine contractions in mothers who received oxytocin during labor was reported
Litorp, H. 2021	Nepal	Cohort Study	Patients were monitored in for uterine contractions with tocography & intermittent auscultation of fetal heart rate every half hour
Moran, AC. 2010	Bangladesh	Cross-sectional study	Reported monitoring of fetal heart rate among 1.9% out of 131 mothers who received oxytocin for labor augmentation.
Nahar, S. 2004	Bangladesh	Observational study	Documented adequately frequent monitoring of fetal heart rate to identify any abnormal fetal heart rate and of uterine activity to identify uterine tachysystole among the mothers who received misoprostol for labor induction and oxytocin for labor augmentation
Rijal, P. 2014	Nepal	Observational study	Patients were monitored in for uterine contractions with tocography & intermittent auscultation of fetal heart rate every half hour
Singh, S. 2012	India	Cross-sectional study (Qualitative)	Unauthorized TBAs reported injecting oxytocin considering the mothers' status of progress of labor or monitoring the mothers for effects of oxytocin

Table 6: Using Uterotonics for labor induction and augmentation with safety (Ruling out contraindication for using oxytocin during labor)

Author, Year	**Country**	**Type of study**	**Ruling out contra-indications for using oxytocin during labor**
Agha, S. 2019	Pakistan	Cross-sectional study	Checks fetal presentation by palpation of abdomen (49.6%). Assessment of mothers during the first stage of labor for vaginal examination- 92.7%
Ara, J. 2010	Pakistan	Prospective Observational Study	Rupture in mothers with previous cesarean scar- 86.7% Evidence of obstructed labor- 23.3%
Aziz, N. 2015	Pakistan	Descriptive study	Labor augmentation with oxytocin in mothers with scarred uterus- 34.42% cases
Chowdhury, G. 2015	India	Descriptive study	84% of all mothers with an obstructed labor received oxytocin during labor
Chuni, N. 2006	Nepal	Descriptive study	Use of oxytocin in mothers with scarred uterus- 44% (out of 25 uterine ruptured cases among mothers with scarred uterus
Hameed, H. 2017	Pakistan	Prospective Observational Study	Augmentation with Oxytocin in mothers with scarred uterus: 17.6%
Hassan, N. 2009	Pakistan	Prospective Observational Study	Augmentation with syntocinon in mothers with scarred uterus: 34.11% Induction with prostaglandin E2 in mothers with scarred uterus: 2.4%, obstructed labor (42.3%)
Hassan, TJ. 1993	Pakistan	Descriptive study	Presence of obstructed labor- 65% Evidence of rupture in mothers with previous uterine scar- 37.7% cases
Khan, S. 2003	Pakistan	Descriptive study	Documented evidence of using oxytocin in 18.18% of ruptured uterus cases in mothers with previous scar
Munim, T. 2002	Pakistan	Prospective Observational Study	Evidence of obstructed labor- 60.86% cases Presence of previous cesarean scar- 39.13% cases
Qazi, Q. 2012	Pakistan	Prospective Observational Study	Documented evidence of obstructed labor and injudicious use of oxytocin during labor in 15.6% cases. Two cases (received labor augmentation at home)- presence of breech presentation and hydrocephalus.
Rajora, P. 2018	India	Descriptive study	Presence of previous uterine scar in 35.71% of cases
Trivedi, RR. 1968	India	Descriptive study	Among the patients who received oxytocin during labor- 19.51% of mothers had babies in transverse lie position,

			2.43% of mothers had previous cesarean scar and 4.87% of mothers had disproportion
Veena, P. 2012	India	Descriptive study	History of labor induction among mothers with scarred uterus in 26.3% of cases

Table 7: Effects of injudicious use of uterotonics during labor on adverse maternal outcomes

Author, Year	Country	Type of study	Maternal Outcome
Ara, J. 2010	Pakistan	Prospective Observational Study	80% of ruptured cases due to oxytocin exposure during labor
Aziz, N. 2015	Pakistan	Descriptive study	54.09% of cases of ruptured uterus were attributed to administration of oxytocin during labor
Batra, K. 2016	India	Descriptive study	16.67% of cases of ruptured uterus due to use of oxytocin during labor
Brohi, ZP. 2012	Pakistan	Prospective Observational Study	Perineal tear was significantly associated with the use of oxytocin for either induction or augmentation of labour ($p<0.001$).
Chuni, N. 2006	Nepal	Descriptive study	Rupture uterus due to oxytocin use during labor in 15.87% cases
Froncezak, N. 2007	Bangladesh	Prospective study (mixed-method)	Postpartum morbidity : 76% of women who received labor augmenting medicine at home and delivered at home, 71% of women who received labor augmenting medicine at a facility and delivered at a facility, and 73% of women who began the labor at home but transferred to a health facility for delivery (emergency transfer to a facility) and received labor augmenting medicine most likely at a health facility, [Postpartum morbidity: perineal tears, pelvic infection, weakness or pain in the leg, urinary tract infection, vaginal tract infection, uterine prolapse, fistula, secondary postpartum bleeding, and/or feeling poorly with no specific morbid condition]
Hameed, H. 2017	Pakistan	Prospective Observational Study	Uterine rupture due to oxytocin during labor- 26.47%
Hassan, N. 2009	Pakistan	Prospective Observational Study	Rupture uterus due to oxytocin use during labor in 85.8% cases .
Hassan, TJ. 1993	Pakistan	Descriptive study	Uterine rupture due to oxytocin exposure during labor- 53.7%
Hussain, S. 2014	Pakistan	Cross-sectional Comparative Study	Frequency of PPH was highest in women induced with oxytocin 14(14.28%) as compared to other two methods. ARM- 12.50% PPH, Oxytocin- 14.28% PPH, Prostaglandin- 9.09% PPH
Khan, S. 2003	Pakistan	Descriptive study	32.35% of cases of ruptured uterus due to oxytocin exposure during labor.

Khaskheli, M. 2014	Pakistan	Cross-sectional study	The misuse of oxytocin resulted in complications in 16(31.37%) cases
Khurshid, R. 2010	India	Descriptive study	27% of ruptured uterus due to oxytocin exposure during labor
Latika, S. 2006	India	Descriptive study	Ruptured uterus due to exposure to labor induction using oxytocin in 5.53% cases
Mishra, SK. 2006	Nepal	Descriptive study	Rupture uterus due to oxytocin use during labor in 61.5% cases
Munim, T. 2002	Pakistan	Prospective Observational Study	Uterine rupture due to oxytocin exposure during labor- 60.86% Bleeding per vagina- 86.75% Shock- 65.21%
Neogi, S. 2018	India	Case-Control Study (Mixed-method)	Statistically significant associations with unregulated oxytocin exposure were seen in the group of women with obstructed or prolonged labour for uterine rupture (RR 4.1, 95% CI 1.7–9.9)
Padhye, SM. 2005 [Nepal]	Nepal	Descriptive study	Rupture uterus due to oxytocin use during labor in 11% of cases
Qazi, Q. 2012	Pakistan	Prospective observational study	Rupture uterus due to oxytocin use during labor in 51.6% cases
Rajora, P. 2018	India	Descriptive study	Uterine rupture dur to oxytocin exposure during labor- 35.71%
Roy, N. 2017	Bangladesh	Cross-sectional study	Uterine rupture due to oxytocin exposure during labor_-66.67% (before admission)
Shah, S. 2016	Pakistan	Cohort study	Risks of uterine rupture among the women (prolonged/obstructed labor) subgroup who were exposed to unregulated oxytocin: RR: 4.1, 95% CI (1.7-9.9), Risks of cervical tear among the women (prolonged/obstructed labor) subgroup who were exposed to unregulated oxytocin RR: 1.5, 95% CI (0.7-3.0)
Trivedi, RR. 1968	India	Descriptive study	23.16% of ruptured uterus cases dur to uterotonic exposure during labor
Veena, P. 2012	India	Descriptive study	Uterine rupture due to uterotonic exposure during labor- 33.3%
Wickramasinghe, D. 2016	Sri Lanka	Cohort study	Mothers who had induction and/or augmentation with oxytocin were 30 times more likely (OR (–) 0.03, 95%CI 0.003–0.38) to have EAS defects. Mothers who underwent induction of labour were 10 times less likely to have EAS defects (OR 10.0, 95 % CI 1.3–74.1).

Table 8: Effects of injudicious use of uterotonics during labor on adverse fetal outcomes

Author, Year	Country	Type of study	Newborn outcome
Acharya, T. 2017	Nepal	Observational study	Foetal distress was found to be the most common reason for caesarean in 64.3% of mothers who received only oxytocin for labor induction and in 20% of mothers who received oxytocin for labor induction only after failure with misoprostol. Suction/oxygen resuscitation: Misoprostol only 18 (20.9), Oxytocin only 9 (25.7), other 1 (11.1) Neonatal resuscitation unit admission: Baby unit admission: Misoprostol only 18 (20.9), Oxytocin only 8 (22.9), Other 1 (11.1), Meconium stained liquor (MSL): 64 (49.2%) patients; MSL: Misoprostol only 42 (48.8), Oxytocin only 16 (45.7), other 6 (66.7).
Brahmawar Mohan, S. 2020	India	Case-control study	Associations Between Administration of Oxytocic and Early Versus Late Death (considering only the babies who did not have any conditions other than the administration of oxytocics during labor [adjusting for skilled birth attendant and place of delivery]: aOR: 1.7 (95% CI =1.4, 2.1). Associations Between Administration of Oxytocic and Early Versus Late Death in Strata Defined by Place of Delivery [adjusted for skilled birth attendant] : Government health Facility: aOR(95% CI): 0.96 (0.59, 1.6); Private health facility: aOR(95% CI): 1.8 (1.2, 2.5); Home birth: aOR(95% CI):1.9 (1.5, 2.4)
Day, LT. 2016	Bangladesh	Cross-sectional Study	[Adjusting for prolonged labor, pre-eclampsia, eclampsia, hospital administration of uterotonics, and Cesarian section] The associations of all

			perinatal mortality outcomes with outside CEmONC uterotonic use: Fresh Stillbirth: OR- 4.0, 95% CI: (3.0,5.3), Early NND: OR- 2.9, 95% CI:(2.1,4.0), Intrapartum causes (Birth Asphyxia): OR- 3.1, 95% CI:(2.2,4.5), All Perinatal Death: OR:3.0, 95%CI: (2.4,3.7)
Ellis, M. 2000	Nepal	Unmatched Case-control study	Induction [n(%)]: encephalopathic infants 12 (9), controls 29 (4.7), odds ratio 2.75, adjusted OR 9.09 (3.32 to 24.83) Augmentation [n(%)]: 50 (39), controls 139 (22.4), odds ratio 2.39, Adjusted OR (95% CI) 3.51 (2.04 to 6.07)
Krishnan, M. 2016	India	Case-control study	Association of induction of labor with oxytocin with birth asphyxia- RR: 3.35, 95%CI: (1.41-1.82)
Litorp, H. 2021	Nepal	Cohort Study	Multivariate regression analyses accounting for socio-economic and obstetric characteristics: Augmentation of labor had a higher risk of neonatal death before discharge (aRR 1.93, 95% CI 1.46-2.56), higher risk of bag-and-mask ventilation of the newborn (aRR 2.10, 95% CI 1.80-2.50), a higher risk of Apgar score <7 at 5 minutes (aRR 1.65, 95% CI 1.49-1.86)
Manandhar, SR. 2010	Nepal	Prospective study (mixed-method)	Oxytocin injection exposure: 50% of all cases (stillbirth and neonatal deaths) Among perinatal deaths, birth asphyxia was the commonest cause (44%).
Moran, AC. 2010	Bangladesh	Cross-sectional study	Among the women with live births who reported oxytocin use, 4.6% reported that their baby had trouble breathing after birth, compared with only 3.0% of babies whose mothers did not report using oxytocin to augment labor.
Mullany, LC. 2013	Nepal	Secondary analysis of a cluster randomized trial	NRD: RR 2.35; 95% CI, 2.18–2.53 (Multivariate analysis)[Restricted to home birth and without any complications] Intrapartum-related NRD: RR:

			2.52; 95% CI, 2.29–2.78) (Multivariate analysis) [Restricted to home birth and without any complications] Risks of neonatal death associated with intrapartum-related NRD (RR 3.78; 95% CI, 2.53–5.66) were also elevated (excluding facility birth and any maternal complication). Intra-partum related moderate to severe NE (RR 3.48; 95% CI, 2.46–4.93); The risks of neonatal death associated with NE (RR 4.47; 95% CI, 2.78–7.19) (excluding facility birth and any maternal complication). Moderate–severe neonatal encephalopathy: RR 1.34; 95% CI, 1.02–1.76 (multivariate analysis) (excluding facility birth and any maternal complication).
Neogi S. 2018	India	Case-Control Study (Mixed-method)	More than 35% mothers of stillborn children reported of receiving uterotonic before coming to the hospitals.
Rijal, P. 2014	Nepal	Observational study.	Fetal distress 80 (46.0%) cases, indication for CS delivery Meconium stained liquor; 15.5% cases indication for CS delivery
Sarvanan, N. 2017	India	Observational study	Foetal distress was the most common reason for LSCS and instrumental delivery and its contribution was 41 (73.2%) and 93(66.4%) in instrumental delivery and LSCS respectively. Incidence of fetal distress: 99 (16 %). Primigravida: Fetal distress: 66 out of 400, multigravida: 34 out of 202. APGAR 1(<7): 34(5.7%), APGAR 5(<7): 10(1.6%). NICU Admission: 3(0.9%) Meconium stained liquor: 79 (13.1%).
Shah, S. 2016	Pakistan	Cohort Study	Statistically significant associations with unregulated oxytocin

			exposures were seen in the group of women with severe birth asphyxia (RR 3.9, 95% CI 2.5–6.1).
Shireen, N. 2010	Bangladesh	Observational study	Exposure to oxytocin during labor: cases- 16%, controls-0%

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CHAPTER 3. QUANTITATIVE ANALYSIS USING NEPAL DHS 2016 & NEPAL SPA 2015 SURVEYS

3.1 INTRODUCTION

Administering oxytocin to speed up the labor after the onset of spontaneous labor and before the delivery of the baby is not a relatively recent issue; it is one of the traditional methods that has been commonly used across the low-, middle- and high-income settings since 1960 (Hidalgo-Lopezosa, P. 2016). The objective of such practice of oxytocin administration is to improve the labor progress for mothers experiencing prolonged labor (Nystedt, A. 2014). However, using oxytocin to treat prolonged labor or dystocia might help reduce the length of labor but has not been proven to increase the normal birth rate among mothers with prolonged labor (Nystedt, A. 2014; Bugg, GJ. 2013). Besides, such practice may contribute to multiple adverse effects, including uterine hyperstimulation and abnormal changes in fetal heart rate, which eventually precipitate the need to conduct emergency cesarean sections (Nystedt, A. 2014; Bugg, GJ. 2013). Given the alarming consequences caused by misuse and overuse of oxytocin for augmenting labor, oxytocin is listed as 'Hight Alert Medicine' by the Institute of Safe Medication Practice (Simpson, KR. 2009). In addition, World Health Organization (WHO) published a guideline on ensuring safety during labor augmentation in 2014, specifying conditions that need to be met for the safe use of oxytocin for labor augmentation (WHO 2014). If conditions for safe use are not met, this can result in babies having difficulty breathing just after birth or even struggling from lack of oxygen while the mother is in labor. Hence, labor augmentation should not be practiced in facilities without surgical capacity; this is one of the prime conditions for safe use. Meeting such conditions is generally not a problem for developed countries with advanced facilities, yet this is a substantial problem in low-income countries with a limited human workforce and health infrastructure. In resource-limited countries in South Asia, administering oxytocin to augment labor is reported to be a common practice in both home deliveries and institutional deliveries, often in a context where frequent monitoring of mothers and fetus and providing

comprehensive emergency obstetric care are unlikely (Brhlikova, P. 2009).

Nepal, a country in South Asia, has reported significant progress in reducing maternal and neonatal mortality rates in recent years, with a 22% increase in institutional deliveries from 2011 to 2016; however, the home delivery rate was still at 40.7% reported in the Nepal Demographic Health Survey (DHS) 2016 among the mothers who delivered within the three years prior to the survey, even most of the mothers who delivered at home were attended by family members (Ministry of Health - MOH/Nepal 2017). In addition, according to the Nepal Service Provision Assessment (SPA) 2015 survey, only 50% of all district-level hospitals reported offering cesarean delivery services (Ministry of Health (MOH)/Nepal 2017). A study by Mullany et al. (2013) documented that in the rural Sarlahi district of Nepal, 32% of women giving birth at home reported receiving injections during labor, mostly from unqualified village doctors; in most instances, the drug injected was oxytocin. Under such circumstances, where conditions for safe use are not met, there is a risk of poor perinatal outcomes, including birth asphyxia, stillbirth, and maternal distress, as reported in several studies conducted in Nepal. For example, a study analyzing cases of uterine rupture in a tertiary center in Eastern Nepal demonstrated that maximum ruptures in the scarred category among the study population were attributed to oxytocic (Chuni, N. 2006). In terms of fetal outcome, a study conducted in another tertiary level hospital (Patan Hospital) in Nepal revealed that the risk of moderate or thick meconium-stained liquor indicating fetal distress was two times higher in cases with labor augmentation compared to non-augmented (Rana, TG. 2003). The Nepal DHS 2016 data demonstrated that 50% of all attended births across all health care settings received medication by injection or through an IV (MOH/Nepal 2017). Facts and statistics around this labor augmentation practice in Nepal reflect that the situation is as alarming as acting upon sooner. Therefore, to improve the quality of care for mothers and babies around birth and to reduce perinatal mortality, it is important to better characterize labor augmentation practices across diverse settings in Nepal. This chapter

aims to investigate the practice of using oxytocin during labor in Nepal, as reported in the Nepal DHS 2016 and Nepal SPA 2015 survey. More specifically, based on the data available in the Nepal DHS 2016 and Nepal SPA 2015 survey, the study will assess to what extent the WHO conditions for labor augmentation is met among the hospitals based births in Nepal in regard to practicing labor augmentation using oxytocin only in the context with the capacity to manage its potential adverse outcomes, including the capacity to conduct cesarean deliveries.

3.2 METHOD

The study will utilize data from two Nationally Representative survey sources, including Nepal Demographic Health Survey (DHS) 2016 and Nepal Service Provision Assessment (SPA) survey-2015. Both DHS and SPA surveys are cross-sectional assessments from the methodological perspective. The DHS provides information on socio-demographic characteristics, health status, and healthcare-seeking behavior among the women and men aged 15-49 years residing in randomly selected households across Nepal. The Nepal SPA Survey assesses the healthcare facilities in the formal sector in Nepal in terms of availability of basic supplies & equipment, and facility readiness to provide quality care to its population.

Survey Methodology of the Nepal DHS 2016 Survey

Districts in Nepal are distributed across seven provinces- Province 1 (this province does not have any specific name), Province No. 2 (Madhesh), Province 3 (Bagmati), Province 4 (Gandaki), Province 5 (Lumbini), Province 6 (Karnali), Province 7 (Sudurpashchim). In the DHS survey, each province is also sub-divided into urban and rural areas that make a total of 14 sampling strata. The 2016 Nepal DHS sampling strategy follows stratified sampling- two stages for rural areas, and three stages for urban areas.

Nepal consists of 75 districts. The districts are divided into urban and rural locations, and those locations are divided into wards. In 2016 Nepal DHS, the wards serve as the primary sampling units (PSUs) for rural areas, and then households for survey were selected from the sample PSUs. In rural areas, the wards are small in size and consist of an average of 104 households. In urban areas, the wards are large; consist of an average of 800 households per ward. Thereby, each ward has a frame of enumeration areas (EAs). Similar to rural areas, wards were selected as PSUs for urban areas in 2016 Nepal DHS.

In the first stage of sampling, a total of 383 wards or clusters were selected from both rural and urban locations with probability proportional to ward size and with independent selection in each sampling stratum. Since urban wards are larger in size, in a second stage of sample selection, one EA was randomly selected from each of the sample urban wards. A household listing was developed for all of the selected sampling clusters (rural wards or urban EAs). The household list served as the sampling frame for the selection of households for the survey. Finally, a fixed number of 30 households per cluster were selected from the household list for the survey. All women age 15-49 who were either permanent residents of the selected households or visitors who stayed in the households the night before the survey were eligible to participate in the interview. Since the objectives of this analysis were developed around the maternal and newborn healthcare practice, particularly related to the issue of uterotonics use during labor, this study will only utilize the birth's questionnaire dataset and the analysis in this study is restricted within the births that happened within the last three years prior to the survey.

Survey methodology of the Nepal SPA 2015 survey

For sampling of SPA survey, a master list of 4,719 formal sector health facilities was obtained from the Nepal Ministry of Health (MoH). From that list, a total of 992 facilities were selected for the survey. The sample included: all nonspecialized government hospitals, all private

hospitals with 100 or more inpatient beds, all Primary Health Care Centers (PHCCs) and a sampled number of private hospitals with at least 15 beds but fewer than 100 beds, health posts, Urban Health Centers (UHCs) and stand-alone HIV Testing and Counselling Sites (HTCs). This study will utilize data collected using the Post-partum client Exit interview Questionnaire dataset and the Inventory Questionnaire dataset. In regard to inventory questionnaire dataset, only data collected from 103 secondary and tertiary level govt. hospitals and 166 private hospitals will be utilized in this analysis. The Post-partum client survey did not involve any observations of delivery services. The post-partum client interviews took place only in facilities that offered delivery services.

Data analysis

Descriptive analysis:

Nepal DHS 2016 survey:

This analysis utilized the birth dataset (questions were asked using the woman's questionnaire) of Nepal DHS 2016, restricted to three years prior to the survey. Hence, a total of 6,148 births (2,761 mothers) out of 26,028 births (9,229 mothers) were considered in the analysis. During the survey, mothers were asked two questions that are specific to labor augmentation or using uterotonics during labor- "While you were in labor (i.e., before the baby was born), were you given an injection or was medicine given through an IV drip?". The mothers who reported 'yes' to the question were asked a further question- "What were you told the medicine was for?" In view of responses reported for all births during the three years prior to the survey, this study determined the proportion of Inj./IV medicine administered during labor, disaggregated by delivery places in terms of health facility, types of area of residence (urban/rural), and women's location in terms of provinces.

Nepal SPA 2015 survey:

We utilized inventory dataset and Postpartum client exit interview dataset from the Nepal SPA Survey 2015 to retrieve and analyze information related to administration of oxytocin during

labor in facilities. The inventory questionnaire collected information from a total number of 992 health facilities that include primary level facilities, secondary level government hospitals, tertiary level hospitals and private hospitals. However, the Post-partum client exit interviews were not conducted in every facility included in the inventory dataset, these interviews were conducted in a total of 110 health facilities that offered delivery services. On the day of interview, a maximum number of five post-partum women were interviewed from each selected facility as they were discharged. The total number of women participated in the post-partum client exit interview is 310.

The inventory dataset has data on variables related to facility types and availability of services, and the post-partum client exit interview datasets includes information on administration of oxytocin during labor and presence of labor companion during labor. Hence to determine the proportion of births administered oxytocin during labor disaggregated by types of health facilities, we merged the two datasets using the facility identification number. After merging the two datasets in SPA, besides assessing the proportion of using oxytocin during labor across different types of facilities, we determined the proportion of births received oxytocin to speed up labor and attended by a labor companion disaggregated by different types of facilities. In addition, the hospitals, where the mothers reported receiving oxytocin during labor in the post-partum client exit interviews (Secondary and tertiary hospitals, private hospitals), were categorized into three categories with respect to conducting cesarean deliveries based on information available in the inventory dataset- 1) 'Apparently ready' – to manage complications due to labor augmentation hospitals, 2) 'possibly ready'- to manage complications due to labor augmentation hospitals and 3) 'definitely not ready' – to manage complications due to labor augmentation hospitals. To develop the cesarean capacity related categorization, a total of four variables were used as reported in the SPA inventory dataset: 1) "Does the facility have a health worker who can perform Cesarean delivery (section) present at the facility or on call 24 hours a day (including weekends and on public holidays)?", 2) "Does this facility have an

anesthetist/anesthetist assistant present in the facility or on call 24 hours a day (including weekends and on NO public holidays?)", 3) "Have Cesarean deliveries been performed in this facility during the past 3 months?", 4) "Has blood transfusion been done in this facility in an obstetric context (i.e., for maternal care) during the past 3 months"? A hospital that responded 'yes' to all fours variables was considered 'Apparently ready' – to manage complications due to labor augmentation hospital, a hospital that reported to conduct at least one cesarean section during the prior three months of the survey, but not all other three criteria were met was considered 'possibly ready' to manage complications due to labor augmentation hospital, and a hospital that reported not to conduct any cesarean section during the prior three months of the survey or reported cesarean sections usually not done in the hospital, was considered 'definitely not ready' – to manage complications due to labor augmentation hospital. We estimated the proportion of labor augmentation (administration of oxytocin during labor) in hospitals (secondary or tertiary govt., hospitals and private hospitals) by the categories related to cesarean capacity as well. The categories with respect to cesarean section capacities in hospital were developed considering the WHO recommended condition for ensuring safety during labor augmentation- "Augmentation of labor should be carried out in facilities where there is capacity to manage its potential outcomes, including adverse effects and failure to achieve vaginal birth". Cesarean section services are usually offered in secondary and tertiary level government hospitals; primary level healthcare facilities by definition do not have the capacity to conduct any cesarean delivery; thereby no primary level facilities were included in this categorized analysis and the linked analysis further described in this chapter.

Nepal DHS 2016 and Nepal SPA 2015 survey linkage and merging of data:

The key assumption of this linked analysis is- a woman who reported giving birth in a secondary or tertiary level government hospital in a given cluster in Nepal DHS, would ideally go to the closest secondary or tertiary level government hospital for that given cluster; a woman who

reported giving birth in a private hospital in a given cluster in Nepal DHS, would ideally go to the closest private hospital for that given cluster. Hence, by geographically linking Nepal DHS 2016 spatial dataset with Nepal SPA 2105 spatial dataset, each DHS cluster's nearest secondary or tertiary level government hospital and private hospital was identified (Figure 2).

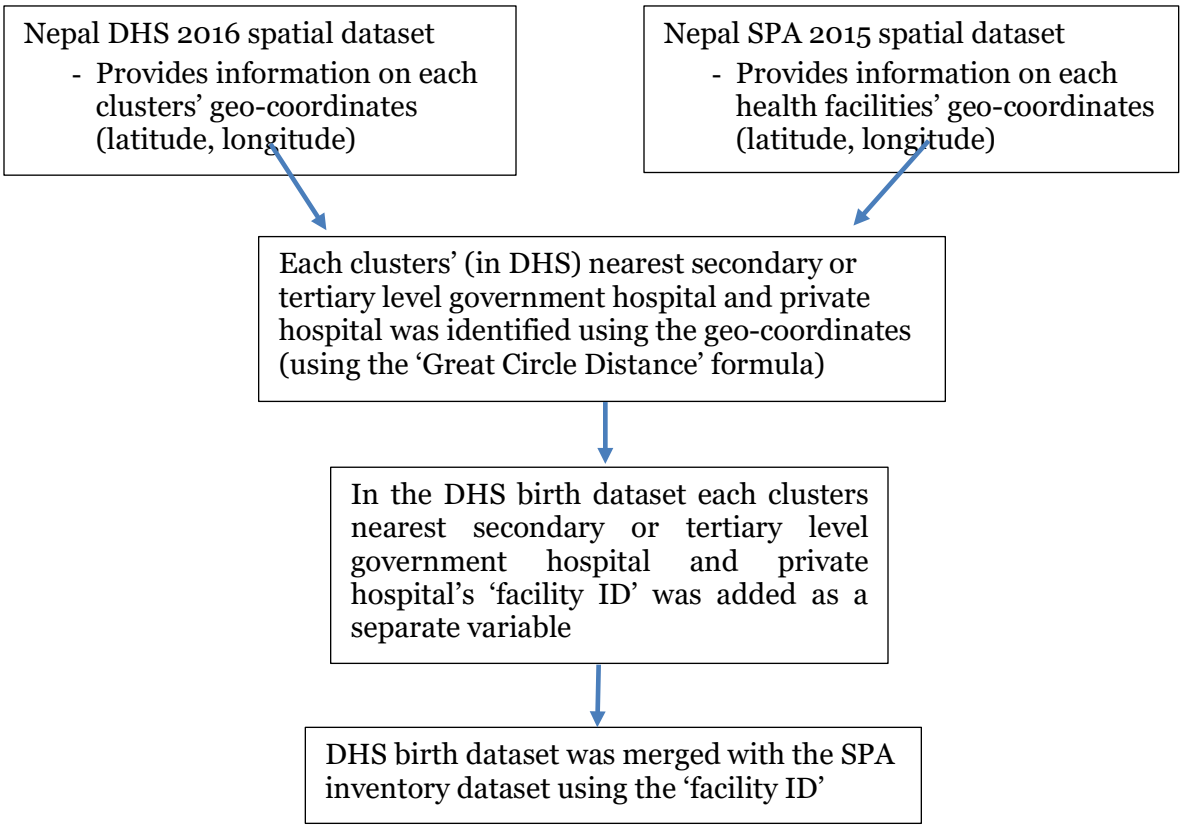

Figure 2: DHS and SPA survey datasets linking strategy

The geographical linkage between clusters in the Nepal DHS 2016 survey and facilities in the Nepal SPA 2015 survey was done using the 'Great Circle Distance' formula. The Appendix A describes the approach of calculating the Great circle distance step by step with STATA codes. The 'Great Circle Distance' is defined as "the shortest distance between two points on the surface of a sphere" ("Great-Circle Distance," 2021), In this analysis, we utilized the central angle formula [Figure 3] to calculate the Great Circle Distance between two points. "The central

angle or central subtended angle (alpha) is the subtended angle at the center of the earth by two lines connecting two points with the center of the earth" ("Great-Circle Distance," 2021). Here, we assumed that one point would be geo-coordinates of a given cluster in the DHS and another point would be the geo-coordinates of a given facility (secondary or tertiary government facility) in the SPA.

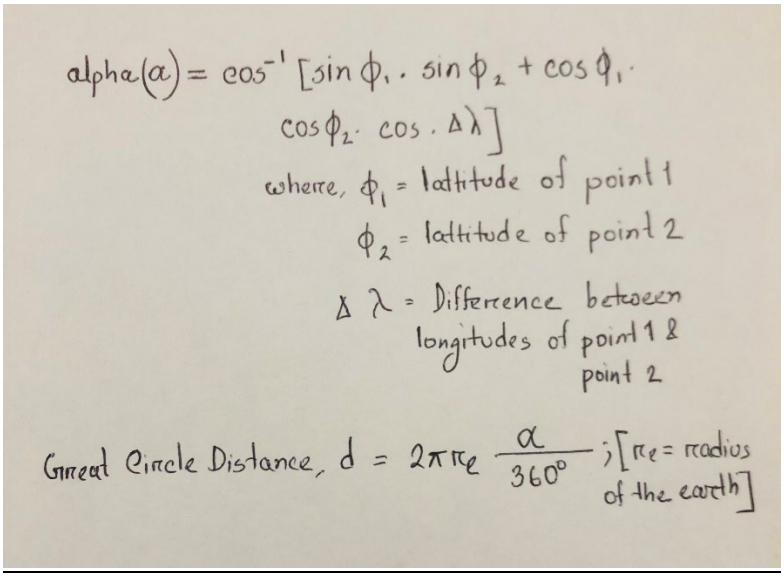

Figure 3: Great Circle distance formula used in our study

Using the Great Circle Distance formula, the distance from each cluster to all secondary and tertiary facilities was estimated. Then the hospital that is located within the minimum distance for a given cluster was identified as the nearest hospital to that given cluster. All calculation regarding this Great Circle Distance calculation was conducted using STATA version 17.0. The STATA codes used for this calculation can be found in the Appendix A.

In the Nepal DHS birth dataset, we created a separate variable defining each DHS clusters' closest secondary or tertiary level government hospital's 'facility ID'. Then we merged the DHS

birth dataset with the SPA inventory dataset using the 'facility ID' for further analysis in regard to 'secondary or tertiary level government hospital' births reported in the DHS clusters. Similar merging was done for conducting further analysis for the private hospital births reported in the DHS clusters.

DHS birth dataset gives information whether a mother in a given cluster reported to receive Inj./IV medicine during labor for hospital births or not; the inventory dataset provides information about whether the hospital where the mother from a given cluster in the DHS reported to receive labor augmentation, was 'Apparently ready' or 'possibly ready' or 'definitely not ready' to manage complications due to labor augmentation in regards to cesarean capacity. Therefore, by utilizing the merged DHS birth dataset and SPA inventory datasets, we conducted bivariate analyses and determined- 1) the proportion augmented among the women giving birth in hospitals in clusters (from DHS data) for which the nearest hospital is categorized as 'Apparently ready' (based on SPA data), 2) the proportion augmented among the women giving birth in hospitals in clusters (from DHS data) for which the nearest hospital is categorized as 'possibly ready' (based on SPA data), 3) the proportion augmented among the women giving birth in hospitals in clusters (from DHS data) for which the nearest hospital is categorized as 'definitely not ready' (based on SPA data). For the bivariate analyses reported in the result section, significance of difference was reported using a chi square (X^2) test (in the cases where relationship was found significant) and a P-value of <0.05 was considered statistically significant.

A multinomial logistic regression model was developed to assess if the women's socio-economic factors in a given cluster reported in the NDHS 2016 survey have any influence on the women's reported Inj./IV medicine receipt status during labor in the nearest government hospitals (secondary or tertiary govt. hospitals) (retrieved from the Nepal SPA 2015 survey) [in the

'possibly ready' for labor augmentation hospitals compared to 'apparently ready' for labor augmentation hospitals and 'definitely not ready' for labor augmentation hospitals compared to 'apparently ready' for labor augmentation hospitals]. Similar model was developed for the births took place and received labor augmentation during labor in private hospitals (reported in the DHS clusters). The model was adjusted for women's parity and age group. The socio-economic factors include- women's level of education and women's wealth index. Hence, the outcome measure in this analysis is labor augmentation (Inj./IV medicine received during labor) in the nearest hospitals categorized into three categories- labor augmentation in 'apparently ready' hospitals, labor augmentation in 'possibly ready' hospitals, and labor augmentation in 'definitely not ready' hospitals. The independent variables in this analysis are- women's education, is a categorical variable with four categories (no education, primary level education, secondary level education and higher education); women's wealth index, is a categorical variable with five categories (Poorest, Poorer, Middle, Richer, Richest); and women's age group–(15-29, 30-44 years) and women's parity- primiparous, multiparous.

To build the model, we selected variables based on our bivariate analysis of the dependent variable and each of the independent variables. Our dependent variable is- women's DHS reported Inj./IV medicine receipt status during labor in the nearest government hospitals (secondary or tertiary govt. hospitals) (retrieved from the Nepal SPA 2015 survey), which was further categorized into three categories- women reported (in the DHS) receiving labor augmentation in 'Apparently ready'- for labor augmentation hospital, women reported (in the DHS) receiving labor augmentation in a 'possibly ready'- for labor augmentation hospital, and women reported (in the DHS) receiving labor augmentation in a 'definitely not ready'- for labor augmentation hospital. Considering the level of P-value <0.2, the following independent variables were included in the model- women's level of education and women's wealth index. Even though, women's types of residence (rural/urban) and women's province had a P value of

less than 0.20 in the bivariate analysis, we did not include these two variables in our model; because when we conducted a three-way crosstabulation among our dependent variable, women's types of residence and women's provinces, we found zero sample for two of the provinces for the 'possibly ready'- for labor augmentation category of the dependable variable and one of the provinces for the 'definitely not ready'- for labor augmentation category of the dependable variable. The model was adjusted for women's parity and women's age. In a bivariate analysis of our dependent variable with women's parity and women's age; women's age was found to have a p-value <0.20. We included 'women's parity' considering its clinical significant relationship with labor augmentation based on findings in existing scientific literature. The multinomial logistic regression model developed for the births took place and received labor augmentation during labor in private hospitals (reported in the DHS clusters) included similar independent variables as the model developed for the govt. hospital births.

No variables were excluded from the final model. Since, all of our independent variables had multiple categories, we did not check for the presence of effect modification. Our purpose was to assess the association of the women's socio-economic factors with our dependent variable; we did not have any one primary independent variable with which we assessed the association of the dependent variables. However, even though, we did not exclude any variable from the final model, we assessed the confounding effect of women's parity and women's age by checking the changes in the coefficient of the independent variables (women's education and women's wealth index) before and after adjusting for the possible confounders (women's parity and age group). More than 10% of changes in the effect of both independent variables , women's level of education and women's wealth index, was identified. However, we could not determine more than 10% of changes for the effect of each categories of both independent variables.

The data management and analysis in this study was conducted using STATA version 17.0. In addition, all the analysis using the DHS dataset and SPA dataset were adjusted for respective sampling weight and complex survey design in STATA.

3.3 RESULTS

DHS analysis

Descriptive analysis:

All the variables in the study were analyzed based on last three years data prior to the survey. Therefore, a weighted sample of 6,148 births (2,761 mothers) out of the total weighted sample of 26,028 births were considered in the analysis. However, out of 6,148 births, responses related to the question "While you were in labor (i.e., before the baby was born), were you given an injection or was medicine given through an IV drip?", was retrieved for 2,330 births. **The question related to Inj./IV medicine receipt status during labor was asked only for the births that were assisted by doctor, nurses/midwives, health assistants (HAs), auxiliary health workers (AHWs), maternal and child health workers (MCHWs) and village health workers (VHWs).** Of these 2,330 responses, 53.9% (95% CI: 51.0%-56.8%)(n=1147) received Inj./IV medicine during labor [Table 9]. Out of 1147 births with history of Inj. or IV medicine administration during labor, among 72.6% (95% CI: 68.9%-76.1%) of births, mothers received the drug to speed up the labor; in 20.4% (95%CI: 17.2%-24.1%) of cases, mothers were told nothing about the purpose of the drug [Table 10].

Table 9:Distribution of births reported in NDHS 2016 (among the births within the last three years prior to the survey) received Inj. or medicine during labor

Responses[1]	Total (n=2330)	% (95% CI)
No	1183	46.1 (43.2-49.0)
Yes	1147	53.9 (51.0-56.8)

CI: Confidence Interval

[1] Responses – Injections received during labor: (Yes/No)?

Table 10:Reasons for Injection or medicine through an IV drip administration during labor

Reported reasons for receiving injection/IV medicine during labor	Total (n=1147)	% (95% CI) among who received Inj. or IV during labor
Speed up labor	780	72.6 (68.9-76.1)
Prevent infection	15	1.1 (0.7-1.9)
Told nothing	279	20.4 (17.2-24.1)
Other	10	0.5 (0.3-1.1)
Don't know	63	5.3 (3.9-7.0)

CI: Confidence Interval

After disaggregating the number of births received Inj. /IV during labor by place of delivery, it was found that the proportion for Inj./IV medication administration during labor was highest for homebirths 66.9% (95%CI: 56.7% - 75.7%) - (among the mothers who delivered in home, attended by a health personnel and responded to the question) [Table 11]. For hospital births, the Inj./IV medication (during labor) was reported to be highest in Private hospitals 64.3% (95% CI: 59.1% - 69.1%) (among the mothers who delivered in private facilities, attended by a health personnel and responded to the question), followed by Govt. hospitals 52.9% (95% CI: 49.1%-56.8%) (among the mothers who delivered in govt. secondary or tertiary level hospitals, attended by a health personnel and responded to the question) [Table 11]. The proportion of Injection/IV medicine administration during labor varied significantly across the five types of place of delivery ($p<0.001$).

Table 11: Distribution of DHS reported births received Inj./IV medicine during labor by facility type

Place of delivery	Total Births[1] (n=2330)	Inj./IV drug received during labor[2]	
		(n=1147)	% (95% CI)
Home	159	99	66.9 (56.7 - 75.7)
Govt. Facility [secondary and tertiary hospitals]	1106	549	53.0 (49.1 – 56.8)
Primary level govt. facilities (PHCCs, HPs)	588	201	40.4 (34.3 – 46.8)
Private facilities	476	298	64.3 (59.1 – 69.1)

CI: Confidence Interval
[1] Total birth - Responded to the Inj./IV medicine question
[2] Inj./IV drug received during labor - Reported in the NDHS 2016 survey for births in last three years
$\chi^2 = 72.32$, df=4, $p<0.001$

[Table 12] and [Table 13] present the distribution of births received Inj./IV medicine during labor within the last three years prior to the survey reported by mothers delivered in govt. facilities (secondary & tertiary hospitals) and private hospitals across seven provinces in Nepal, respectively. For reported births in secondary and tertiary hospitals, all the provinces had >40% reporting Inj./IV drip medication (during labor) except for province 6 and province 7 [Table 12]. The proportion of Injection/IV medicine administration during labor for secondary or tertiary govt. hospital births in the last three years prior to the survey varied significantly across seven provinces of Nepal ($p<0.001$). For reported births in private hospitals, all the provinces had >40% reporting Inj./IV drip medication during labor, with the highest proportion of 74.3% (95% CI: 64.7% – 81.9%) in province 2 [Table 13]; this distribution was also found significant ($p=0.02$).

Table 12:Distribution of Inj./IV medication drip administration (during labor) among secondary and tertiary hospital births (Govt. hospitals) by provinces

Province	Total Births[1] (n=1106)	Inj./IV drug received during labor in Govt. Hospitals[2]	
		(n=549)	% (95% CI)
Province no. 1	150	71	43.7 (34.8 - 53.1)
Madhesh	201	140	70.9 (62.4 – 78.1)
Bagmati	150	83	53.9 (45.4 – 62.4)
Gandaki	158	70	43.8 (34.2 - 53.9)
Lumbini	188	98	53.6 (44.9 - 62.1)
Karnali	135	48	34.7 (26.1 - 44.1)
Sudurpashchim	124	39	31.5 (22.7 – 41.9)

CI: Confidence Interval
[1] Total birth in secondary or tertiary hospitals (responded to the Inj./IV medicine question)
[2] Inj./IV drug received during labor in Govt. hospitals for births in last three years
$\chi^2 = 60.72$, df=6, P value<0.001

Table 13:Distribution of Inj./IV medication drip administration (during labor) among private hospital births by provinces

Province	Total Births[1] (n=476)	Inj./IV drug received during labor in Private Hospitals[2]	
		(n=298)	% (95% CI)
Province no. 1	119	67	56.6 (45.8 – 66.9)
Madhesh	146	109	74.3 (64.7 – 81.9)
Bagmati	40	21	63.1 (46.9 – 76.8)
Gandaki	39	19	45.8 (29.9 – 62.5)
Lumbini	81	53	65.4 (55.1 – 74.5)
Karnali	21	12	54.6 (33.4 – 74.2)
Sudurpashchim	30	17	57.2 (36.5 – 75.6)

CI: Confidence Interval
[1] Total birth in Private hospitals (responded to the Inj./IV medicine question)
[2] Inj./IV drug received during labor in Private hospitals for births in last three years
$\chi^2 = 15.11$, df=6, p- 0.03

[Table 14] and [Table 15] presents information on the distribution of Inj./IV medicine administration during labor by type of residence (urban or rural) among births in secondary & tertiary hospitals (Govt. hospitals), and Private hospitals, respectively. Even though, the proportion of Inj./IV medicine administration during labor was high in both urban and rural areas for births in govt. hospitals and private hospitals, no significant association was found between Inj,/IV medicine administration (during labor) and place of residence (p>0.05) .

Table 14:Distribution of Inj./IV medication drip administration (during labor) among secondary & tertiary (govt.) hospital births by types of place of residence

Place of Residency	Total Births[1] (n=1106)	Inj./IV drug received during labor[2]	
		(n=549)	% (95% CI)
Urban	797	398	52.6 (48.1 – 57.0)
Rural	309	151	53.9 (46.2 – 61.3)

CI: Confidence Interval
[1] Total birth in secondary and tertiary level govt. hospitals responded to the Inj./IV medicine question
[2] Inj./IV drug received during labor - Reported in the NDHS 2016 survey for births in last three years
χ^2 = 0.1630, df=1, p- 0.77

Table 15: Distribution of Inj./IV medication drip administration (during labor) among Private hospital births by types of place of residence

Place of Residency	Total Births[1] (n=476)	Inj./IV drug received during labor[2]	
		(n=298)	% (95% CI)
Urban	285	182	65.9 (58.7 – 72.4)
Rural	191	116	62.3 (54.4 – 69.6)

CI: Confidence Interval
[1] Total birth in private hospitals responded to the Inj./IV medicine question
[2] Inj./IV drug received during labor - Reported in the NDHS 2016 survey for births in last three years
χ^2 = 0.6540, df=1, p- 0.50

SPA analysis

Descriptive analysis:

A total of 310 mothers were interviewed when they were discharged from a health facility regarding the care they received for delivery and postpartum care; however, one mother did not report any information related administration of oxytocin during labor (labor augmentation). Among the mothers who provided information related to labor augmentation and delivered in Govt. Hospitals hospital (central level govt. hospitals, district level govt. hospitals, regional and sub regional level govt. hospitals and zonal level govt. hospitals), 24.5% (95% CI: 18.8%, 31.3%) received oxytocin to speed up labor [Table 16]. Among the mothers who provided information related to labor augmentation and delivered in a private hospitals, 24.3% (95% CI: 13.8%, 39.1%) received oxytocin to speed up labor [Table 16]. no significant association was found between oxytocin used during labor and type of facility for the reported births in the postpartum client exit interview SPA survey ($p>0.05$) .

Table 16:Distribution of births reported to receive oxytocin to speed up labor by types of facilities reported in the Nepal SPA 2015 survey Post-partum client exit interview

Facility type	Total Births[1] (n=309)	Oxytocin used during labor[2]	
		(n=71)	% (95% CI)
Govt. hospitals (secondary and tertiary level)	204	48	24.5 (18.8 – 31.3)
Private hospitals	94	20	24.3 (13.8 – 39.1)
PHCCs	10	3	31.8 (10.5 – 65.1)

CI: Confidence Interval

[1] Total birth – Total mothers interviewed and responded to the Inj./IV medicine question in the postpartum client exit interview survey

[2] Oxytocin used during labor - Reported in the Nepal SPA 2015 postpartum client exit interview survey

$\chi^2 = 0.1540$, df=2, p- 0.90

Among the mothers who received oxytocin during labor, a labor companion was not present in

73.8% (95%CI: 58.6%, 84.8%) and 86.9% (95%CI: 65.3%, 95.9%) of cases in govt. hospitals (secondary & tertiary hospitals) and private hospitals, respectively [Table 17].

Table 17:Distribution of births received oxytocin during labor and attended by a labor companion during labor by types of facilities (among mothers who received labor augmentation) reported in the Nepal SPA 2015 survey Post-partum client exit interview

Facility type	Total Births[1] (n=71)	Yes, a labor companion present during labor		No, a labor companion was not present during labor	
		(n=18)	% (95% CI)	(n=53)	% (95% CI)
Govt. hospitals (secondary and tertiary level)	48	12	26.2 (15.2 – 41.4)	36	73.8 (58.6 – 84.8)
Private hospitals	20	4	13.1 (4.1 – 34.7)	16	86.9 (65.3 – 95.9)
PHCCs	3	2	57.1 (6.7 – 96.1)	1	42.8 (3.9 – 93.3)

CI: Confidence Interval

[1] Total birth – Total mothers reported to receive oxytocin during labor in the SPA survey (in the postpartum client exit interview survey)

The secondary & tertiary hospitals (Govt. hospitals) and private hospitals where post-partum women were interviewed, were categorized into three categories in regard to cesarean capacity 1) 'Apparently ready'-for labor augmentation (a surgeon who can perform cesarean sections and a anesthetist were available, and that the hospital had done at least one cesarean delivery and at least one blood transfusion in an obstetric context over the preceding 3 months), 2) 'Possibly ready'-for labor augmentation (at least one cesarean section was conducted over the preceding 3 months, but all four conditions were not met to be considered 'apparently ready' for labor augmentation) and 3) 'definitely not ready'-for labor augmentation (no cesarean section was done in the preceding three months or cesarean section services are usually not provided in the hospital). Among the post-partum mothers who delivered in 'Apparently ready' govt. hospitals, 21.7% (95% CI: 15.2%- 29.9%) of mothers received oxytocin during labor; for private hospitals,

this proportion is 24.4% (95% CI: 13.7% - 39.6%) [Table 18].

Table 18:Distribution of births (reported in the Nepal SPA 2015 survey Post-partum client exit interview) received oxytocin during labor in hospitals 'Apparently ready'- for labor augmentation

Facility type[1]	Total Births[2] (n=228)	Oxytocin used during labor	
		(n=49)	% (95% CI)
Secondary & tertiary govt. hospitals	138	30	21.7 (15.2 – 29.9)
Private hospitals	90	19	24.4 (13.7 – 39.6)

CI: Confidence Interval
[1] Facility type- Hospitals that were categorized as 'Apparently ready- for labor augmentation'
[2] Total births – Total mothers reported to receive oxytocin during labor in a 'Apparently ready- for labor augmentation' hospital in the SPA survey (in the postpartum client exit interview survey)

Among the post-partum mothers who delivered in 'possibly ready' govt. hospitals, 31.9% (95% CI: 16.9% - 51.7%) of mothers received oxytocin during labor [Table 19]. Only three women were interviewed from private hospitals that are considered 'possibly ready' hospitals and none of them reported to receive oxytocin during labor [Table 11].

Table 19:Distribution of births (reported in the Nepal SPA 2015 survey Post-partum client exit interview) received oxytocin during labor in hospitals 'Possibly ready'- for labor augmentation

Facility type[1]	Total Births[2] (n=34)	Oxytocin used during labor	
		(n=10)	% (95% CI)
Secondary & tertiary govt. hospitals	31	10	31.9 (16.9 – 51.7)
Private hospitals	3	0	

CI: Confidence Interval
[1] Facility type- Hospitals that were categorized as 'possibly ready- for labor augmentation'
[2] Total births – Total mothers reported to receive oxytocin during labor in a 'Possibly ready- for labor augmentation' hospital in the SPA survey (in the postpartum client exit interview survey)

A total of 35 mothers were interviewed from govt. hospitals (secondary and tertiary level) that

were considered 'definitely not ready-for labor augmentation', 28.9% (95% CI: 15.1% - 48.3%) of them reported to receive oxytocin during labor [Table 20].

Table 20:Distribution of births (reported in the Nepal SPA 2015 survey Post-partum client exit interview) received oxytocin during labor in hospitals 'Definitely not ready'- for labor augmentation

Facility type[1]	Total Births[2] (n=36)	Oxytocin used during labor	
		(n=9)	% (95% CI)
Secondary & tertiary govt. hospitals	35	8	28.9 (15.1 – 48.3)
Private hospitals	1	1	

CI: Confidence Interval
[1] Facility type- Hospitals that were categorized as 'definitely not ready- for labor augmentation'
[2] Total births – Total mothers reported to receive oxytocin during labor in a 'Definitely not ready- for labor augmentation' hospital in the SPA survey (in the postpartum client exit interview survey)

Nepal DHS 2016 birth dataset and Nepal SPA 2015 inventory dataset linked and merged analysis

Using the geographical coordinates (latitude and longitude) provided in the DHS and SPA spatial datasets, each DHS cluster's nearest government hospital (secondary or tertiary) and private hospital where SPA 2015 survey was conducted, were identified. After geographical linkage between DHS's clusters and SPA's hospitals (secondary or tertiary and private), Nepal DHS 2016 birth questionnaire dataset was merged with the Nepal SPA 2015 inventory dataset using facility ID.

For reported births in secondary or tertiary level (govt.) hospitals:

[Table 21] reports findings on distribution of reported govt. hospital births in clusters in DHS received Inj./IV medicine during labor in the closest hospitals identified from SPA categorized by safety for labor augmentation (in regard to cesarean section capacity). Out of 1121 reported secondary and tertiary level govt. hospital births (within the last three years) in DHS, data

related to Inj./IV medicine received during labor (labor augmentation) and readiness for labor augmentation in the closest secondary or tertiary govt. hospitals were available for 1106 births. For a total of 565 govt. hospital births reported in DHS clusters, for which the closest govt. hospitals can be considered 'Apparently ready'-for labor augmentation (all 4 of the following criteria met: surgeon and anesthetist available, blood available, and cesarean deliveries done over the preceding 3 months, according to SPA data); 50.4% (95% CI: 45.7% - 55.2%) of these births reported to receive Inj./IV medicine during labor. Among those giving birth in govt. hospitals in DHS clusters for which the closest govt. hospitals are categorized as 'possibly ready'-for labor augmentation (cesarean deliveries done over the preceding 3 months, but all 4 criteria of 'Apparently ready'-for labor augmentation were not met, according to SPA data), 57.5% (95% CI: 48.4% - 66.1%) of births reported to receive Inj./IV medicine during labor. For reported govt. hospital births in DHS clusters located within a closest distance from govt. hospitals that are considered 'definitely not ready'- for labor augmentation (no caesarean deliveries over the preceding 3 months or cesarean deliveries are usually not offered in that hospital, according to SPA data), 55.0% (95% CI: 47.5% - 62.7%) reported to receive Inj./IV medicine during labor.

Table 21:Distribution of reported births (in DHS clusters) received oxytocin during labor among the closest hospitals (govt.) (identified from SPA) categorized by readiness for labor augmentation

Facility type[1]	Total Births[2] (n=1106)	Oxytocin received during labor	
		Yes (n=549)	% (95% CI)
'Apparently ready' for labor augmentation	565	273	50.4 (45.7 – 55.2)
'Possibly ready' for labor augmentation	158	92	57.5 (48.4 – 66.1)
'Definitely not ready' for labor augmentation	383	184	55.0 (47.5 – 62.7)

CI: Confidence Interval

[1] Facility type- closest secondary or tertiary govt. hospitals (identified from SPA) categorized by readiness for labor augmentation with respect to availability of cesarean capacity

[2] Total births – Total mothers reported to receive Inj./IV medicine during labor in a secondary or tertiary level govt. hospital in the NDHS 2016 survey

[Table 22] reports information on proportion of births received Inj./IV medicine during labor in secondary or tertiary hospitals (govt.) with a CEmONC guideline available or not. Out of 1121 govt. hospital births reported in DHS, data related to labor augmentation and CEmONC guideline availability were retrieved for 1092 births. A total of 544 births out of 1092 births reported to receive Inj./IV medicine during labor; of these, 53.7% (95% CI: 44.5%, 62.8%) of the births reported to receive Inj./IV medicine during labor in secondary or tertiary hospitals in clusters for which the nearest secondary or tertiary hospitals do not have a CEmONC guideline available [Table 22].

Table 22:Hospital births in which injections were given during labor by availability of CEmONC guidelines

Facility type[1]	Total Births[2] (n)	CEmONC guideline-available[3]		CEmONC guideline- not available[3]	
		(n)	% (95% CI)	(n)	% (95% CI)
Govt. hospitals (secondary and tertiary level)	544	265	46.2 (37.2 – 55.5)	279	53.7 (44.5 – 62.8)

CI: Confidence Interval

[1] Facility type- closest secondary or tertiary govt. hospitals from each DHS cluster (identified from SPA)

[2] Total births – Inj./IV medicine received during labor reported by women delivered in a **secondary or tertiary hospitals** across DHS clusters

[3] CEmONC guideline (available/not available)- reported in the SPA inventory survey

For reported births in Private hospitals:

[Table 23] reports findings on distribution of reported private hospital births in clusters in DHS received Inj./IV medicine during labor in the closest private hospitals identified from SPA categorized by safety for labor augmentation (in regard to capability to perform timely emergency cesarean section). Out of 525 reported private hospital births (within the last three years) in DHS, data related to Inj./IV medicine received during labor (labor augmentation) and readiness for labor augmentation in the closest private hospital were available for 476 births. For a total of 139 private hospital births reported in DHS clusters, the closest private hospitals

are considered 'Apparently ready'-for labor augmentation (identified from SPA); 69.7% (95% CI: 60.9% - 77.4%) of these births reported to receive Inj./IV medicine during labor. Among the private hospital births reported in DHS clusters for which the closest private hospitals are categorized as 'possibly ready'-for labor augmentation, 52.5% (95% CI: 37.4% - 67.1%) of births reported to receive Inj./IV medicine during labor. For reported private hospital births in DHS clusters located within a closest distance from private hospitals that are considered 'definitely not ready'-for labor augmentation, 62.5% (95% CI: 55.9% - 68.7%) reported to receive Inj./IV medicine during labor.

Table 23:Distribution of reported births (in DHS clusters) received oxytocin during labor among the closest private hospitals (identified from SPA) categorized by readiness for labor augmentation

Facility type[1]	Total Births[2] (n=476)	Oxytocin received during labor	
		Yes (n=298)	% (95% CI)
'Apparently ready' for labor augmentation	139	94	69.7 (60.9 – 77.4)
'Possibly ready' for labor augmentation	27	16	52.5 (37.4 – 67.1)
'Definitely not ready' for labor augmentation	310	188	62.5 (55.9 – 68.7)

CI: Confidence Interval

[1] Facility type- closest private hospitals (identified from SPA) categorized by readiness for labor augmentation with respect to availability of cesarean capacity

[2] Total births – Total mothers reported to receive Inj./IV medicine during labor in private hospitals in the NDHS 2016 survey

Table 24:Distribution of births received oxytocin during labor in private hospital with CEmONC guideline available or not

Facility type[1]	Total Births2 (n)	CEmONC guideline-available[3]		CEmONC guideline- not available[3]	
		(n)	% (95% CI)	(n)	% (95% CI)
Private hospitals	209	25	11.7 (6.3 – 20.5)	184	88.3 (79.4 - 93.7)

CI: Confidence Interval
[1] Facility type- closest private hospitals from each DHS cluster (identified from SPA)
[2] Total births – Inj./IV medicine received during labor reported by women delivered in private hospitals across DHS clusters
[3] CEmONC guideline (available/not available)- reported in the SPA inventory survey
$\chi^2 = 5.38$, $p < 0.05$

[Table 24] reports information on proportion of births received Inj./IV medicine during labor in private hospitals with a CEmONC guideline available or not. Out of 525 private hospital births reported in DHS, data related to labor augmentation and CEmONC guideline availability retrieved for 331 births. 209 out of 331 births reported to receive Inj./IV medicine during labor; of these, 88.3% (95% CI: 79.4% - 93.7%) of births reported to receive Inj./IV medicine during labor in private hospitals in clusters for which the nearest private hospital do not have a CEmONC guideline available [Table 24].

Multinomial logistic regression analysis

Assessing the influence of women's socio-economic factors (reported in the NDHS 2016 survey) on receiving labor augmentation in hospitals that are 'possibly ready-for labor augmentation' compared to in hospitals that are 'Apparently ready-for labor augmentation' and in hospitals that are 'definitely not ready-for labor augmentation' compared to in hospitals that are 'Apparently ready-for labor augmentation' (adjusted for women's age and parity):

Table 25 and Table 26 presents results from the adjusted multinomial logistic regression model for reported births in DHS that received labor augmentation in secondary or tertiary govt. hospitals (govt. hospitals) and in private hospitals, respectively

Table 25:Adjusted multinomial logistic regression analysis for assessing the association of women's socio-economic factors with labor augmentation received (for the reported births in DHS) in the nearest secondary or tertiary govt. hospitals to each DHS cluster (hospitals were identified from SPA)

Variable	*Compare to "***Apparently ready***" for labor augmentation outcome*				
	Possibly ready			**Definitely not ready**	
	RRR (95%CI)	**p-value**		**RRR (95%CI)**	**p-value**
Women's level of education (*Reference: No education*)					
Primary	0.42 (0.13, 1.32)	0.137		0.29 (0.15, 0.57)	**<0.001**
Secondary	0.54 (0.17, 1.67)	0.282		0.38 (0.17, 0.83)	**0.016**
Higher	0.94 (0.34, 2.60)	0.913		0.57 (0.23, 1.40)	0.223
Women's wealth index (*Reference: Poorest*)					
Poorer	2.71 (0.83, 8.79)	0.097		0.60 (0.23, 1.61)	0.311
Middle	1.82 (0.48, 6.89)	0.379		1.81 (0.69, 4.69)	0.220
Richer	2.11 (0.56, 8.04)	0.271		1.30 (0.46, 3.66)	0.618
Richest	0.56 (0.11, 2.94)	0.490		0.78 (0.28, 2.18)	0.630
Women's parity (*Reference: Primiparous*)					
Multiparous	1.79 [0.85, 3.80)	0.126		1.29 (0.77, 2.15)	0.328
Women's age (*Reference: 15-29 years*)					
30-44 years	0.34 (0.09, 1.22)	0.098		0.50 (0.24, 1.05)	0.067

RRR: Relative risk ratio
CI: Confidence Interval

Table 26:Adjusted multinomial logistic regression analysis for assessing the association of women's socio-economic factors with labor augmentation received (for the reported births in DHS) in the nearest private hospital to each DHS cluster (hospitals were identified from SPA)

Variable	*Compare to "***Apparently ready***" for labor augmentation outcome*				
	Possibly ready			**Definitely not ready**	
	RRR (95%CI)	**p-value**		**RRR (95%CI)**	**p-value**
Women's level of education (*Reference: No education*)					
Primary	0.35 (0.09, 1.28)	0.112		1.52 (0.59, 3.95)	0.385
Secondary	0.21 (0.03, 1.48)	0.117		2.56 (1.12, 5.82)	**0.026**
Higher	0.99 (0.16, 5.92)	0.989		3.72 (1.20, 11.47)	**0.023**
Women's wealth index (*Reference: Poorest*)					
Poorer	0.02 (<0.01, 0.72)	**0.033**		0.13 (0.01, 1.42)	0.093
Middle	0.11 (<0.01, 2.69)	0.175		0.19 (0.02, 2.08)	0.174
Richer	0.02 (<0.01 0.77)	**0.035**		0.16 (0.01, 1.57)	0.114
Richest	0.07 (<0.01, 1.17)	0.065		0.04 (<0.01, 0.38)	**0.006**
Women's parity (*Reference: Primiparous*)					
Multiparous	0.27 (0.13, 0.56)	**0.001**		0.89 (0.46, 1.74)	0.739
Women's age (*Reference: 15-29 years*)					
30-44 years	0.99 (0.19, 4.93)	0.986		1.65 (0.66, 4.13)	0.279

RRR: Relative Risk Ratio
CI: Confidence Interval

Secondary or tertiary govt. hospitals:

For reported births that received labor augmentation in secondary or tertiary level govt. hospitals, the adjusted multinomial logistic regression analysis [Table 25] did not find any association between women's socio-economic status and labor augmentation in hospitals

categorized into 'apparently ready', 'possibly ready' and 'definitely not ready' for labor augmentation. However, for labor augmentation in 'definitely not ready' hospitals compared to labor augmentation in 'apparently ready' hospitals, the association of women's level of education was found significant. The risk of labor augmentation in a 'definitely not ready' hospital compared to labor augmentation in a 'apparently ready' hospital is 71% [RRR: 0.29, 95% CI: 0.15, 0.57] lower for women with primary level education compared to women with no education (p<0.001). Similarly, the risk of labor augmentation in a 'definitely not ready' govt. hospital compared to labor augmentation in a 'apparently ready' govt. hospital is 62% [RRR: 0.38, 95% CI: 0.17, 0.83] lower for women with secondary level education compared to women with no education (p value- 016).

Private hospitals:

For private hospitals, the risk of labor augmentation in 'possibly ready' hospitals compared to labor augmentation in 'apparently ready' hospitals was not found associated with women's education; but the association was found significant for women's wealth index and women's parity [Table 26]. The risk of labor augmentation in a 'possibly ready' private hospital compared to labor augmentation in a 'apparently ready' private hospital is 98% [RRR: 0.02, 95% CI: <0.01, 0.72] lower among mothers with poorer wealth index compared to mothers with poorest wealth index (p=0.033). The risk of labor augmentation in a 'possibly ready' private hospital compared to labor augmentation in a 'apparently ready' private hospital is 98% [RRR: 0.02, 95% CI: <0.01, 0.77] lower among mothers with richer wealth index compared to mothers with poorest wealth index (p=0.035). The women who had already given birth to more than one child during labor augmentation compared to women who were giving birth to their first child when they received drug for labor augmentation, were at 73% [RRR: 0.27, 95% CI: 0.13, 0.56] lower risk of receiving labor augmentation in a 'possibly ready' hospital compared to receiving labor augmentation in a 'apparently ready' hospital.

For nearest private hospitals to the DHS clusters where women reported to receive labor augmentation in a private hospital, a significant association was found between women's socio-economic factors and the risk of labor augmentation in 'definitely not ready' hospitals compared to labor augmentation in 'apparently ready' private hospitals [Table 26]. The risk of labor augmentation in a 'definitely not ready' private hospital compared to labor augmentation in a 'apparently ready' private hospital is 2.5 [RRR: 2.56, 95% CI 1.12, 5.82] times more likely for women with secondary level education compared to women with no education (p=0.026). For women with higher education compared to no education, a higher risk for labor augmentation in 'definitely not ready' private hospitals compared to labor augmentation in 'apparently ready' hospitals was reported. The risk of labor augmentation in a 'definitely not ready' private hospital compared to labor augmentation in a 'apparently ready' private hospital is 3.7 [RRR: 3.72, 95%CI: 1.20, 11.47] times more likely for women with higher level education compared to women with no education (p=0.023). Besides, the association between women' wealth index for women in richest wealth index compared to women in poorest wealth index and labor augmentation in 'definitely not ready' private hospitals compared to 'apparently ready' private hospitals was found significant; the women in richest wealth index compared to women in poorest wealth index are at 96% [RRR: 0.04, 95% CI: <0.01, 0.38] lower risk to receive labor augmentation in a 'definitely not ready' hospital compared to labor augmentation in a 'apparently ready' hospital.

3.4 DISCUSSION

Our bivariate analysis utilizing the DHS 2016 survey data restricted to the births took place within the last three years prior to the survey documented that among the births that took place in home and attended by a health personnel (**assisted by doctor, nurses/midwives, health assistants (HAs), auxiliary health workers (AHWs), maternal and child health workers (MCHWs) and village health workers (VHWs))**, 66.9% (95% CI: 56.7%, 75.7%)

reported receiving Inj./IV medicine during labor at home, for births took place in government hospitals (secondary and tertiary level public hospitals) and private hospitals and attended by health personnel, these proportions are 52.9% (95% CI: 49.1%, 56.8%) and 64.3% (95% CI: 59.1%, 69.1%), respectively.

These proportions are considerably higher than reported from the SPA survey. In the SPA study, the question related to injections during labor was asked only to a small sample of post-partum clients from selected facilities during client-exit interviews. Only 204 Post-partum clients who reported giving births in a govt. hospital (secondary and tertiary level hospitals) were interviewed; 24.5% [95% CI: 18.8%, 31.3%] of these reported receiving oxytocin during labor. Concerning births that took place in a private hospital reported by post-partum clients in the SPA client exit interview survey, out of a total number of 94 post-partum clients interviewed, 24.3% [95% CI:13.8%, 39.1%] of mothers reported receiving oxytocin during labor.

In Nepal SPA 2015 survey, the post-partum client exit interview was conducted only in the health facilities that offer delivery services. Out of the total 992 health facilities, 623 health facilities were reported to provide delivery and newborn care. Out of those 623 health facilities that offer delivery and newborn service, only 98 health facilities are secondary/tertiary level hospitals (district level and above) and 96 health facilities are private hospitals, and 429 health facilities are primary level health facilities (PHCC and below). The Nepal Health Facility survey data collectors conducted at clients exit interview with the postpartum clients when they were discharged from a facility. On the day of the data collectors' visit, if a large number of postpartum women got discharged, then the data collectors systematically selected a maximum number of five postpartum women on that particular day. Hence, only a total of 310 postpartum clients were selected for an interview; of these, 309 clients reported information related to labor augmentation.

Sampling strategy could be a factor which the proportion for labor augmentation in hospitals in the SPA survey seems under representative compared to the labor augmentation proportion in the DHS surgery. For example, in the SPA dataset, on a visit to a particular facility, the data collectors got a total of 7 postpartum clients in the hospital, the data collectors systematically selected 5 postpartum clients for interview out of those 7 postpartum clients; similarly, on a particular visit the data collectors got 35 postpartum clients in a regional level hospital, from them the data collector interviewed 5 postpartum clients (information collected from Nepal SPA 2015 inventory dataset). Since they followed a systematic sampling and took a maximum of 5 clients per hospital, the interval for selecting 5 out of 7 postpartum clients is different from the interval for selecting 5 out of 35 clients. Even though the process introduced randomness to the data, but the quality of the estimate is questionable (Siegel, AF. 2016). It is not possible to get an idea of the standard error of these types of data. Besides, the data collectors visited each hospital only once, it is possible that for a particular hospital, the labor augmentation rate among the postpartum women who got discharged is low on the day of the data collector's visit, but any other day the proportion might be higher for that hospital. Therefore, if a labor augmentation rate among the postpartum is estimated low from the interview data, it does not necessarily mean that the data is nationally representative.

However, the SPA inventory dataset contains information related to availability and readiness specific healthcare service in a larger sample of health facilities (includes all nonspecialized government hospitals and all private hospitals with 100 beds or more, all PHCC and a random sample of all other types of facilities). Therefore, we merged the SPA inventory dataset with the DHS birth dataset, and by linking the labor augmentation proportion reported in the DHS dataset with the availability and readiness information (with regard to cesarean section capacity) of all secondary- tertiary level hospitals and private level hospital, we characterized the

labor augmentation practice in the hospitals in Nepal (based on our assumption, a woman in a given cluster who reported giving birth in a secondary-tertiary level government hospital would go to the nearest hospital). By geographically linking DHS data with the SPA data, we identified that among the reported hospital births that took place in hospitals with limited capacity and no capacity to conduct cesarean delivery, a considerable proportion received oxytocin during labor. This finding implies evidence of labor augmentation in hospitals most likely without adequate readiness to manage complications due to labor augmentation in the context of Nepal.

We adjusted our multinomial logistic regression model for women's parity and age because both of these have clinical significance in causing prolonged labor (Greenberg, MB. 2007; Vahratian, A. 2006). Besides, women who have already experienced labor once and have already given birth once might have the idea of using oxytocin to speed up labor. We found evidence from a study conducted in Bangladesh reported a lower chance of using oxytocin during labor among the women who already experienced two or more deliveries (Moran, AC. 2010). Moran et al. (2010) also reported increased chances of using oxytocin to augment labor among the women with any education compared to no education and among the women who already have knowledge of using saline or injections to augment labor compared to women without any such knowledge. However, Moran et al. (2010) did not find any significant association between women's wealth index and using oxytocin for labor augmentation. A review of oxytocin use during home deliveries in Uttar Pradesh in India reported that oxytocin use during labor was found more common among women with more education and higher socio-economic status. Our multinomial logistic regression did not show any association of women's socio-economic factors (level of education and wealth index) with their risk of receiving labor augmentation in a 'possibly ready-for labor augmentation' hospital compared to a 'apparently ready-for labor augmentation' hospital and in a 'definitely not ready-for labor augmentation' hospital compared to 'apparently ready-for labor augmentation' hospital for government hospital births. However,

for private hospital births, the association of women's socio-economic factors (level of education and wealth index) with their risk of receiving labor augmentation in a 'definitely not ready-for labor augmentation' hospital compared to a 'apparently ready-for labor augmentation' hospital was found significant. Our geographically linked analysis is the first such type of study that utilized two Nationally Representative Dataset in Nepal to assess the labor augmentation practice in every level of health service delivery in Nepal and to provide evidence on the inappropriate practice of labor augmentation in the hospital setting with respect to following WHO's conditions to ensure safety for mothers and babies during labor augmentation. The reportable findings will serve as robust justifications for the Nepal Ministry of Health & the Nepal OBGYN Society to believe that labor augmentation not following the WHO labor augmentation recommendations is commonly practiced in diverse setting in Nepal which may contribute to unexpected adverse consequences in mothers and babies in Nepal, and such injudicious practices of labor augmentation requires further investigation.

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CHAPTER 4. DISCUSSION

4.1 SUMMARY OF FINDINGS

This thesis consists of a systematic literature review on available literature related to uterotonic use during labor in the context of South Asia and a quantitative analysis linking two nationally representative surveys in Nepal to explore the practice of labor augmentation in Nepal.

In light of the WHO recommendations for labor augmentation, any labor that received uterotonics (commonly oxytocin) during labor for augmentation (or induction), not in compliance with the WHO's recommendations, was considered unsafe labor augmentation. If we outline the major points in the WHO recommendations that must be followed to ensure safety for both mothers and babies in the event of labor augmentation are as follows:

1) there should be clear medical indication that the expected benefit of augmentation outweighs the harm,
2) clinical assessment of the mother should be performed before using oxytocin to augment labor to exclude scarred uterus, cephalopelvic disproportion, abnormal presentation and position of the baby,
3) “the mother received labor augmentation should never be left unattended”,
4) oxytocin during labor should be administered using a controlled infusion rather than using IM injections or IV bolus,
5) conduct close monitoring and assessment of the mother's uterine contractions and fetal heart rate at least every thirty minutes, and
6) augmentation should be done in facilities with capacities to manage any adverse outcomes including adequate capacity to conduct cesarean deliveries.

To comply with all those conditions, the first and foremost requirement is that any uterotonic, particularly oxytocin, should not be used during labor in a home-birth setting and a primary

level health facility. For any birth in a home-birth setting use of oxytocin for labor augmentation, it is impossible to fulfill all the conditions for ensuring safety during labor augmentation recommended by WHO, specifically the condition related to capacities to conduct cesarean delivery. The widespread inappropriate use of oxytocin during home births has been reported as a particular matter of concern in other review studies as well (Flandermeyer, D. 2010; Jeffery, P. 2007). Besides, extensive availability of oxytocin at low-cost, which is definitely welcoming considering its proven benefit in reducing Post-partum hemorrhage (if the drug is used after the delivery of the baby), has recently raised concern over potential adverse outcomes in case of improper administration of oxytocin before the delivery of the baby (during labor for labor induction or augmentation) (Lovold, A. 2008). Hence, it is considered crucial to look for evidence on the use of oxytocin during labor in a homebirth setting and outside of a comprehensive level facility. Our literature review identified 16 studies presenting evidence of labor augmentation at home or outside of CEmONC setting, and in many cases, the proportion of using oxytocin during labor at home was higher than 40%. A narrative review on oxytocin during home deliveries in Uttar Pradesh, India, demonstrated the use of oxytocin for labor augmentation in home deliveries with a varying range of 48.2% to 74.7% (Jeffery, P. 2007). Such high percentages of oxytocin use for labor induction or augmentation is threatening since health workers from informal health systems, including untrained health workers, traditional 'dais,' are not aware of the systemic effect of oxytocin when it is used before the delivery of the baby and the clinical recommendations of using oxytocin during the intrapartum period (during labor) (Lovold, A. 2008).

Administering oxytocin during labor using an IM injection or IV bolus is regarded a dangerous practice. If a drug is given through an IV push injection, it delivers the complete dose of the drug directly to the bloodstream; hence the onset of the action happens within a short period of time; if a controlled infusion pump is not used, it is difficult to adjust the level of dose with uterine

contraction level (Lovold, A. 2008). Hence, oxytocin during labor is recommended using ideally a controlled infusion pump or at least using the IV drip infusion method. Using a controlled infusion pump is considered a safe delivery method of drugs. The use of controlled infusion pumps for the administration of an intravenous drug is common in high-income contexts, but in low-income country contexts, the widespread availability of such costly and technical resource-demanding equipment is challenging (Abu-Haydar, E. 2021). However, IV drip infusion is also considered a safer method (not as safe as with the controlled infusion pump) when harmful consequences of the drug may happen. By calculating and monitoring the drops per minute, the dosage rate of IV infusion of oxytocin can be controlled. WHO and other normative bodies recommend low-dose administration via IV drip infusion or controlled infusion pump, increasing the rate slowly by 1-4 milliunits/minute (2-8 drops/minute) with monitoring of uterine contractions and fetal heart rate pattern at intervals of a minimum of 20 minutes until the contraction pattern reaches at three to four contractions per 10 minutes (Litorp, H. 2021). However, we found evidence of administering oxytocin using IM injections/IV bolus injections in 12 studies. This inappropriate practice of administering oxytocin using the IM/IV injection method was also reported in other studies conducted with a specific focus on lower-income countries, including countries in South Asia (Burgod, C. 2021; Flandermeyer, D. 2010; Jeffery, P. 2007; Lovold, A. 2008).

Oxytocin should not be administered in mothers with previous uterine scar (e.g., previous cesarean section); this is a strong recommendation by WHO and should not be ignored at any cost since non-compliance with this condition carries a heightened risk of the ruptured uterus. In our review, we found 10 studies explicitly reported incidence of a ruptured uterus in a scarred uterus due to oxytocin administration during labor. The European Association of Perinatal medicine also corroborated a similar recommendation and provided evidence of uterine rupture among women with exposure to oxytocin during labor (Nunes, I. 2021). A 10-year retrospective

review investigating the incidence and etiology of uterine rupture at a teaching hospital in Southwestern Nigeria also reported that the injudicious use of oxytocin was an identified contributor to 41% of ruptured uterus cases (Ezechi, OC. 2004).

Uterine hyperstimulation in the mothers also leads to a reduced oxygen level in a fetus, severe adverse outcomes like stillbirth and early neonatal death. Oxytocin augments uterine contractions, and after each contraction, fetal oxygen saturation drops; fetal oxygen recovers during the interval between two uterine contractions (Johnson, N. 1994). In the event of uterine hyperstimulation, if the interval is too short, the fetus remains hypoxic, and the compromised status of the fetus can be identified by detecting increased variability in the fetal heart rate pattern (Johnson, N. 1994; Bakker, PC. 2007). Hence, it is critical to frequently monitor uterine activity and fetal heart rate (i.e., every 15-30 minutes) if oxytocin is used to augment/induce the labor. A study assessing the role of uterine activity on fetal outcome reported that uterine hyperactivity, among the cases augmented or induced with oxytocin, is associated with low pH in the umbilical cord artery (Bakker, PC. 2007). Nevertheless, to prevent all potential negative consequences in mothers and babies due to oxytocin administration during labor, WHO strongly recommends monitoring augmented mothers for uterine contractions and fetal heart rate at least every thirty minutes and ensuring a constant labor companion for mothers. We searched for evidence documented in the related studies in South Asia in regard to WHO's frequent assessment of mothers and fetuses and the presence of labor attendant conditions. The findings we gathered are limited, not clear, and did not provide any satisfactory impression about the situation in South Asia, specifically regarding the frequency of assessment and ensuring the continuous presence of a labor companion. Only four studies that were conducted in a tertiary level healthcare setting clearly indicated that labor was monitored for uterine contractions and fetal heart rate at least every thirty minutes; however all of these studies were conducted in a tertiary level healthcare setting (Rijal, P. 2014; Acharya, T. 2017; Litorp, H. 2021;

Nahar, S. 2004). Only one study reported that labor was not attended by a labor companion; rest of the 48 studies did not provide any information regarding this condition (Cederfledt, J. 2016). Besides, fourteen studies presented findings reported on clinical assessment of the mothers before administering oxytocin during labor to rule out contra-indications; of these, only two provided positive findings such as examination for fetal position and presentation and internal vaginal examinations for assessing cervical dilatation before administering oxytocin to induce/augment labor. Administering oxytocin during labor without assessing for a previous cesarean section and the presence of cephalopelvic disproportion was a common finding in most of the ruptured uterus related studies (17 studies) that we retrieved from South Asia; noncompliance with this WHO recommendations for labor augmentation contributed a significant proportion of ruptured uterus among mothers.

Flandermeyer et al.'s (2010) literature review on using oxytocin in case of home births in low-income countries indicated that both providers (healthcare provider, particularly TBAs) and the users (mothers) oxytocin for labor augmentation is considered a 'modern practice' and is perceived as a useful medicine to make the delivery easy for mothers. Our review also found a similar positive perception toward using oxytocin during labor among the TBAs (Singh, S. 2012) (Moran, AC. 2010). Jeffery et al. (2007) also reported a positive attitude regarding using oxytocin during labor among both mothers and informal health providers; besides the authors indicated that the rural health workers and informal health providers lack the knowledge of WHO's recommendations/conditions for labor augmentation and possible adverse effects of labor augmentation using oxytocin in home-birth setting and in a setting without monitoring and surgical capacity. The most common maternal adverse outcome identified from the included studies in our review is the ruptured uterus. Another literature review that put together studies on using oxytocin for both during labor and PPH prevention reported association of labor augmentation using oxytocin with developing ruptured uterus in 2-44% of cases; the

studies that reported findings regarding oxytocin use for labor augmentation with uterine rupture in the review were conducted in multiple countries, including Nigeria, Sudan, Nepal, and Bahrain (Lovold, A. 2008). Aside from the incidence of rupture uterus, our review also identified several other significant adverse outcomes among mothers who received oxytocin during labor, including emergency cesarean section, cervical tear, perineal tear, external anal sphincter injury and, requiring intensive care admission.

With respect to fetal outcomes due to exposure to oxytocin during labor, Lovold et al.'s (2008) study grouped together findings from three studies conducted in low-income country settings, including Benin, Congo, and Senegal, and reported a higher risk of stillbirth and neonatal resuscitation associated with the use of oxytocin during labor compared to no such use of oxytocin during labor [RR: 1.9 (95%CI: 1.1, 3.4)]. Our review also identified multiple studies that reported a higher risk of stillbirth and birth asphyxia with using oxytocin during labor. A case-control study conducted in a tertiary hospital in Uganda found a significant association of labor augmentation using oxytocin with birth asphyxia, reported 5.76 times higher odds of oxytocin exposure among the cases (term babies with a 5 minute APGAR score 4 or less birth asphyxia) compared to controls (term babies with a 5 minute APGAR score more than 4 birth asphyxia) [OR: 5.76 (95% CI: 2.20-15.05)] (Kaye, D. 2003). Another case-control study from rural Guatemala found a significantly higher proportion of intrapartum mortality among cases who received intramuscular oxytocin injection during labor than among controls who did not receive such injections during labor (Bartlett, AV. 1991). Our review also found evidence of several other adverse fetal outcomes reported in the included studies- neonatal encephalopathy, neonatal respiratory depression, meconium-stained liquor, early neonatal death, Apgar score <7 at 5 minutes.

By reviewing literature related to oxytocin use during labor in South Asia, we identified that

oxytocin administration to accelerate labor is prevalent in both home birth and hospital birth settings in Nepal. Besides, considerable risks of developing dangerous maternal and fetal outcomes due to injudicious use of oxytocin during labor, including uterine rupture, stillbirth, fetal distress, early neonatal death, neonatal respiratory depression, and neonatal encephalopathy, were also manifested in several studies in Nepal. Hence, utilizing the Nepal DHS 2016 survey and Nepal SPA 2015 survey, we investigated the use of oxytocin for labor augmentation in different levels of facilities. By geographically linking the Nepal DHS 2016 survey with the Nepal SPA 2015 survey, we assessed the proportions of labor augmentation using oxytocin that were likely happened in facilities that are 'apparently ready- for labor augmentation' (in the sense that a surgeon and anesthetist were available, as was blood, and that the hospital had done cesarean deliveries over the preceding 3 months), 'possibly ready- for labor augmentation' (having done at least some cesarean deliveries over the past 3 months but not meeting all 4 conditions to be categorized as "apparently ready") and 'definitely not ready- for labor augmentation' (no cesarean deliveries over the past 3 months). The information related to labor augmentation were retrieved from the Nepal DHS 2016 survey, and the information on readiness to perform emergency cesarean deliveries was retrieved from Nepal SPA 2015 survey. We restricted our analysis using the Nepal DHS 2016 data to births within the three years prior to the survey. According to our analysis findings, 53.9% (95% CI: 51.0-56.8) reported to receive Inj./IV medicine during labor (among the births that were assisted by doctor, nurses/midwives, health assistants, auxiliary health workers, maternal and child health workers and village health workers); of these 72.6 % (95% CI: 68.9-76.1) of births received such medicine to speed up the labor. Labor augmentation at attended home births and primary level facility was found quite high in this sample:

66.9% (95% CI: 56.7-75.7) among births at home, attended by a health worker,

40.4% (95% CI: 34.3-46.8) among births at PHHCCs and HPs,

53.0% (95% CI: 49.1-56.8) among births at government hospitals, and

64.3% (95% CI: 59.1-69.1) among births at private hospital births.

When we looked for the government hospital (secondary or tertiary level), labor augmentation proportions disaggregated by provinces, we found that all provinces had a labor augmentation rate of more than 30%. For private hospital births reported in 2016 DHS, all provinces had a labor augmentation rate of 40%. There were differences in proportion in labor augmentation between provinces for both government hospitals and private hospital births. No differences were found by urban/rural place of residence. For both government hospital births and private hospital births, province 2 has the highest proportion for labor augmentation among all provinces 70.9% (95% CI: 62.4%, 78.1%) in case of government hospital births (secondary and tertiary level hospital), 74.3% (95% CI: 64.7%, 81.9%) in case of private hospital births. Ashish et al.'s (2020) study on quality of delivery and newborn services in facilities in Nepal reported that province 2 (Madhesh) has the lowest proportions of facilities that provide delivery and newborn service. According to a report on analysis of several indicators of SPA 2015 survey, 10.8% of health facilities (secondary and tertiary level hospital and private hospitals) in province 2 (Madhesh) carried out at least one cesarean section over the preceding three months, carried out at least one blood transfusion in obstetric context over the preceding three months, and carried out all other seven CEmONC signal functions at least once in the preceding three months (Aryal, KK. 2018). However, the proportion of health facilities (secondary and tertiary level government hospitals and private hospitals) that carried out all nine CEmONC signal functions is considerably low in all provinces- 8.8% in province 1 (Province No. 1) , 13.6% in province 3 (Bagmati Province), 5.6% in province 4 (Gandaki Province), 17.3% in province 5 (Lumbini Province), 7.1% in province 6 (Karnali Province) and 13.2% in province 7 (Sudurpashchim Province) (Aryal, KK. 2018).

We identified the closest government and private hospital to each DHS cluster using the

geospatial data of both the Nepal DHS 2016 survey and Nepal SPA 2015 survey and assessed whether those hospitals are “apparently ready- for labor augmentation,” “possibly ready- for labor augmentation,” or “definitely not ready- for labor augmentation” (based on readiness to provide emergency cesarean delivery service) and assessed the reported labor augmentation rate using DHS reported data, across those three categories of hospitals.

In the DHS-SPA linked analysis, our assumption that a woman in a given cluster who reported giving birth in a government hospital would go to the government hospital closest to that given cluster, and a woman in a given cluster who reported giving birth in a private hospital in the DHS would go to the private hospital closest to that given cluster. Based on this assumption, the following percentages received oxytocin during labor in government hospitals:

50.4% (95% CI: 45.7-55.2) of those delivering in a “apparently ready -for labor augmentation”

57.5% (95% CI: 48.4-66.1) of those delivering in a “possibly ready- for labor augmentation”, and

55.0% (95% CI: 47.5, 62. 7) of those delivering in a “definitely not ready- for labor augmentation”.

For private hospital births reported in the DHS, these proportions were 69.8% (95% CI: 60.9-77.4), 52.6% (95% CI: 37.4-67.1), and 62.5% (95% CI: 56.0-68.7), respectively. Such high proportions of labor augmentation in the “possibly ready- for labor augmentation” and “definitely not ready- for labor augmentation” hospitals indicates that a considerable proportion received that Inj./IV medicine during labor in a facility without the basic capacities for conducting a cesarean section: availability of surgeon and anesthetist, conducting at least one cesarean section within the last three months prior to the SPA 2015 survey, and conducting blood transfusion at least once in the prior three months of the SPA survey.

Among births reported in a government hospital [based on our assumption, the closest one to each cluster] and receiving an Inj/IV medicine during labor, the proportion giving birth in hospitals without a CEmONC guideline available was 53.8% (95% CI: 44.5-62.8). Among births received Inj./IV medicine taking place in a private hospital, 88.3% (95% CI:79.5-93.70) were in facilities lacking a CEmONC guideline. The availability of a CEmONC guideline in a comprehensive level hospital is important since a CEmONC guideline provides information on several comprehensive maternal and newborn healthcare interventions, including cesarean delivery, safe blood transfusion, assisted vaginal delivery, manual removal of placenta, abortion, providing oxytocin and antibiotics and neonatal resuscitation. A report on Nepal SPA 2015 survey indicator analysis also documented that 75% of all district level hospitals in Nepal that provide delivery and newborn care do not have a guideline for delivery care available, for zonal level government hospitals and private hospitals, the proportions of unavailability of a guideline on delivery care are 72.8% and 99.5%, respectively (Aryal, KK. 2018).

Our analysis indicates that the practice of labor augmentation in every level of healthcare delivery is significantly high. In case of home delivery and primary level facility delivery, such high proportion of labor augmentation rate (66.9% in homebirths, 40.4% in primary level hospital births- among the births attended by health workers) certainly put both mothers and babies at high risk for morbidities and mortalities due to oxytocin use during labor. Even for the secondary and tertiary level hospital births and private hospital births in Nepal, ensuring safety for augmented mothers is challenging because the national average of all hospitals that carried out all nine CEmONC signal functions over the preceding three months of the survey is only 11.5% (Aryal, KK. 2018); labor augmentation proportion in government hospitals (secondary and tertiary level hospital) and private level hospitals are also quite high. Even in our DHS-SPA linked analysis, we found that a higher proportion of mothers in DHS clusters who gave birth in

a ‘possibly ready’ and ‘definitely not ready’ hospital (from SPA survey) received augmentation during labor. Overall, our analysis findings report that a significant proportion of mothers in Nepal received inappropriate administration of oxytocin during labor which eventually put them at an extensive risk of having all deadly consequences of labor augmentation identified in our literature review. This potential problem needs further investigation.

4.2 IMPLICATIONS

From the literature review, we found evidence that using oxytocin during labor is common, in South Asia, at every level, including home, primary level facilities, and secondary-tertiary level health facilities. Using oxytocin during labor is certainly dangerous considering what we know based on the WHO conditions for labor augmentation for ensuring safety and the adverse effects of labor augmentation using oxytocin on both mothers and fetuses. Even for births that are augmented in a secondary or tertiary level health facilities, in many cases, WHO's conditions for labor augmentation are not met, particularly with regard to ruling out contra-indications and adequately frequent monitoring for uterine contractions and fetal heart rate (at least every thirty minutes). In most healthcare settings in low-income countries, usually a partograph is used to document the progress of labor and identify any abnormality in labor; for example, a health worker can identify labor dystocia by monitoring the cervical dilatation per hour. Hence, using a partograph to document labor can help monitor labor when a health worker duly plots every finding in the partograph from the beginning of the labor as the labor progresses and use the findings in the partograph to identify any abnormality in labor. However, whether the partograph is utilized only to document labor or it is also used as a decision-making aid based on the findings plotted in the partograph is still equivocal (Dalal, AR. 2018). Besides, if a health worker is not aware of the evidence-based criteria to identify normal labor, using a conventional partograph that has an inappropriate action line may cause an incorrect diagnosis of labor dystocia, thereby resulting in unnecessary labor augmentation using oxytocin.

A partograph, a low-cost monitoring tool for intrapartum care for mothers, is proven to be effective in the early identification of maternal complications and thereby reducing maternal and neonatal morbidity and mortality (Khan, ANS. 2018). The gold standard labor monitoring tool-'Partograph' was developed around the groundbreaking study of Friedman (Zhang, J. 2002), which eventually helped health workers identify any pathology in labor and thereby taking any early intervention (Dalal, AR. 2018). The modified partograph by WHO has two lines- alert line and action line; the alert line starts from 4 cm cervical dilatation with a slope of 1cm/hr cervical dilation and ends will the full dilatation of the cervix at 10 cm; the action line is drawn parallel to the alert line at 4 hours right to the alert line (Dalal, AR. 2018). The interval of 4 hrs is used to diagnose any delay in the active phase, so appropriate interventions can be taken if any delays in labor are diagnosed. The criteria for plotting a partograph that have been used so far to diagnose any arrest of labor or labor dystocia or prolonged labor and thereby taking actions like labor augmentation using oxytocin are grounded on Friedman's historical study on labor progress pattern (Dalal, AR. 2018). However, the definition of labor dystocia is still an issue of controversy. The parameters for defining stages of labor were developed based on Friedman's study on 500 women at term in 1955 (Zhang, J. 2002). Friedman plotted the relationship between duration of labor and rate of cervical dilatation per hour as a sigmoid curve and divided the first stage of labor into two phases- latent phase and active phase. The definition for both active and latent phases was structured considering Friedman's study- the latent phase ends, and the active phase starts with the cervical dilation of 4 cm (Zhang, J. 2002). Based on Friedman's data, the duration of the latent phase was found on average to be about 8 hours in first time mothers (nullipara) and 5.3 hours in parous mothers (Zhang, J. 2010; Zhang, J. 2002). Prolonged labor or labor dystocia was defined, based on Friedman's work, as cervical dilation in the active phase <1.2 cm/hr in nulliparous women and <1.5 cm/hr in parous women (Zhang, J. 2010; Zhang, J. 2002). This definition is still in use in the conventional WHO

modified partograph (Dalal, AR. 2018). Friedman's study on labor pattern from 1955 was based on an obstetric population that is quite different from today (Zhang, J. 2002). Maternal ages and body mass index had changed significantly since the year 1955, as have normal fetus size (Zhang, J. 2002). More recent studies have examined the labor progress pattern in much larger samples.

In a multicenter retrospective observational study using data from 12 clinical centers, conducted between 2002 to 2008, Zhang et al. (2010) reported that labor progress did not follow any clear-cut rule like the Friedman curve. The authors utilized labor progress data from 62,415 parturients in their study and indicated that the active phase of labor did not start at 4 cm cervical dilatation for every patient. Besides, the authors did not find any specific threshold regarding normal cervical dilatation per hour in the active phase, as suggested by the Friedman curve. They recommended that 6 cm instead of 4 cm may be the more appropriate cut-off point for starting the active phase of labor.

A review of relevant literature by Béranger et al. (2017) supported what Zhang et al. (2010) suggested regarding starting cut-off point for the active phase of labor, recommended not to diagnose labor dystocia before 5–6 cm of cervical dilation. A separate study from Zhang et al (2002) that utilized data from women delivered from 1992 to 1996 reported that the threshold of <1.2cm/hr dilatation in nulliparous and 1.5 cm/hr cervical dilatation in parous women in the active phase is not appropriate to define labor dystocia. Zhang et al. (2010) found variations in the labor progression among women in an active phase. Based on their findings, Zhang et al. (2010) also suggested that for a woman in the active phase, the median time needed to progress from one centimeter of cervical dilation to the next became shorter as the labor advances. They also recommended that women can continue normal labor without any intervention as long as maternal and fetal vital status remains normal. In addition, the authors affirmed to use a 6 cm

of cervical dilatation as an appropriate cut-off point for the start of the active phase. Since the labor progression pattern for the current obstetric population differs significantly from what the criteria for normal labor and prolonged labor established by Friedman, the use of partographs using action lines based on Friedman's findings may contribute to inappropriate overuse of augmentation with oxytocin.

Therefore, further quantitative and qualitative researches are needed to understand the healthcare workers' knowledge regarding normal and abnormal labor and evidence-based criteria to identify labor dystocia. In addition, further hospital-based quantitative studies utilizing hospital-based data are needed to assess the most common indications reported in the hospital record when oxytocin is administered to speed up labor and what criteria they used to diagnose prolonged labor. A large-scale prospective study with measurable indicators incorporating all of the WHO's labor augmentation recommendations to assess the hospital's and health workers' compliance to those conditions in the event of labor augmentation using oxytocin is imperative. Even though there is a WHO recommendation for ensuring safety during labor augmentation using oxytocin is available, a specific evidence-based guideline on using oxytocin during labor incorporating indications, contra-indications, the criteria should be met to ensure safe labor augmentation for mothers and babies, and the possible potential adverse outcomes in mothers and babies should be made available in all level of healthcare facilities. The guideline should be written in an easy language so that healthcare workers with any level of education can easily understand the guideline and they can better inform the mothers and other lower-level health workers in both urban and rural areas in lower-income countries.

Further observational studies, including case-control or cohort studies, assessing the association of uterine rupture with using oxytocin during labor in a hospital setting controlling for any other risk factors among the mothers, would strengthen available evidence to inform policy and

practice in the maternal and newborn health arena. In addition, facility-based programs with healthcare workers and community-based programs for mothers and lower-level trained and untrained healthcare workers to increase their knowledge and awareness regarding safe and unsafe use of oxytocin during labor is crucial to ensure a safe maternal and newborn healthcare practice in lower-income countries.

4.3 STRENGTHS OF THE STUDY AND FURTHER LIMITATIONS

Literature review analysis

Our literature review includes diverse types of studies with multiple outcomes. We did not include only those studies that assessed the outcomes of injudicious use of oxytocin during labor; qualitative and quantitative studies presented widespread birth practices in rural and urban settings by different levels of providers that provided information related to oxytocin were included in this review. Even though we did not include any review study, but if we identified any review study relevant to our topic during our abstract screening phase, we checked the bibliography of those review studies for any other relevant study conducted in the South Asian context. The included studies in our review also have some limitations. Most of the studies did not specifically differentiate the route of administration of oxytocin during labor; for example: if a study reported that IV oxytocin was administered during labor, we could not differentiate if the oxytocin was administered using an IV drip infusion method (which is considered safe) or IV push injection method (which is considered unsafe). All of the rupture uterus studies reported evidence of rupture uterus cases among the mothers with a previous uterine scar, but a very few of them reported the proportion of scarred ruptured uterus cases with a history of oxytocin exposure during labor. There are studies that provided evidence of oxytocin use during labor, also provided information on monitoring of uterine contractions and fetal heart rate, but the exact frequency of assessment of uterine contractions and fetal heart rate (whether it was every thirty minutes or not, as per the recommendation) among the mothers who received oxytocin

during labor was not reported in most of the studies. If we could not retrieve specific information related to compliance to the WHO's safe labor augmentation conditions for any study that provided evidence of using oxytocin during labor, we assumed that the WHO conditions for labor augmentation were not met for that particular setting in the study.

Quantitative analysis using Nepal DHS 2016 and Nepal SPA 2015 data

Our Nepal DHS and SPA linked analysis was developed based on the assumption that a mother in a given DHS cluster who reported giving birth in a hospital would go to the nearest hospital from that cluster; this assumption is not true for all women; some women certainly may bypass the nearest government hospital. In addition, to ensure confidentiality, in the DHS spatial dataset, the location of DHS urban clusters are usually displaced up to 2 kilometers and rural clusters are displaced up to 5 kilometers, and 1% of rural clusters are usually displaced up to 10 kilometers (compared to the actual location of those clusters); the geolocation of health facilities in the SPA survey is not displaced. This displacement introduces a random error to the data. Since we did not adjust our quantitative analysis for this random error, it is highly likely that we introduced a non-differential misclassification bias in our study when we created those three categories- labor augmentation received in a 'apparently ready- for labor augmentation' hospital, labor augmentation received in a 'possibly ready-for labor augmentation' hospitals and labor augmentation received in a 'definitely not ready-for labor augmentation' hospitals. Besides, in the DHS survey, the mothers were asked if they received any 'Inj./IV medicine during labor'; throughout our analysis, we considered the Inj./IV medicine the mothers received is Oxytocin. However, since the question was asked to mothers who were attended by health workers during childbirth, the medicine would most likely be 'oxytocin'.

In our quantitative analysis, we utilized two nationally representative survey data in Nepal. DHS collects self-reported data from a large number of a randomly selected population. We restricted

our analysis within the last three years prior to the survey, utilizing data from a sample of 2330 births considering our variable of interest. The question on the administration of Inj./IV medicine during labor was asked to the mothers who were attended by health personnel; hence data on augmentation of deliveries attended by untrained births attendants, dais, traditional birth attendants, friends or relatives were not available. Additionally, our analysis utilized selective variables from both the Nepal 2016 DHS survey and Nepal 2015 SPA survey; hence in our SPA descriptive analysis, as well as in our linked analysis, our sample size was relatively smaller compared to the whole DHS sample [compared to 6148 total response in the DHS (restricted to last three years of data), the labor augmentation response was available for 2330 births; the SPA survey was conducted with only 310 post-partum mothers). A reduced sample size caused larger standard errors and wider confidence intervals for several proportions and logistic regression models in our analysis. For a wider confidence interval, we cannot say that all sample proportions that we got for our measures precisely represent the true population proportion. However, our analysis still provides reportable findings to meet the primary purpose of this study to assess the practice of using oxytocin during labor in different levels of healthcare delivery in Nepal, to document evidence on labor augmentation without following the WHO's recommendations/conditions, and thereby drawing the respective policymakers and scientific communities' attention to this issue to develop further research.

In our quantitative analysis, from the reported births in Nepal DHS 2016 survey (restricted to births over the preceding three years), we found a high proportion of labor augmentation reported for home births, primary level facility births, and government hospital births. Considerably lower rates were documented from client exit interviews from the Nepal SPA 2015 survey. The sample for the client exit interviews, however, was drawn from a limited number of facilities and the sample was small, so it is less likely to give a valid representative picture than the DHS data. In addition, the provider survey questionnaire in the SPA survey does not have

any component about their practice in regard to using Inj./IV medicine during labor.

Our linked analysis found that 50.4% of all births delivered in a 'apparently ready-for labor augmentation' hospital received Inj./IV medicine during labor (based on our assumption, a mother in a given cluster would go to the nearest govt. hospital). We categorized all the hospitals into 'apparently ready', 'possibly ready' and 'definitely not ready' to manage complications for labor augmentation based on only four measures of readiness for providing emergency cesarean delivery, making use of data elements available in the SPA survey dataset: presence of a surgeon, presence of an anesthetist, having done at least one cesarean delivery and at least one blood transfusion in an obstetric context over the previous three months of the survey. However, even just as measures of readiness to provide emergency cesarean delivery, this is not a robust set of criteria.

Having conducting at least one cesarean delivery over the past several months is no guarantee that the hospital clearly has the capacity to competently conduct cesarean deliveries. For conducting clinical procedures in hospitals, there is a volume-outcome relationship; if a volume of a clinical procedure is relatively high, then the outcome of that procedure in regard to patient safety is usually high (Levaillant, M. 2021). Hence, asking the volume of cesarean section in the last three months rather than asking only if at least a cesarean section was done would ensure credibility regarding a hospital's capacity to conduct cesarean sections.

Even in hospitals where WHO’s conditions for labor augmentation are met, having a high proportion of labor augmentation is a matter of concern. It is possible that the administration of oxytocin to augment labor is utilized as a 'crowd control' strategy to make spaces for new patients admitted to busy hospitals. A narrative review reported that unnecessary labor augmentation using oxytocin was documented in home deliveries practiced by busy local health-

workers to manage their workload/patient load per day (Jeffery, P. 2007); this injudicious practice poses a serious health risk for both mothers and babies; such practices in a homebirth setting and lower-level facility is undoubtedly dangerous and needs attention from appropriate authorities and policymakers.

4.4 CONCLUSIONS

This thesis provides evidence that labor augmentation using oxytocin is a prevalent practice in the context of South Asia, and in many cases, WHO's recommended conditions for labor augmentation to ensure safety for mothers and babies are not followed, which contributes to deadly outcomes in both mothers and fetuses. This is of particular concern in low-income countries, including countries in South Asia, and needs to be recognized as a grave problem resulting in significant preventable maternal and neonatal mortality and morbidity. Further qualitative and quantitative studies can help to better characterize the extent to which both home-based and hospital-based healthcare workers are knowledgeable about the safe practice of labor augmentation and as well as barriers to ensuring the WHO's recommendation/conditions for labor augmentation in hospital birth setting. Clear guidelines are needed in low-income country settings, explaining normal and abnormal labor, indications and contraindications for using oxytocin during labor, and the WHO's conditions/recommendations for labor augmentation.

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APPENDICES

Appendix A

STATA codes for calculating minimum distance from a DHS cluster to a SPA health facility and finding out the closest SPA facility to each DHS clusters (using the Great circle distance formula):

*__Creating a file for DHS reference clusters__

```
use "C:\Users\rafat\Documents \NPGEAFL.dta"
keep DHSCLUST LATNUM LONGNUM
rename DHSCLUST id
rename LATNUM vlat
rename LONGNUM vlong
gen vsin=sin(vlat*_pi/180)
gen vcos=cos(vlat*_pi/180)
gen dummy=1
save DHSdata_geography.dta, replace
```

*** Reading the SPA file and making it wide**

```
use "C:\Users\rafat\Documents \ NPGE71FLSR.dta"
keep spafacid latnum longnum
rename spafacid spaid
rename *num vspa*
gen vspasin=sin(vspalat*_pi/180)
gen vspacos=cos(vspalat*_pi/180)
gen dummy=1
```

*** We put all of the health facilities onto a single long line**

```
levelsof spaid, local(lspaid_codes)
rename v* v*_
reshape wide vspalat_ vspalong_ vspasin_ vspacos_, i(dummy) j(spaid)
```

*** We attach that line to each of the reference clusters**

```
joinby dummy using DHSdata_geography.dta
```

*** Then we calculate the difference in longitude between the longitudes of the reference cluster and all facilities**

```
gen cosdeltalong=.
quietly foreach lspaid of local lspaid_codes {
replace cosdeltalong=cos((vlong-vspalong_`lspaid')*_pi/180)
*Generate the distance angle (alpha)
gen
delta_angle_`lspaid'=(180/_pi)*acos(vsin*vspasin_`lspaid'+vcos*vspacos_`lspaid'*cosdeltalo
ng)
}
```

*** Now we find the minimum angle and the cluster with the minimum angle**

```
egen min_angle=rowmin(delta_angle_*)
```

*** Then we find the cluster for which that is the angle and then generate minimum distance**

```
gen nearest_spaid=.
gen nearest_spalat=.
```

```
gen nearest_spalong=.

quietly foreach lspaid of local lspaid_codes {
replace nearest_spaid  =        `lspaid' if delta_angle_`lspaid'==min_angle
replace nearest_spalat = vspalat_`lspaid' if delta_angle_`lspaid'==min_angle
replace nearest_spalong=vspalong_`lspaid' if delta_angle_`lspaid'==min_angle
}
keep id vlat vlong min_angle nearest*
order id vlat vlong nearest* min
gen min_distance=min_angle*111
```

*The factor of 111 comes from comparisons with an online calculator

* using two points at longitude 84 east, at latitudes 28 and 29 N:

https://www.nhc.noaa.gov/gccalc.shtml