A RETROSPECTIVE COHORT STUDY TO DETERMINE THE CLINICAL OUTCOMES OF NEONATES BORN TO MOTHERS ON OPIOID SUBSTITUTION THERAPY (OST) WITH METHADONE IN KENYA

A research proposal in partial fulfillment for the degree of Masters of Medicine (Paediatrics and Child Health), University of Nairobi.

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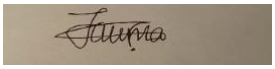
H58/11413/2018

MMED PAEDIATRICS AND CHILD HEALTH

DECLARATION

This dissertation proposal is my original work and has not been presented for the award of a degree in any other university.

Signed 

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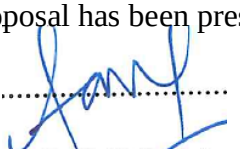
Signed..... 

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ABBREVIATIONS:

AIDS	Acquired Immuno-deficiency Syndrome
CDC	Centers for Disease Control and prevention
CNS	Central Nervous System
DOT	Directly Observed Therapy
HIV	Human Immunodeficiency Virus
JOOTRH	Jaramogi Oginga Odinga Teaching and Referral Hospital
LBW	Low Birth Weight
LTFU	Loss to follow up
MAT	Medication Assisted Treatment
MAM	Monoacetylmorphine
MNTRH	Mathari National Teaching and Referral Hospital
MOH	Ministry of Health
NASCOP	National AIDS and STI control programme
OST	Opioid Substitution Therapy
PEPFAR	President's Emergency Plan for AIDS Relief
PWID	People who inject drugs
STI's	Sexually Transmitted Infections
WHO	World Health Organization

DEFINITIONS OF TERMS:

Defaulter: – patient who has missed his/her methadone dose for five or more consecutive days but less than 30 days.

Loss to follow up / Non-compliant: - patient who has missed her dose for more than 30 days.

Neonatal death: – Death within the first 28 days of life

Opioid substitution therapy (OST)- A replacement drug (methadone, buprenorphine) offered to persons who are opioid dependent in a supervised clinical setting (WHO, 2011)

ABSTRACT:

Background: Heroin addiction is a universal encumbrance. Currently in Kenya, the estimate of heroin users is between 18,000 to 33,000. The use of heroin during pregnancy has been associated with high incidence of prematurity, low birth weight, higher number of neonates born experiencing Neonatal Abstinence Syndrome (NAS) and neonatal mortality. Globally, there has been marked improvement in the neonatal outcomes since the introduction of methadone as a gold standard treatment of heroin addiction.

Objective: To determine the clinical outcomes of neonates born to mothers on Opioid Substitution Therapy (OST) with methadone in Kenya.

Utility: This is the first program evaluation of the newborn outcomes among babies of women on OST with methadone in Kenya and will form the basis for future program planning and improvement of the current case-management plans.

Methodology:

This was a retrospective cohort study. It was a countrywide multicenter study carried out at six of the largest Medication assisted treatment (MAT) clinics in Kenya. The study population was mothers on opioid substitution therapy (OST) with methadone and their neonates born in the period 1st January 2015 to 31st December 2019.

Data collection: A predesigned stratified data collection tool was used in collecting relevant data in files of women who met the inclusion criteria. There was no sampling done due to the limited number of infants born in this programme. Data obtained from study population through data collection forms were checked for completeness and accuracy and entered into a password protected database.

Data analysis: The data collected was entered into a Microsoft Excel spreadsheet, cleaned and transferred to STATA version 11.2 for analysis. Descriptive statistics of the study population were summarized as medians and ranges for continuous data and proportions

computed for categorical variables. Proportions were used as estimates of the prevalence of LBW. NAS and neonatal mortality.

For the secondary objectives, logistic regression analysis was conducted in order to test the factors associated with the three main outcome variables i.e LBW, NAS and neonatal mortality.

Univariable and multivariate logistic regression analysis was carried out to determine the independent predictors of LBW. NAS and neonatal mortality. A p-value of 0.20 was used for the univariate analysis to determine the variables to be included in the multivariable model where their associations with the odds of the outcomes were tested at a 5% significance level.

Two way interactions between the variables in the final model were fitted and their significance assessed.The Hosmer-lemeshow goodness of fit was computed in order to assess how well the model fit the data with a p-value>0.05 indicating a well fitting model.

Results: A total of 81 mother infant pairs were included in the study. The median age of the mothers was 31years, 95.1% had some formal education and 80.3% were unemployed. All the women on OST were previous heroin users. The other most commonly used drug in this population of women was cannabis at 87.7%. Overall, 39.7 of the babies were low birth weight (LBW) and median birthweight was 2550g.The maternal factors associated with LBW included history of heroin IVDU (p=0.004, AOR=5.7) and heroin used during pregnancy (p=0.002, AOR=37.05). Overall, 35% of neonates developed NAS. Maternal use of benzodiazepines was associated with a significantly reduced risk of NAS (p=0.045, AOR=0.97,95%CI = 0.10-0.97). Overall, 8.7% of the babies died. Death was significantly associated with methadone dose (p=0.031, AOR=0.97) and cocaine use (p=0.007, AOR =12.85).

Conclusion: The outcomes of neonates born to mothers on OST was poor. There was a high number of LBW neonates,1 in 3 babies developed NAS and 1 in 10 babies died.

CHAPTER 1. INTRODUCTION AND LITERATURE REVIEW

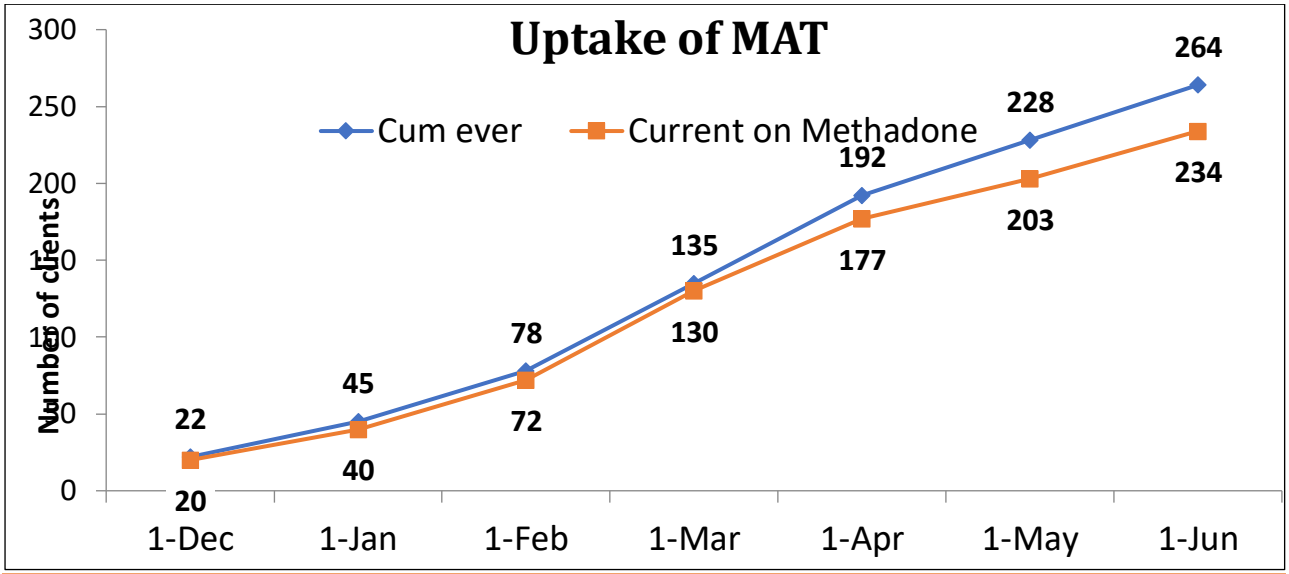
1.1 Background

Heroin addiction has been a burden in Kenya over the past 3 decades. In Africa, approximately 680,000 to 2.9 million people are using opiates (1).In Kenya, the prevalence of opiate users is at 0.7% of the total population. The highest number of users is in the age group between 15 to 64 years.(2)

1.1.1Opioid Substitution Therapy (OST) with methadone in Kenya

The Opioid Substitution Therapy **(**OST) with methadone programme was initiated in Kenya in 2014.It was funded by the Center of Disease Control programme (CDC) in partnership with a Ministry of Health (MOH) programme, National AIDS and STI control programme (NASCOP) as a harm reduction strategy in the population with heroin addiction(3).

Currently there are seven centers that offer OST with methadone under the Medication Assisted Treatment (MAT) clinics in Kenya. These include Mathari National Teaching and Referral Hospital (MNRTH), Jaramogi Oginga Odinga Teaching and Referral Hospital (JOOTRH), Ngara Health Center, Kisauni Health Center, Kombani Kwale Health Center, Malindi sub county hospital and Karuri Health Center MAT clinics. The program aims to achieve the best outcome if methadone is taken daily for at least 2 years (4). The introduction of OST with methadone in Kenya has shown overall improvement in survival, reduction of crime rates, social functioning and ultimately birth outcomes. This study is evaluating the impact of this program on perinatally methadone exposed newborns.



- 49(19%) females
- MMT dose; 58mg (Range 15mg - 170mg).

FIGURE1: Uptake of Medication Assisted Treatment (MAT) services in 2015 (1)

1.1.2 Heroin

The mechanism of heroin entry into the body includes smoking, snorting and injecting(5). It is distributed faster to the brain when injected or smoked and the effects last longer(5). Heroin is broken down to monoacetylmorphine (MAM), a potent Mu receptor agonist acing in the central nervous system (CNS)(6). There is agonistic action on the central nervous system opioid receptors Mu, kappa and delta. Mu receptor activation leads to respiratory depression, analgesia, miosis, reduced gastrointestinal motility, physiologic dependence and euphoria(6). Heroin use during pregnancy has effects on the foetus that include neonatal abstinence syndrome (NAS), deficits in cognitive and motor ability, lower IQ, heart defects, respiratory insufficiency and reported higher rates of low birth weight and prematurity (7).

1.1.3 Burden of Heroin

There is evidence of drug abuse through the injection route in 179 countries in the world as of 2018. Of these, only 86 are offering OST. Coverage of OST in sub-Saharan Africa as of 2017 was found in 36 of the 54 countries and reaching approximately 645,000 to 3 million people. It remains unavailable in most countries(8). The below representation of global availability of OST in the community and prison shows Kenya as being amongst the few countries where OST with methadone is available at both the community and prisons.

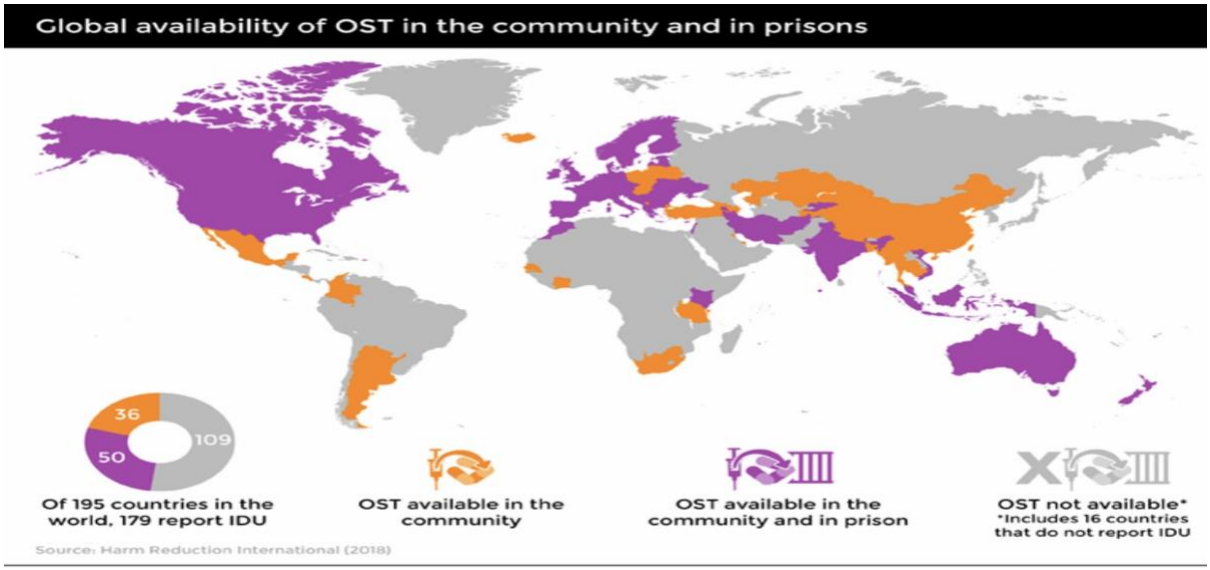


Figure 2. Global availability of OST in the community and prisons. Harm reduction International 2018 (9)

1.2 Effects of Opioid use on birthweight

The majority of females who use intravenous heroin are in the reproductive age group. The use of heroin during pregnancy has shown an association with a decrease in the birth weight and a higher rate of low birth weight(10).Hulse G K *et al* did a meta-analysis of 18 studies done between 1966 and 1996 and found a median of 489g decrease in birthweight in infants born to females on heroin alone by 489g, and 279g (229-328g) in infants born to mothers on

methadone. In those who used methadone and heroin concomitantly during pregnancy, the mean decline in birthweight was 557g (403-710g) and 395g (311-478) for those whose mothers were on methadone with or without the use of heroin during the pregnancy. There was a direct relationship observed between the dose of methadone used by the mother in the first trimester and infant's birthweight; the higher the methadone dose the larger the infant. However, the use of heroin while on methadone treatment may counteract the birthweight advantage observed when only methadone is used(10).

A five-year prospective study on perinatal addiction outcome and management was carried out on 278 women who depended on drugs who delivered at the Philadelphia general hospital. Mothers who were drug dependent and received no antenatal care had a significantly higher prevalence of low birth weight at 47.6% than only 18.8% among new born babies of women with previous intensive counselling and good antenatal care($P<0.001$). In the same study the prevalence of LBW was 20% among newborn babies of women who were both non-drug users and did not have antenatal care. The babies who were born to mothers who were on methadone with intensive care and good antenatal care follow up had a lower occurrence of low birth weight similar to babies born to mothers not addicted with good antenatal care and follow up. Low birthweight among drug users maybe due to the use of the drug itself but also other attendant factors among them poor antenatal follow up, poor maternal nutrition and concurrent infections. Improvement in maternal care, maternal nutrition, antenatal care follow up and management of infections is associated with stability in methadone treatment hence the likelihood of better birth outcomes in terms of birthweight(6).

A retrospective study of174 females abusing narcotics being followed up in drug dependency antenatal clinics found that most of them were enrolled in methadone programs and were followed up prior to the third trimesters of pregnancy (11).The adherence to methadone declined as pregnancy advanced, 35% highest in pre pregnancy and first trimester, 32% and 24% in the second and third trimester respectively. There was no methadone use in 9%. In this

cohort, 49% continued abusing heroin despite stabilization. Similar to other studies the mean birthweight for heroin users was 500grams lower than that of the methadone users, 2746g (±721g mean SD) versus 3224g (±681 mean SD) ($p<0.0001$). The mean gestational age of delivery in heroin users (37.1± 3.4 weeks mean ±SD) and for methadone users (39 ±2.7 weeks; mean ±SD.) There were 3 neonates who died and 5 born as stillbirths hence the perinatal mortality rate was at 43/1,000(11). The perinatal mortality rate in USA in this year of study was 10/1000. This study unveiled the need for improvement in birth outcomes (birthweight) through management with methadone as low birth weight is associated with neonatal mortality. The increasing use of heroin in females in the prime of their child bearing age is associated with higher numbers of undersized neonates with greater problems associated with low birth weight (LBW)11

1.3 Neonatal Abstinence Syndrome (NAS)

Neonatal Abstinence Syndrome **(**NAS) results from abrupt disruption of the foetus being exposed to substances abused by the mother in the course of pregnancy(12). Exposure to methadone and heroin in the course of pregnancy predisposes to the risk of Neonatal abstinence syndrome which is associated with systemic and autonomic nervous system dysfunction that often needs medication and longer hospital stay(13) .The onset of withdrawal symptoms is dependent on the half-life of the drug, the amount of time the user has been abusing the drug and the last dose the mother had before delivery. For heroin, the inception of withdrawal symptoms begins from 24 to 36 hours. It can delay for up to five to seven days(14).NAS withdrawal symptoms due to maternal opiate use is present in 40 to 90% of all infants exposed antenatally. Opioid withdrawal in neonates is characterized by CNS and autonomic presentation like hypertonia, high pitched cry, nasal congestion, failure to thrive, diarrhea, temperature variability, poor feeding, tremors, and hyperirritability (14).

A year long case control study on Neonatal abstinence syndrome (NAS) following maternal treatment with methadone recruited 32 infants exposed to maternal methadone treatment and 32 control never exposed to methadone (15)The median gestational age (40 weeks) and birthweight (2830g) was lower compared to the control cohort. Twelve (37%) developed NAS and were treated for the symptoms with median hospitalization of 8 days. For the infants who did not receive medical therapy, the average hospital admission was 4 days, ranging between 2 to 9 days which was longer than the control group that was 3 days, range of 1-7 days ($p<0.05$). There was no dissimilarity in the occurrence of NAS in babies of mothers who were taking a low methadone dose (<20mg) compared to those taking a higher dose (>20mg) (15)

There are newer safer drugs for OST. A retrospective cohort study was carried on 609 pregnant women dependent on opioids being treated with methadone and buprenorphine.They found that infants born to both cohorts developed neonatal abstinence syndrome (NAS). The infants exposed to buprenorphine needed medication fewer times and for a lesser period when compared to the methadone group. This study revealed that regardless of the opioid substitution treatment used, infants are prone to develop NAS(16) .

A multi-centre double-blind randomized control study to compare buprenorphine and methadone use as OST was carried out. One seventy-five pregnant women were recruited. Sixteen (18%) of 89 taking methadone and 28 (33%) of 86 taking buprenorphine were terminated. Out of the 131 neonates (73 methadone and 58 buprenorphine exposed) were included in the neonatal outcome evaluation. Neonates exposed to buprenorphine required less morphine to manage the NAS compared to those on methadone mean dose of 1.1mg compared to 10.4 mg, and had a shorter duration of hospital admission of 10 days as compared to 17.5 days. The number of days of therapy in methadone exposed neonates was longer at an average of 9.9 days compared to buprenorphine exposed at 4.1 days. The prevalence of NAS was similar in the 2 groups ($p=0.26$).These findings showed that buprenorphine can be used as a substitute to methadone for the management of opioid dependence in the course of pregnancy

as it has an added advantage in reducing severity of NAS although issues of lower adherence rates should be considered(17).

In Stony Brook University, New York, a retrospective cohort study was carried out in 2019 to compare the outcomes of pregnancy amongst women on methadone and buprenorphine in MAT clinic. Neonates excluded in the study were those less than 24weeks at delivery, known anomalous fetus and multiple gestation. A total of 314 women were recruited, 136 (43.3%) on buprenorphine and 178 (56.7%) on methadone. Both groups had the same incidence of NASbut the premature delivery rate was higher with methadone exposed with 35/178 (19.7%) neonates compared to 14/136 (10.3%) on buprenorphine ($p<0.01$). The methadone exposed neonates mean birthweight was 2815 ± 570g and buprenorphine 3167± 558g ($p<0.01$). There was need for treatment for withdrawal symptoms in 82 (46.1%) neonates who were methadone exposed versus 36 (26.3%) neonates exposed to buprenorphine. The duration of hospital stay with methadone was 11.2 days and buprenorphine 9.7 days. MAT use of buprenorphine is favorable in terms of higher birthweights, fewer preterm deliveries, reduced need for NAS management with morphine and shorter hospital stay(18)

Withdrawal symptoms will vary depending on the kind of opioid used, dose, how many times a day its used, gestational age and maternal metabolism. An estimated 50 to 70% of neonates born to mothers who are opioid dependent require treatment for withdrawal symptoms (19). Preterm infants have a reduced probability of withdrawal symptoms and NAS is not as severe as compared to term infants(20).This is due to shorter exposure of the drug in utero, immaturity of the liver and kidneys hence unable to fully excrete the drug, reduced placental transmission, minimal fat storage hence less deposition of opioids and inability of the CNS to express NAS symptoms due to immaturity of the brain(14)

1.3.1 Standardization of Diagnosis of NAS

The Finnegan scoring system is an international NAS scoring protocol. It is commonly used in scoring the severity of the disease. Scoring is essential for initiation, monitoring and termination of treatment of neonates. A score is made within three hours of life, and repeated every three to four hours, with on-demand feeding and care. The criteria that is used for scoring is illustrated in table 1.

Table 1. Modified Finnegan Scoring System(21)

Finnegan Scoring System

System	Symptoms	Points	Score		
Central Nervous System	Excessive high pitched (or other) cry (< 5 min) Continuous high pitched (or other) cry (> 5 min)	2 3			
	Sleep < 1 hour after feeding Sleep < 2 hours after feeding Sleep < 3 hours after feeding	3 2 1			
	Hyperactive Moro reflex Moderately hyperactive Moro reflex	2 3			
	Mild tremors when disturbed Moderate-severe tremors when disturbed	1 2			
	Mild tremors when undisturbed Moderate-severe tremors when undisturbed	3 4			
	Increased muscle tone	1			
	Excoriation (eg. Chin, knees, elbows, toes, nose)	1			
	Myclonic jerks (twitching/jerking of limbs)	3			
	Generalized convulsions	5			
Metabolism Vasomotor Respiratory	Sweating	1			
	Hyperthermia (37.2 – 38.2°C) Hyperthermia (≥ 38.4°C)	1 2			
	Frequent yawning (>3-4/interval)	1			
	Molting	1			
	Nasal stuffiness	1			
	Frequent sneezing (> 3-4/interval)	1			
	Nasal flaring	2			
	Respiratory rate > 60/min Respiratory rate > 60/min with retractions	1 2			
Gastro-intestinal	Excessive sucking	1			
	Poor feeding (infrequent/uncoordinated suck)	2			
	Regurgitation (≥2 times during/past feed) Projectile vomiting	2 3			
	Loose stool Watery stool	2 3			
	TOTAL SCORE				

Babies are not woken up to score. The Finnegan scoring system is modelled for use on term infants and allowances should be made for preterm infants(15)

Non pharmacological interventions of NAS includes swaddling, swaying, negligible sensory and environmental stimulation (quiet environment and low light), maintenance of temperature stability, feeding and breastmilk feeding can aid in reducing the need for pharmacologic involvement.(22).Pharmacologic intervention begins when a baby has three consecutive

Finnegan scores of greater or equal to eight or when the average of two scores or two consecutive scores is greater than twelve. Morphine is the drug of choice and mainstay of management(22)

1.4 Neonatal Mortality

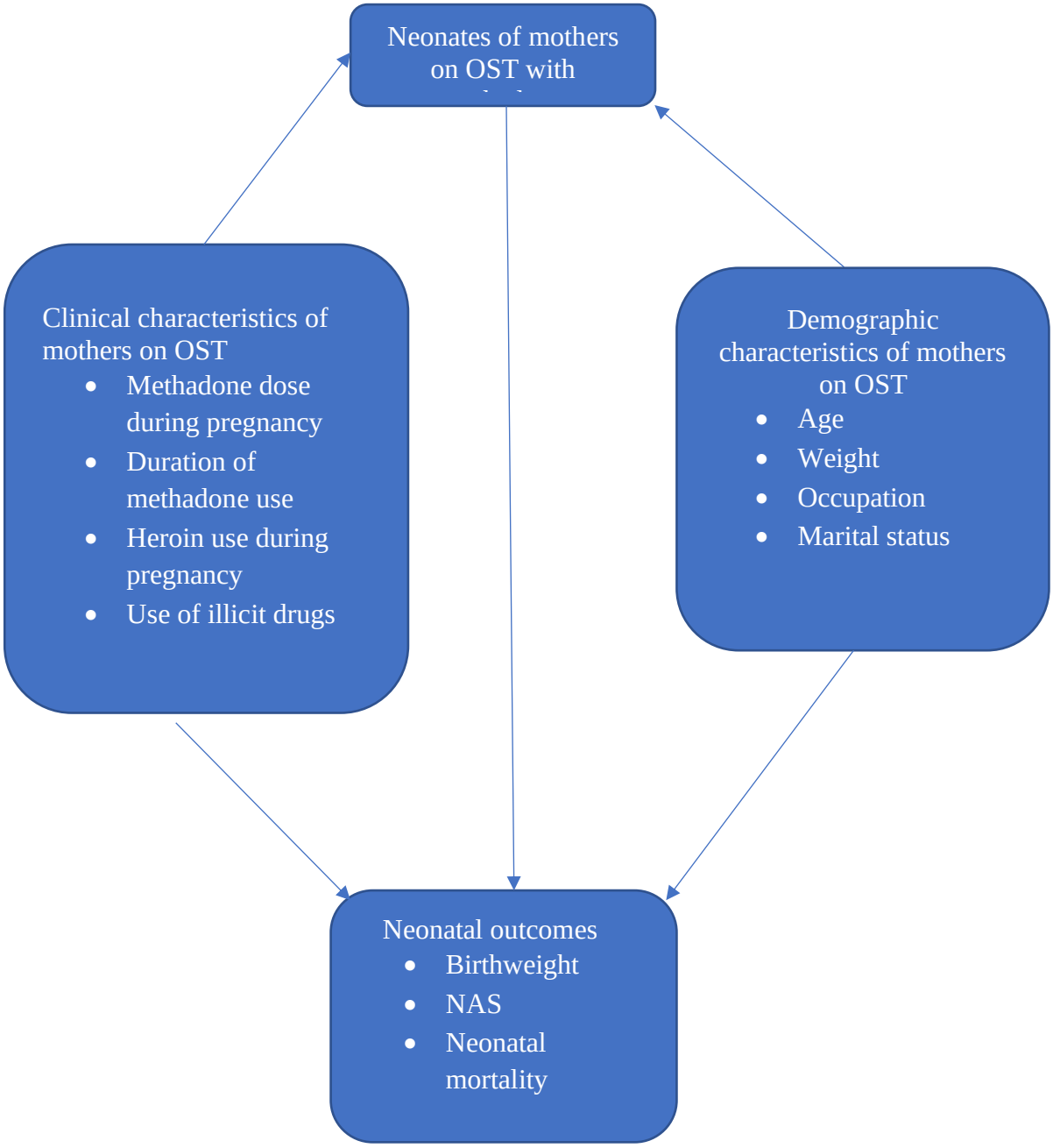
There is a higher chance of neonatal mortality when heroin and methadone are used together during pregnancy compared to the use of methadone alone. This might be due to high risk behavior implicated with heroin use(23).A sequential retrospective cohort study was done in Western Australia by Hulse G *et al* on women on treatment for opioid dependence with methadone, buprenorphine and naltrexone to assess birth outcomes between 2001 and 2011. The study showed that exposure to methadone prenatally was associated with high prevalence of mortality (2 versus 0.2/100 livebirths) and more congenital anomalies (10.6 versus 4.4 per 100 livebirths) when compared to a control group. The rate of neonatal mortality and congenital anomalies in buprenorphine and naltrexone group showed no difference from the control.(24)

TABLE 2. SUMMARY OF LITERATURE REVIEW

TITLE	STUDY DESIGN	STUDY POPULATION	RESULT (PUBLISHER)
Differential effects of maternal heroin and methadone use on birthweight. (Bronx, NYC .1976)	Retrospective cohort study	337 infants in relation to history of maternal heroin and methadone usage	LBW noted in babies born to mothers abusing heroin. Higher birthweight noted in mothers on methadone treatment. (Stephen R. Kandall, susan Albin, et al.)
Relationship between maternal use of heroin and methadone and infant birth weight (Western Australia, Nov. 2006)	Metanalysis	Papers indexed in the database from 1966 to July 1996 were identified using heroin, opiate, methadone, substance abuse,fetal development, pregnancy complications ,neonatal diseases and abnormalities ,infant-newborn ,birthweight and all subheadings	Relative risk of LBW in heroin users was higher than methadone users. Heroin use while on methadone may counteract the birthweight advantage gained from methadone alone. (Hulse GK, Milne E, English DR, Holman CD)
Effects of buprenorphine, methadone and heroin on the course of pregnancy and BW of newborns (Czech Republic ,2002-2007)	Prospective randomized comparative study	117 mothers and their infants .47 on heroin, 32 on methadone and 38 on buprenorphine.	LBW, highest number IUGR in heroin addicted women. (Tomas Binder, Blanka Varrinoka)
Predictors of neonatal outcomes amongst methadone and or heroin dependent population (Sydney, Australia. April 2013	Retrospective cohort study	183 opioid using pregnant women. 107 used methadone only,61 used methadone and	No difference in the frequency of LBW neonates or the rate of prematurity between methadone only, methadone and heroin and heroin only groups.

		heroin and 15 used heroin only.	(Victoria Buckley, Abdalvahed Razaghi, Paul Haber)
Low birth weight of infants associated with maternal heroin use (New York City,1966-1967)	Retrospective cohort study	706 infants born to mothers on heroin.	Increasing use of heroin by women in their prime child bearing years is also producing excess of undersized infants with all the problems associated with LBW. (S. Bumenthal, L. Bergner. F.Nelson)
A retrospective cohort study of birth outcomes in neonates exposed to naltrexone in utero: A comparison with methadone, buprenorphine and non- opioid exposed neonates. (Western Australia,2017)	Retrospective cohort study	68 naltrexone-exposed, 199 methadone-exposed, 124 buprenorphine-exposed and 569 non-opioid-exposed neonates	Exposure of methadone prenatally was associated with high incidence of mortality.(Kelty E, Hulse GK)

FIGURE 3: CONCEPTUAL FRAMEWORK



1.5 Study Justification and Utility

Heroin use has been a menace with lack of proper intervention before the initiation of MAT clinics. Majority of the women in the OST program using methadone are within child bearing age hence clinical outcomes of babies born while in the program is of utmost importance to guide in their intervention and management. With the foundation of life being nurtured during infancy, assessment of infants born to this cohort is of great importance. Previous studies carried out in the West show the effect of heroin and methadone use during pregnancy having adverse outcomes in gestation and delivery dates, birthweight and increased prevalence of NAS. There is paucity of studies on clinical outcomes of neonates born to mothers on methadone in Africa and in Kenya which informs the need for this study. Data obtained from this study will identify the gaps in interventions that will help improve neonatal outcomes of neonates born to mothers on methadone. My findings will serve as a reference point and provide baseline data for future interventions and further studies.

CHAPTER 2. RESEARCH QUESTION AND STUDY OBJECTIVES

Research questions

- What are the clinical outcomes of neonates born to mothers on Opioid Substitution Therapy (OST) with methadone in Kenya?
- Which sociodemographic and clinical characteristics of the mothers are associated with the clinical outcomes of neonates born to mothers on OST with methadone in Kenya?

Primary Objectives

To determine the clinical outcomes of neonates born to mothers on Opioid Substitution Therapy (OST) with methadone in Kenya.

Secondary objectives

I. To describe Sociodemographic and clinical characteristics of mothers on Opioid Substitution Therapy (OST) with methadone and their neonates.

II. To determine an association between birthweight, Neonatal Abstinence Syndrome (NAS) and neonatal death and maternal dose of methadone, maternal duration of methadone use, maternal duration of heroin use, heroin use during pregnancy and use of other illicit drugs.

CHAPTER 3. RESEARCH METHODOLOGY

3.1Study Design

This was a retrospective cohort study.

3.2. Study Population

The Study population was neonates and their mothers on OST with methadone.

3.3. Study Location

The study was a countrywide multicenter study carried out in six Medication assisted treatment (MAT) clinics in Kenya. Mathari National Teaching and Referral hospital (MNTRH), Jaramogi Oginga Odinga teaching and referral hospital (JOOTRH), Malindi sub county hospital, Ngara Health Center, Kisauni Health Center and Kombani Kwale MAT clinics. The technical and financial support of these clinics is from the President's Emergency Plan for AIDS Relief (PEPFAR). These are outpatient facilities that cater for patients who inject drugs (PWID) and have accepted to use Opioid Substitution Therapy (OST) with methadone. They come for a daily dose of methadone between 6am and 3 pm. The clinics run all week to cater for the need of the patients and because methadone is to be received daily for better outcomes. These are one stop shop centers. They cater for the management of comorbidities e.g., those on antiTBs and ARVs are given their medication concomitantly with their daily methadone dose. The patients are managed for any other illnesses as the clinics have medical staff who see sick patients on a daily basis. These are directly observed therapy (DOT) clinics. Expectant females are closely followed up at the facility and reminded to take their supplements and given priority doctor's appointments. The clinics are run by a consultant who supervise the running of the facilities. Under them are medical officers, clinical officers, nurses, social workers, psychologists, counsellors and support staff. There is a standardized case record used in all these clinics. I worked as a medical officer for 2 years in one of the MAT clinics before enrollment to the paediatrics masters program.

3.4. Study period

I reviewed records in the various MAT facilities between 1st January 2015 to 31st December 2019.

3.5. Inclusion Criteria

Each patient fulfilled the criteria below so as to be included.

- Neonates born to mothers on OST with methadone at various MAT clinics.

3.6. Exclusion Criteria

Patients who fit the below were excluded from this study.

- Mothers on heroin not in the MAT program.

3.7. Sample Size Determination

Due to the limited number of infants born to mothers in the MAT programme countrywide, I included all eligible infants in my study.

3.8. Patient recruitment procedure

A waiver of consent was obtained from the UON-ERC in order to study potential medical records. In the various MAT facilities ,I introduced the research assistant and provided a copy of the approval letter from UON-ERC,county ministry of health approvals and administration permission. Potential study participants were identified from the MAT clinic database between 1st January 2015 and 31st December 2019. Information obtained included maternal sociodemographic, clinical characteristics and neonatal outcomes. Information obtained was used to retrieve files for perusal for suitability of the inclusion criteria. Files of mothers on OST who delivered while on the programme were used for data abstraction. The records retrieved were reviewed only by the principal investigator and a trained research assistant. Each eligible record during the study period had a study serial number allocated. In case of a missing file,

the said file was skipped and the study serial number was allocated to the next file. There was no sampling done due to the limited number of infants born in this programme. The data was then abstracted into a standard data collection tool (Appendix III). The data collection tool contained abstracted information from the medical records. The medical records was kept in a locked cabinet at the discretion of the researcher alone until the collection of data was finished and then sent back to the records office. A computer with passwords was only accessible by the research team. In case of an active file, I ensured that there were no interruption of service by collecting the data myself and keeping the medical file in the current service where the patient was. After completion of data collection, the database was cleaned of serial study numbers and medical file allocation to be left with abstracted data.

3.9. Data Collection

Following identification of the study participants and waiver of informed consent obtained, a predesigned stratified data collection tool was used in collecting relevant data. It will be able to capture patient's sociodemographic and clinical characteristics which include duration of heroin use, duration in the MAT program, dose of methadone, abuse of other narcotics, compliance status and neonatal outcome information e.g., birth status, birth weight and NAS. The files were retrieved from the medical records department starting with the most recent patients who delivered going backwards that met the inclusion criteria.

3.10. Data Management and Analysis

After ensuring that the questionnaires were complete and properly filled in, the data collected was entered into a Microsoft Excel spreadsheet, cleaned and transferred to STATA version 11.2 for analysis.

The overall descriptive statistics of the study population was summarized in tables.Median values and their IQ ranges were computed for the maternal age and weight, number of previous deliveries, duration of heroin use, methadone dose given prior to delivery, treatment duration and the number of missed doses. Proportions were computed for categorical variables such as marital status, occupation, educational level, parity, history of abortion, mode and place of delivery, pregnancy outcome, presence and treatment of chronic illnesses and use of illicit drugs. The proportions of neonates who had low birth weight (LBW), Neonatal Abstinence Syndrome (NAS) and neonatal mortality were computed and used as estimates for the prevalence of these three conditions in the target population.

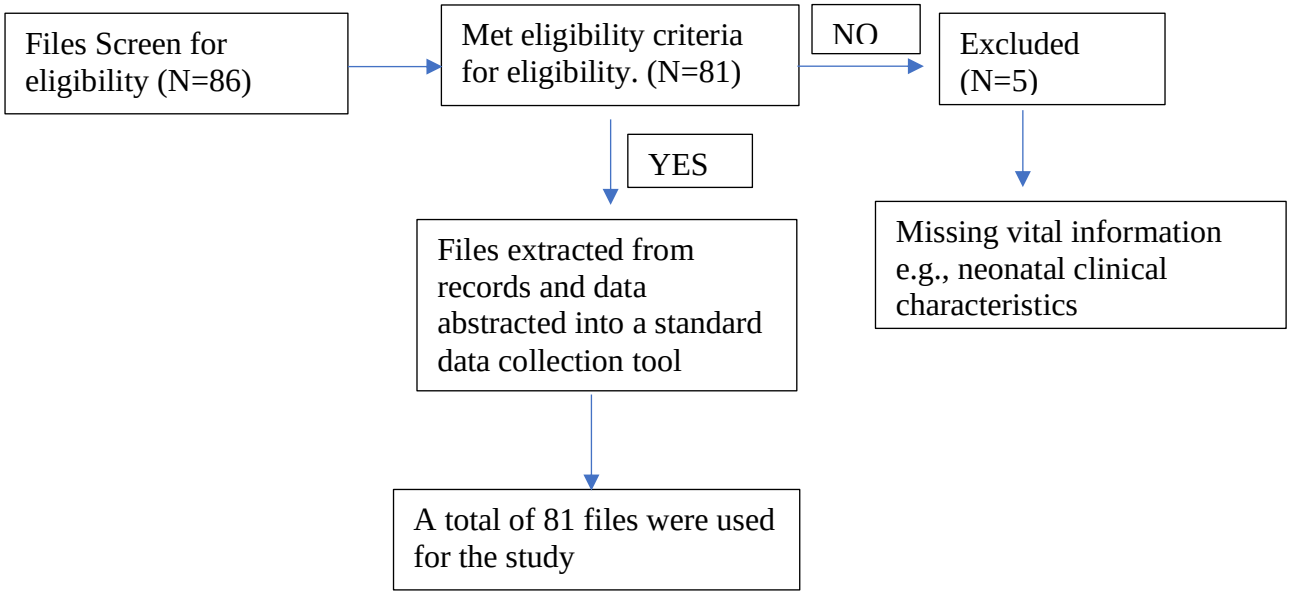
Logistic regression analysis was conducted in order to test the factors associated with the three main outcome variables i.e LBW, NAS and neonatal mortality. Univariable logistic regression analysis between each predictor variable and each outcome of interest was conducted at a liberal p-value of 0.20 (Dohoo et al., 2012). The variables with a p-value <0.20 were added to the multivariable model where their associations with the odds of the outcomes were tested at a 5% significance level. Non-significant variables were eliminated from the multivariable model if they did not result in >30% change in the coefficient of the significant variables (Dohoo et al., 2012). Two way interactions between the variables in the final model were fitted and their significance assessed.The Hosmer-lemeshow goodness of fit was computed in order to assess how well the model fit the data with a p-value>0.05 indicating a well fitting model.

3.11. Ethical considerations

- I sought ethical approval from University of Nairobi and Medication assisted therapy clinics. Authorization was obtained from the various counties health administrations.
- There was confidentiality through security of patient's information by serialization of subject's identity.
- Justice through Adjudication of fairness to subjects in the study was ensured.
- Beneficence in that information obtained will be shared with the various facilities.
- No harm was done to the study participants as this was a retrospective study with no contact or involvement in the patient's health.

CHAPTER 4: RESULTS

FIGURE 4: SCREENING AND ENROLMENT



A total number of 81 women were enrolled in the retrospective cohort study. Among them, 47 (58%) were from coastal region. Nairobi county had 31(34.4%) and Kisumu county 3 (3.7%).

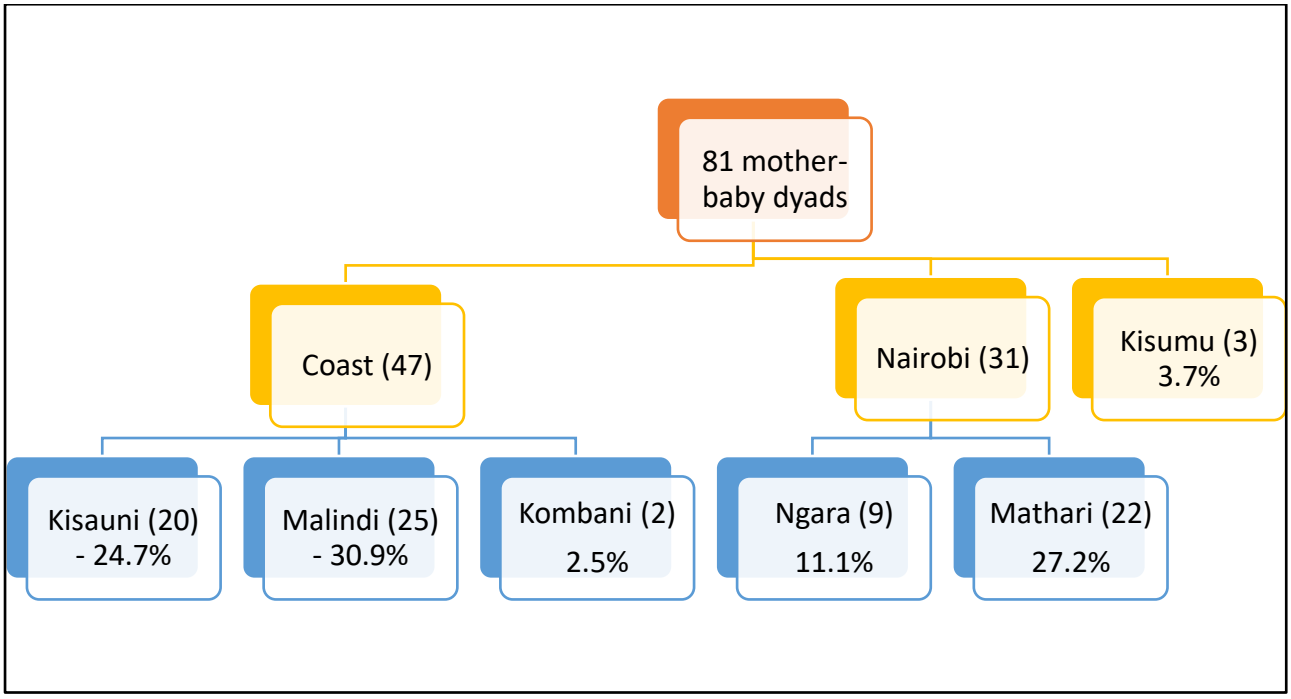


Figure 5: Countrywide distribution of the mother-baby dyads

4.1 SOCIODEMOGRAPHIC AND CLINICAL CHARACTERISTICS OF MOTHERS ON OPIOID SUBSTITUTION THERAPY (OST)

Sociodemographic characteristics: The average maternal age was 30.1 (median 31; range: 20-48) years with the mean recorded weight at the time of delivery being 57.03 (median 54; range: 31-96) kg. Majority study participants 57 (70.4%) were married. While 77(95%) mothers reported to have some form of formal education, only 16 (20%) were in a form of employment. Most of the women, 45(55.6%) had primary level of education and out of the 20% in employment, 14(17.3%) had blue collar jobs and only 2(2.5%) had white collar jobs.

Pregnancy and delivery characteristics: Roughly 3/5 of the mothers were multiparous with an average of 2 successful deliveries (median 2; range: 1-7) births. Only 5 (6.2%) had a history of abortions. Majority of mothers 77 (95.1%) delivered in a health facility via SVD 73(90.12%).

Clinical characteristics: Total number of women with chronic illness were 57 among them 18 (22%) with HIV, and one each with hypertension, tuberculosis, mental illness, asthma, Hepatitis C Virus (HCV) and Peptic ulcer disease (PUD). None of the mothers had diabetes or cancer. While 24 (29.6%) had a form of chronic illness, a slightly lower proportion of 20 (24.7%) mothers were on medication.

Substance use

Heroin-The mothers in this study had used heroin for a mean of 7.36 (median 6; range: 1-22) years. Only 26 (32.1%) had a positive history of heroin use during pregnancy, for an average of 4.2 (median 2.5; range: 1-9) months. Forty-three (53.1%) mothers were IV heroin drug users.

Cannabis and tobacco – the most abused drugs in this population were cannabis and tobacco. A big proportion of 71 (87.7%) and 65 (80.3%) reported to be using cannabis and tobacco respectively.

Other drugs -Fifty-two (64.2%) and 48(59.3%) were users of benzodiazepines and alcohol respectively. Only 20(24.6%) and 15 (18.5%) of the mothers reported that they were using amphetamines and cocaine respectively.

Opioid substitution therapy: On average, the mothers had been on OST for 22 (median 20; range: 1-60) months and were receiving an average of 97.16 (median 90; range: 10-245) mg of methadone just before delivery. Each mother had missed an average of 2.5 OST doses

TABLE 3. MATERNAL DESCRIPTIVE STATISTICS, n =81

Variable	Frequency n (%)/median (IQR
Age	31 (7.0)
Weight (kg)	54.0(13.5)
Marital status	
Married	57 (70.4)
Single	19 (23.5)
Separated	5 (6.2)
Occupation	
Unemployed	65 (80.3)
Blue collar	14 (17.3)
White collar	2 (2.5)
Level of education	
No formal	4 (4.9)
Primary	45 (55.6)
Secondary	28 (34.6)
Tertiary	4 (4.9)
Number of deliveries	2(2)
Parity	
Uniparous	32 (39.5)
Multiparous	49 (60.5)
History of abortion	5 (6.2)
Facility of birth	77 (95.1)
Mode of delivery	
SVD	73 (90.1)
CS	8 (9.9)
Pregnancy outcome	
Live	80 (98.8)
Still	1 (1.2)
Presence of chronic illness	57 (70.4)

HIV	18 (22.2)
Diabetes	0(0)
Hypertension	1 (1.2)
Tuberculosis	1 (1.3)
Mental illness	1 (1.2)
Malignancy	0(0)
Asthma	1 (1.2)
HCV	1 (1.2)
PUD	1 (1.2)
On medication for chronic illness	20 (24.7)
Overall duration of heroin use (years)1-22	6(7)
Heroin use in pregnancy	26 (32.1)
Duration of heroin use in pregnancy (months) 1-9	2.5
IVDU	43 (53.1)
Cannabis	71 (87.7)
Tobacco	65(80.3)
Benzodiazepines	52 (64.2)
Alcohol	48 (59.3)
Amphetamines	20 (24.7)
cocaine	15 (18.5)
Methadone dosage before delivery (mg)10 245mg	90(70)
Duration of OST/treatment (months)1-60	20(22)
Missed OST doses 0-56	2(1)

4.2 CLINICAL OUTCOMES OF NEONATES BORN TO MOTHERS ON OPIOID SUBSTITUTION THERAPY WITH METHADONE

Gestational age and birthweight: The median gestational age of the neonates was 39 (range: 20-42) weeks while the mean birthweight was 2585.77 (median 2550; range: 500-5000) grams. Roughly two-fifths (39.7%) of the neonates had low birth weight and of this, seven (22.6%) had very low birth weight (<1500g).

Hospital stay: The babies born to mothers on OST with methadone during the study period stayed in hospital for an average of 8.7 (median: 3; range: 0-56) days.

Neonatal conditions: Although the majority (87.65%) were born without any neonatal condition, five (6.2%) and three (3.7%) developed respiratory distress syndrome (RDS) and neonatal sepsis (NNS) respectively. Only one (1.2%) neonate presented with congenital anomalies and 1 (1.2%) with perinatal asphyxia.

Neonatal abstinence syndrome (NAS): Withdrawal symptoms were recorded in 28 (35%) of the neonates with a similar proportion having Neonatal Abstinence Syndrome (NAS). Only 17 (21.25%) done some form of pharmacologic intervention given.

Neonatal mortality: Seven (8.64%) of the infants died within the first 14 days of life. The average time to death was 5.6 (median: 5, range: 1-14) days.

Table 4: Neonatal Descriptive Statistics, N=81

Variable	Frequency n (%) Median (IQR)
Gestation (weeks) 20-42	39(4)
Birthweight (500-5000g)	2550(1200)
Birthweight categories <1500 ≥1500 but <2500 ≥2500 (Normal)	 7 (8.97) 24 (30.77) 47 (60.26)
Withdrawal symptoms	28 (35)
NAS	28 (35)

Neonatal death	7 (8.7)
Duration before neonatal death (1-14days)	5(11)
Neonatal condition RDS NNS Congenital anomalies	 5 (6.2) 3 (3.7) 1 (1.2)
asphyxia	1(1.2)
Pharmacologic intervention	17 (21.2)
Duration of hospital stay (0-56 days)	3(6)

4.3 FACTORS ASSOCIATED WITH LOW BIRTH WEIGHT

RESULTS FROM THE UNIVARIABLE ANALYSIS (P < 0.20)

From the univariable analysis, methadone dose was associated with increased odds of LBW. For every unit increase in methadone use the odds of LBW was OR=1.0 (95% CI 1.0,1.02), p=0.047. There were 18 (38.3%) of 47 mothers of babies with normal weight who reported heroin use during pregnancy compared to 7 (22.5%) of 31 mother of LBW infants. Mothers of LBW were significantly less likely to report heroin use during pregnancy OR = 0.47 (95CI 0.17, 1.31), p= 0.14. There were 23 (74.2%) of 31 mothers who had history of benzodiazepine use and developed LBW babies compared to 26 (55.3%) of 47 mothers with history of benzodiazepine use with neonates with normal weight. This showed twice the risk of LBW in mothers who abused benzodiazepines OR=2.32, (95% CI 0.86,6.24), p=0.0876.

A positive history of amphetamine use was seen in 11(35.5%) of 31 mothers of LBW infants. Nine (19.1%) of mothers who used amphetamines delivered normal weight infants. The odds of LBW were roughly twice higher in the mothers with history of amphetamine use OR=2.32 (95%CI 0.83,6.53), p=0.1086. History of cocaine use was reported in 9 (29%) of 31 mothers with LBW infants compared to 6 (12.8%) of 47 mothers with normal weight infants. The use

of cocaine was associated with almost thrice the odds of LBW OR=2.80, (95%CI 0.88,8.87), p=0.0774.

The above factors were significantly associated with low birth weight at a 20% significance level. These factors were added to the multivariable model. The duration of methadone use, duration of heroin use in pregnancy, use of cannabis, tobacco and alcohol were not associated with LBW.

Table 5: Results of the univariable logistic regression of factors associated with LBW, p<0.20

Variable	**BW>2500g n= 47(%) Median**	**BW<2500g n= 31(%) Median**	**OR (95%CI)**	**LRT P-value**
*Methadone dose (10-245mg)	**85**	**100**	**1.01 (1.0,1.02)**	**0.047**
Duration of methadone use (1-60months)	**23**	**18**	**1.01 (0.97,1.04)**	**0.9**
*Heroin use in pregnancy	**18 (38.2)**	**7 (22.6)**	**0.47 (0.17,1.31)**	**0.140**
Duration of heroin use in pregnancy (1-9months)	**2.5**	**2.0**	**0.92 (0.69,1,23)**	**0.6**
*IVDU	**23 (49)**	**20 (64.5)**	**1.90 (0.75,4.82)**	**0.174**
Cannabis	**40 (85.1)**	**28 (90.3)**	**1.63(0.39-6.87)**	**0.5**
Tobacco	**36 (76.6)**	**26 (83.9)**	**1.59 (0.49, 5.13)**	**0.4**
*Benzodiazepines	**26 (55.3)**	**23 (74.2)**	**2.32 (0.86,6.24)**	**0.0876**
Alcohol	**27 (57.4)**	**21 (67.7)**	**1.56 (0.60,4.02)**	**0.4**
*Amphetamines	**9 (19.1)**	**11 (35.5)**	**2.32 (0.83,6.53)**	**0.1086**
*Cocaine	**6 (12.8)**	**9 (29)**	**2.80 (0.88,8.87)**	**0.0774**

**Factors added to the multivariable model, p<0.20*

RESULTS OF THE MULTIVARIABLE LOGISTIC REGRESSION (P<0.05)

In the multivariable model, at a p-value of < 0.05, heroin use in pregnancy (OR=37.05, p-value=0.002,95%CI[3.80,361.78]) and being an IVDU of heroin (OR=5.7, p= 0.004, 95%CI[1.72,18.92]) were the only factors associated with low birthweight . Among the 47 mothers with normal weight babies,18(38.2%) and 23(49%) used heroin in pregnancy and were IVDU respectively compared to7(22.6%) and 20(64.5%) of the 31 mothers with LBW babies who used heroin in pregnancy and were IVDU respectively.

A mother who had history of IVDU with heroin and did not use heroin in pregnancy had roughly 6 times higher odds of getting a low birthweight baby compared to a mother who was not an IVDU and did not use heroin in pregnancy (OR 5.7;p= 0.04,95% CI [1.72, 18.92]).

In a non-IVDU mother who reported using heroin in pregnancy, the odds of delivering a low birth weight baby was roughly 37 times higher than that of a non-IVDU mother who also did not use heroin in pregnancy (OR 37.05; p=0.002, 95% CI [3.79,361.78]).

There was no statistically significant association between methadone dose and use of benzodiazepines, amphetamines and cocaine and the odds of delivering a LBWneonate. The model had a good fit with a hosmer lemeshow p-value >0.05.

Table 6: Results of the multivariable logistic regression model of factors associated with LBW (P<0.05)

Variable	**Values**	**LBW- n= 47 (%)**	**LBW+ n= 31 (%)**	**aOR (95%CI)**	**LRT P-value**
IVDU	**Yes**	**23 (49)**	**20 (64.5)**	**5.7 (1.72,18.92)**	**0.004**
IVDU (-ve) # Heroin use in pregnancy (+)		**-**	**-**	**37.05 (3.80,361.7)**	**0.002**

*aOR : Adjusted Odds ratio

4.4 FACTORS ASSOCIATED WITH NEONATAL ABSTINENCE SYNDROME (NAS)

RESULTS FROM THE UNIVARIABLE ANALYSIS (P < 0.20)

In the univariable logistic regression, mothers on a longer duration of methadone use had greater likelihood to develop NAS (OR=1.02, [95%CI 0.99,1.06],p=0.1868).The duration of methadone use of mothers whose babies developed NAS was 24.5 months compared to a median of 19.5 months in mothers whose babies did not develop NAS .

Eighteen (64.3%) of 28 infants whose mothers who were heroin IVDU developed NAS compared to 25 (48.1%) infants whose mothers were IVDU without NAS manifestation. Being a heroin IVDU mother had almost twice a higher chance of infant developing NAS (OR=1.94, [95%CI 0.76,5.00], P=0.1632). There was positive history of benzodiazepine use in 15 (53.6%) of 28 mothers whose babies developed NAS vs 36 (69.2%) of 52 on benzodiazepines without NAS. Use of benzodiazepines showed a reduced risk of NAS (OR=0.51, [95%CI 0.20,1.32], p=0.1671).

Positive alcohol use was recorded in 21(75%) of mothers with NAS compared to 27 (51.9%) who did not develop NAS. Mothers who used alcohol had almost thrice more likelihood of their neonates developing NAS (OR=2.78, [95%CI 1.01,7.66], p=0.0409). Amphetamine use was reported in 11(39.3%) of 28 mothers who had babies who developed NAS compared to 9(17.3%) of 52 mothers who had used amphetamines but their infants did not develop NAS. History of amphetamines use had thrice the likelihood of developing NAS (OR=3.09, [95%CI 1.09,8.79], p=0.0332). There was no association between the methadone dose, heroin uses in pregnancy, abuse of cannabis, tobacco, cocaine and development of NAS.

These factors had a statistically significant association with NAS at a 20% level of significance hence were added to the multivariable logistic regression model for further analysis.

Table 7: Results of the univariable logistic regression of factors associated with NAS, p<0.20

Variable	NAS- n= 52 (%) Median	NAS+ n= 28 (%) Median	OR (95%CI)	LRT P-value
Methadone dose (10-245mg)	**90**	**85**	**0.10 (0.99,1.0)**	**0.3**
*Duration of methadone use (1-60months)	**19.5**	**24.5**	**1.02 (0.99,1.06)**	**0.1868**
Heroin use in pregnancy	**18 (34.6)**	**7 (25)**	**0.63 (0.23,1.76)**	**0.4**
Duration of heroin use in pregnancy (1-9months)	**2.0**	**4.0**	**1.16 (0.89,1.52)**	**0.3**
*IVDU	**25 (48.1)**	**18 (64.3)**	**1.94 (0.76,5.00)**	**0.1632**
Cannabis	**45 (86.5)**	**25 (89.3)**	**1.30 (0.31,5.46)**	**0.7**
Tobacco	**43 (82.7)**	**21 (75)**	**0.63 (0.21,1.92)**	**0.4**
*Benzodiazepines	**36 (69.2)**	**15 (53.6)**	**0.51(0.20,1.32)**	**0.1671**
*Alcohol	**27 (51.9)**	**21 (75)**	**2.78 (1.01,7.66)**	**0.0409**
*Amphetamines	**9 (17.3)**	**11 (39.3)**	**3.09 (1.09,8.79)**	**0.0332**
Cocaine	**8 (15.4)**	**7 (25)**	**1.83(0.59,5.73)**	**0.3**

*Factors added to the multivariable logistic regression model, p<0.20

RESULTS OF THE MULTIVARIABLE LOGISTIC REGRESSION (P<0.05)

In the multivariable analysis, at a p-value of 0.05, only a positive history of use of benzodiazepines by the mothers was a significant predictor of NAS in this population. There was a positive history of benzodiazepine use in 36 of the 52 (69.2%) mothers whose babies did not develop NAS compared to 15 of the 28 (53.6%) mothers whose babies developed NAS. Neonates born to mothers with a prior history of benzodiazepine use had roughly 70% less odds (OR=0.31, 95% CI [0.10; 0.97], p=0.045) of developing NAS compared to their counterparts, controlling for the confounding effect of duration of methadone use, IVDU, alcohol and amphetamine use. Removing the non-significant variables namely duration of methadone use (OR=1.01[95%CI 0.98,1.05],p=0.5), IVDU (OR=1.6[95%CI 0.56,4.58],p=0.4)

, alcohol (OR=2.76,[95%CI 0.90,8.43],p=0.08) and amphetamine (OR=3.12,[95%CI 0.88,11.08],p=0.08) use resulted in a change of 42.7% on the coefficient of benzodiazepine use, showing significant confounding effect of these factors on the effect of history of benzodiazepine use by the mother on development of NAS by the baby. The model had a good fit with a Hosmer Lemeshow P-value of 0.2341.

Table 8: Results of the multivariable logistic regression of factors associated with NAS, p<0.05

Variable	**NAS- n= 52(%) Median**	**NAS+ n= 28(%) Median**	**aOR (95%CI)**	**LRT P-value: 0.0202**
Duration of methadone use (1-60months)	**19.5**	**24.5**	**1.01(0.98,1.05)**	**0.5**
IVDU	**25 (48.1)**	**18 (64.3)**	**1.60(0.56,4.58)**	**0.4**
Benzodiazepines	**36 (69.2)**	**15 (53.6)**	**0.31(0.10,0.97)**	**0.045**
Alcohol	**27 (51.9)**	**21 (75)**	**2.76(0.90,8.43)**	**0.08**
Amphetamines	**9 (17.3)**	**11 (39.3)**	**3.12(0.88,11.08)**	**0.08**

4.5 FACTORS ASSOCIATED WITH NEONATAL MORTALITY

RESULTS FROM THE UNIVARIABLE LOGISTIC REGRESSION ANALYSIS (P < 0.20)

In the univariable model, at a liberal p-value of < 0.20, the dose of methadone given to the mothers prior to delivery ,history of benzodiazepine use and history of cocaine use were found to be significant predictors of neonatal death in this population. The mean methadone dose prior to delivery in mothers whose babies died was 60mg compared to a median dose of 92.5 mg in those whose babies survived. This showed that higher the methadone dose the less likely occurrence of neonatal death (OR =0.98 [95%CI 0.96,1.0], p=0. 0313). Six (85.7%) of 7 mothers who had history of benzodiazepine use lost their neonate compared to 46 (62.2%) of 74 mothers whose neonates did not die despite history of benzodiazepine use. History of use

of benzodiazepine had almost four times the risk of neonatal mortality (OR=3.65 [95%CI 0.41,31.94], p=0.1842).

Reported cocaine use was in 4 (57.1%) of 7 mothers whose neonates died compared to 11(14.9%) of mothers who abused cocaine but the babies survived. History of use of cocaine by the mother had roughly 7 times higher odds of neonatal death (OR 7.64 [95%CI = 1.50,38.91], p=0. 0156). All these factors were added to a multivariable logistic regression model. There was no association between duration of methadone, heroin use in pregnancy, duration of heroin use in pregnancy, IVDU, use of cannabis, tobacco, alcohol and amphetamines.

Table 9: Results of the univariable logistic regression of factors associated with neonatal mortality, p<0.20

Variable	**Neonatal Mortality- n= 74 (%) Median**	**Neonatal Mortality+ n= 7 (%) Median**	**OR (95%CI)**	**LRT P-value**
*Methadone dose (10-245mg)	**92.5**	**60.0**	**0.98 (0.96,1.0)**	**0.0313**
Duration of methadone use (1-60months)	**18.5**	**29.0**	**1.02 (0.97,1.08)**	**0.4**
Heroin use in pregnancy	**23 (31.1)**	**3 (42.9)**	**1.66 (0.34,8.04)**	**0.5**
Duration of heroin use in pregnancy (1-9months)	**2.0**	**3.0**	**1.05 (0.73,1.50)**	**0.8**
IVDU	**38 (51.4)**	**5 (71.4)**	**2.37 (0.43,13.0)**	**0.3**
Cannabis	**65 (87.8)**	**6 (85.7)**	**0.83 (0.09,7.72)**	**0.9**

Tobacco	**59 (79.7)**	**6 (85.7)**	**1.53 (0.17,13.65)**	**0.7**
*Benzodiazepines	**46 (62.2)**	**6 (85.7)**	**3.65(0.41,31.94)**	**0.1842**
Alcohol	**44 (59.5)**	**4 (57.1)**	**0.91 (0.19,4.36)**	**0.9**
Amphetamines	**19 (25.7)**	**1 (14.3)**	**0.48 (0.05, 4.27)**	**0.5**
*Cocaine	**11 (14.9)**	**4 (57.1)**	**7.64 (1.50, 38.91**	**0.0156**

*Factors added to the multivariable model, p<0.20

RESULTS OF THE MULTIVARIABLE LOGISTIC REGRESSION

In the multivariable model, at a p-value of <0.05, methadone dose (p-value=0.031, OR=0.97, 95%CI [0.95,1.0]) and history of cocaine use (p-value=0.007, OR=12.85, 95%CI [2.0,82.39]) were significantly associated with neonatal death. The median methadone dose used on mothers whose babies did not die during the neonatal period was 92.5mg compared to a median dose of 60mg used on mothers whose babies died during the neonatal period. A positive history of cocaine use was recorded in 11of 74 (14.9%) mothers whose babies did not die during the neonatal period compared to 4 of the 7 (57.1%) mothers whose babies died in the neonatal period.

For every unit increase of the dose of methadone given to a mother as treatment, the odds of getting a neonatal death decreased by roughly 3% (OR=0.97, 95% CI [0.945; 0.997]), controlling for the confounding effect of history of cocaine use by the mother.Neonates born to mothers with a positive history of cocaine use had roughly 13 times higher odds of dying during the neonatal period compared to their counterparts whose mothers had no history of cocaine use (OR=12.85, 95%CI[2.0;82.39]).

There was no significant association between a history of benzodiazepine use and neonatal death.There was a 23.31% change in the coefficient of methadone dose when the predictor 'cocaine' was dropped from the final model and a 20.39% change in the coefficient of cocaine when the predictor variable 'methadone dose' was omitted from the model. This shows that the two variables 'methadone dose' and 'history of cocaine use' confounded each other as predictors of neonatal death.The model had a good fit (Hosmer-Lemeshow p-value= 0.1055).

Table 10: Results of the multivariable logistic regression of factors associated with neonatal death, p<0.05

Variable	**Values**	**Neonatal Mortality- n= 74 (%)**	**Neonatal Mortality+ n= 7 (%)**	**aOR (95%CI)**	**P-value**
Methadone dose (10-245mg)	**10-245**	**92.5mg**	**60mg**	**0.97 (0.95,1.0)**	**0.031**
Cocaine	**Yes No**	**11 (14.9)**	**4 (57.1)**	**12.85 (2.0,82.39)**	**0.007**

CHAPTER 5: DISCUSSION

This study provides new data on women on OST with methadone in Kenya and the clinical outcomes of their neonates.All women in this study were heroin user (IVDU or smoking) in addition to other drugs before initiated in to the program and some during the Medication Assisted Treatment (MAT) programme. In sociodemographic characteristics of mothers on Opioid Substitution Therapy (OST) with methadone, the median age of mothers was 31. An almost similar median age of 35.1 was seen in a study by Wang P *et al*(25).There was a high number of unemployed women (80%) and a similar trend was seen in the study by Richardson *et al* that showed 70% of population on OST reported unemployment at any point of follow up (26). This may be due to the erratic behavior and polydrug abuse side effects. Potential interference between employment-related activity and methadone dispensing policies (Directly Observed Therapy (DOT) represents another plausible systemic barrier to employment among individuals enrolled in Medication Assisted Treatment (MAT) with methadone.

In terms of delivery, 95.1% of the women delivered in a health facility and 90.1% had a spontaneous vertex delivery. This is roughly 30% more than hospital deliveries by skilled attendant in Kenya seen in the study by Ochako *et al*(27) . This may be due to the proximity of mothers on OST to health facilities as they attend one daily, continuous health education during pregnancy and the presence of skilled attendants to guide them in the pregnancy course as they take methadone hence the high numbers of hospital deliveries.The most abused drug in mothers on OST with methadone was cannabis (87.7%) followed by tobacco (80.6%). These study findings were similar to findings by Ngarachu et *al* which showed 84.8% cannabis use amongst those enrolled in MAT clinic (28). This is due to easy availability of cannabis and tobacco in this population and it is a cheaper drug compared to the other drugs abused.

The majority of mothers with chronic diseases had HIV (22%). This is roughly four-fold higher than the numbers on Kenya national HIV survey 2020 (6.6%). This may be attributed to by the fact that the majority of the women were intravenous drug users (IVDU) before and during the OST with methadone programme with sharing needles and inappropriate sexual behavior.
The needle and syringe programme (NSP) by Ministry of Health (MOH) through NASCOP has helped reduce the rate of HIV transmission. The OST with methadone programme was initiated as a harm reduction strategy in populations with heroin addiction (3).

In this study, we noted a high number of low birthweight babies (39.7%). This was almost four times the number in the Kenyan population as per the study by Kitui *et al* (29). Blandthorn J *et al* (30) showed similar statistics in neonates who had LBW with prevalence at 29%. High number of LBW in this cohort can be attributed to gestation at birth. Other factors include intrauterine growth restriction, lifestyle factors may have played a part as females on opioids have poor dietary habits and living conditions. Concomitant infections and poor antenatal care follow up may play a role in the small sized babies delivered.

There was no association between methadone use and LBW. The findings are similar to was findings by Kandall *et al* and a meta-analysis by Hulse G. *et al* who found a higher birthweight in babies exposed to methadone in utero(31)(10). This suggests the higher the methadone dose the larger the neonate hence a positive effect. The use of methadone and heroin in pregnancy counteracts the birthweight advantage observed when methadone is used alone. These findings are contrary to findings by Kelty *et al* which showed association of methadone with higher odds of low birth weight (24).

Heroin use during pregnancy increased chances of low birthweight thirty-seven times (AOR=37.05, p=0.002). Similar findings have been documented by Hulse, English *et al* (10). Hulse, English *et al* showed reduction of birthweight by 489g (95% CI 284—693 g). Mothers with history of IVDU without heroin use during pregnancy had six times more chances of low birthweight (AOR=5.7, p=0.004). No other illicit drug use was associated with low birthweight in this population.

Majority of the neonates (87.7%) born to mothers on OST with methadone were born without any neonatal conditions. Related findings have been documented by Blandthorn *et al* with more than half the neonates not presenting with medical conditions excluding Neonatal Abstinence Syndrome (NAS). The most common neonatal conditions were respiratory distress syndrome (6.2%) and Neonatal sepsis (3.7%). The two conditions fall under the top ten neonatal conditions in Kenya similar findings are seen in the study by Nabwera *et al* (32).

The average hospital stay for neonates born to mothers on OST with methadone was 8.7 days. Almost similar duration was shown in studies by Staszewski *et al* (11.2 days) and N. J Shaw *et al* (8.5days)(15,18).Tolia *et al* study showed there is a longer duration of hospital median 13-19 days) stay as most neonates developed opioid associated complications (13).

Neonatal Abstinence Syndrome (NAS) was recorded in 35% of the neonates. This percentage agrees with studies carried out by Jones *et al* (41%) and Shaw *et al* (37%) (17) (15). The prevalence of NAS in our study was lower compared to the study done by Brogly *et al* (58%) and Alroomi *et al* (42%) (33,34). This may be attributed to the small sample size in our study. There was no difference in the occurrence of NAS in neonates whose mothers were taking a lower or higher dose of methadone or duration of methadone use. Similar correlation is seen in Shaw *et al* study (15).In regards to pharmacologic interventions, a lower proportion of neonates who developed NAS (21.25%) received intervention. This is contradictory to Staszewski *et al* (46.1%) where all neonates who presented with NAS were all managed at the hospital facility(18). This might be attributed to lack of proper guidelines for NAS management and lack of a standard scoring protocol (Finnegan score) in various facilities in Kenya. Finnegan scoring system is used internationally to know when to initiate pharmacotherapy.

Use of benzodiazepines was protective against NAS (aOR=0.31, P=0.045). Roughly 70% of mothers who had history of benzodiazepine use their neonates did not develop NAS. Similar findings were documented by Blandthorn *et al* (64%) (30).This may be explained by benzodiazepine use as an antiseizure agent and management of status epilepticus. Its mechanism of action is action on the GABAA receptors by increasing conductance hence promoting a state of CNS depression. This may lead to inability of the neonate exposed in utero to benzodiazepines to mount a seizure response (NAS). There was no relationship between NAS and heroin or any other drugs abused by mothers in this cohort.

Internationally, there is promulgation for use of buprenorphine instead of methadone as management for heroin addiction in pregnant women in the Medication Assisted Treatment (MAT) clinics. Studies done have revealed better neonatal outcomes especially in terms of lower NAS statistics, higher birthweight and shorter hospital stay on buprenorphine. The studies include Meyer *et al,* Staszewski *et al* and Jones *et al* (16–18)

In babies born to mothers on OST with methadone, 7 (8.7%) died before completing 28 days of life. The outcome in this study is higher than the national neonatal mortality as per the Kenya Demographic and Health Survey (KDHS2014). The study findings were similar to reports from a meta-analysis by Hulse *et al* which showed high neonatal mortality in females using methadone and heroin during pregnancy (increased relative risk 6.37 (95% CI 2.57±14.68) (23).Our study showed the relationship between the maternal methadone dose and neonatal

mortality. The higher the methadone dose, the lesser the risk for neonatal mortality (aOR=0.97, p=0.031). Related findings have been documented by Milne *et al*(10). This shows the advantage of methadone as gold standard for treatment in heroin addiction.

Notably, 57.1% of the neonates born to mothers with a history of cocaine use in this population succumbed. These neonates had roughly 13 times higher odds of dying during the neonatal period (aOR=12.85, p=0.007). Similar findings are seen in the study by MacGregor *et al*(35).There was no relationship between heroin use in pregnancy and neonatal mortality. This is contrary to study by Fricker *et al* that showed higher neonatal mortality in women who used heroin during pregnancy(36).

There was one still birth out of 81 deliveries. Julie *et al* had similar findings in her study (1 still birth)(30) . This number was way lower than other studies carried out by Ellwood *et al* (5 still births out of 182) and Brogly *et al* (11.39/1000 births)(11,33). This might be attributed to the small sample size of our population.

5.1 CONCLUSION

- There was a high rate of unemployment amongst the women in this programme.
- The most common chronic disease in this cohort was HIV.
- Cannabis was the most abused drug in this population.
- 4 out of 10 women on OST with methadone delivered low birthweight neonates.
- The risk factors for low birth weight in the study included heroin use during pregnancy and history of intravenous heroine drug use.
- Just over 1 in 3 babies had Neonatal Abstinence Syndrome (NAS).
- Benzodiazepine use by mothers on OST with methadone appeared protective to NAS.
- Roughly 1 in 10 babies died. Maternal use of methadone in utero reduced the risk of death.
- History of cocaine use increased the risk of neonatal mortality 12-fold.

5.2 RECOMMENDATIONS

- Education at health facilities on identification and management of Neonatal Abstinence Syndrome (NAS).
- Recommend adoption of the Finnegan scoring system in all facilities which is the main international scoring protocol for NAS.
- Emphasis of methadone uptake in population of heroin users within child bearing age.
- Consideration of buprenorphine use to expand the treatment choices of pregnant women on OST in Kenya.
- Additional research in maternal factors and neonatal outcomes e.g., head circumference, neurodevelopmental milestones and growth.
- Advocate for programs aimed at improving maternal health in special populations like drug users.

5.3 STRENGTHS

- MAT OST with methadone clinics are controlled programs with an existing database.
- This study depicts the nationwide picture (all who fit the inclusion criteria in Kenya were added).

5.4 STUDY LIIMITATIONS

- Lack of a comparative cohort.
- Lack of baseline studies to use for comparison in our Kenyan setup.
- Small sample size despite it being a nationwide study.
- Missing files and information in >5 file records that were important in the study. e.g., neonatal outcome information was missing

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APPENDICES

Appendix I: Time Frame- Starting from 1st January 2015 to 31st December 2019

ACTIVITY	ESTIMATED TIME
Development of proposal and presentation	January to February 2020
Submission of proposal for ethical approval	March 2020
Data collection	May to October 2020
Data analysis	November to December 2020
Dissertation writing	January to March 2021
Poster presentation	March 2021
Dissertation submission	April 2021

APPENDIX II: STUDY BUDGET

Category	Remark	Unit	Unit cost	Total (Kshs)
Proposal development	1.Printing drafts 2.Proposal copies	1000 1000	5 8	5000 8000
Data collection	1.Stationery 2.Training research assistants 3.Research assistant 4.Transportation and accommodation fee countrywide visit	60 3 10 weeks 4	100 3000 1500/week x3 25,000	6000 9000 45000 100,000
Data entry	Data clerk	1	7000	7000
Data analysis	Statistician	1	35000	35000
Thesis write up	1.Printing drafts 2.Printing thesis	1000 10	5 1500	5000 15000
Contingency fund			20000	20000
ERC proposal processing fee			2000	2000
Total				**257,000**

Appendix III: Data Collection Tool

Study eligibility checklist

Date---------- study serial number ----------

Data collectors' initials----------

A) Inclusion criteria (if any of the inclusion below is marked "NO" the file is not included in the study)

- Any history of pregnancy YES( ) NO ( )
- Patient gave birth while on OST treatment with methadone YES ( ) NO ( )

B) Participants details

1.Age in completed years [ ]

2.Weight [ ]kgs

3.Marital status Single [ ] Married [ ] Separated /Divorced [ ] Widowed [ ]

4.Residence [ ]

5.Occupation. Blue collar [ ] White collar [ ]. Unemployed [ ]

6.Employement status [ ]

7.Level of education. Primary [ ] Secondary [ ] Tertiary [ ] No education [ ]

8. Date of enrollment at MAT clinic [ ]

C) INFORMATION ON DISEASE

9.Duration of heroin use. Years [ ] Months [ ]

10.Intravenous drug user (IVDU). YES [ ] NO [ ]

11.Other drugs abused. cannabis [ ] cocaine [.] amphetamines [ ] Alcohol [ ] Benzodiazepines [ ] Tobacco [ ]

12. Any chronic illness. HIV [ ] Diabetes [ ] Hypertension [ ] Tuberculosis [ ] Mental illness [ ] Cancer [ ] others specify _____

D) PREGNANCY AND POSTNATAL INFORMATION

13. Parity [ ]

14.Type of delivery SVD [ ] Caesarian section [ ]

15.Outcome of each pregnancy .Live birth ( ) still birth ( )

16.Any neonatal medical condition during neonatal period. NNS [ ] Perinatal asphyxia [ ] RDS [ ] Congenital anomalies [ ] Pneumonia [ ]

17.Any neonatal death YES ( ) NO ( ) . IF YES, how long after birth HOURS [ ] DAYS [ ]

18.Delivery at a health facility YES [ ] NO [ ]. If YES, duration of hospital stay post-delivery. Weeks [ ] Days [ ]

19. Gestational age at delivery [ ] weeks

20. Birthweight [ ] grams

21. Presence of withdrawal symptoms (irritability, tremors, sweating, high pitched cry, nasal stuffiness, frequent sneezing) in the neonate YES ( ) NO ( )

22. Presence of NAS. YES [ ] NO [ ]

23.Need for pharmacological intervention for the withdrawal symptoms in the neonate if present YES ( ) NO ( )

E) TREATMENT INFORMATION

24.Final Methadone dosage before delivery [ ] mg

25.Duration of methadone treatment before delivery. [ ] months

26.Missed OST during pregnancy. Weeks [ ] Days [ ]

27.Medication for any chronic illnesses during pregnancy YES [ ] NO [ ]

28. Use of heroin during pregnancy YES [ ] NO [ ]. If YES , Duration [ ]

Appendix IV: Request for Waiver of Informed Consent

UNIVERSITY OF NAIROBI

(UoN)

COLLEGE OF HEALTH SCIENCES

P O BOX 19676 Code 00202

Telegrams: varsity

(254-020) 2726300 Ext 44355

KENYATTA NATIONAL HOSPITAL (KNH)

P O BOX 20723 Code 00202

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Telegrams: MEDSUP, Nairobi

KNH-UoN ERC

Email: uonknh_erc@uonbi.ac.ke

Website: http://www.erc.uonbi.ac.ke

Facebook: ttps://www.facebook.com/uonknh.erc

Twitter: @UONKNH_ERC

(To be submitted with Application for ERC Review of Research)

Exempt studies to be defined

KNH-UoN ERC

REQUEST FOR WAIVER OF INFORMED CONSENT

(Not Required for Exempt Studies)

Project Title: A RETROSPECTIVE COHORT STUDY TO DETERMINE CLINICAL OUTCOMES OF INFANTS BORN TO MOTHERS ON OPIOID SUBSTITUTION THERAPY WITH METHADONE IN KENYA

Principal Investigator and Institutional affiliation: __.

DR. JULLIET AUMA OMWOHA, UNIVERSITY OF NAIROBI SCHOOL OF

MEDICINE, DEPARTMENT OF PAEDIATRICS AND CHILD HEALTH

Date: 24TH JUNE 2020

Under special circumstances, investigators may request one of three types of waivers to obtaining written informed consent from research participants.

1. **Alteration of informed consent.**

   With this waiver, the investigator may provide to the participants a consent which does not include or which alters one or all of the required elements. Examples of when this waiver might be applicable would be, when a researcher is conducting secondary data analysis and the participants cannot be located or when requiring informed consent might somehow actually have negative consequences for research participants.

2. **Waiver of parental permission**.

   This waiver would be used in cases where something may be legal for a child to do (i.e. contraception) without parental permission and obtaining parental permission would violate that privacy. An example of this type of waiver would be a survey on children (which would require parental permission) but the survey is about their experience on contraception usage.

3. **Waiver of written documentation** that informed consent was obtained. With this waiver, the investigator would be required to read or provide the informed consent form to a participant, but would not need to obtain the participant's signature on the consent form. Examples of when this waiver might be applicable would be some internet or phone surveys or when signing the form might have some negative consequence for the participant. It must be emphasized that these waivers will be given only when there are compelling reasons for doing so.

The Ethics and Research Committee determines which type of consent applies to your research, but please indicate the type that you are requesting.

☒ **Waiver or alteration of the informed consent process.** *(Complete Section I)*

☐ **Request for waiver of parental permission.** *(Complete Section II)*

☐ **Waiver of written documentation of consent.** *(Complete Section III)*

I. Request for waiver or alteration of the consent process (Not required for Exempt studies)

I believe that this protocol is eligible for waiver or alteration of required elements of the informed consent process because the protocol meets all of the following criteria: (Provide protocol-specific supporting information for each criterion that justifies the findings for the following :)

1. The research presents no more than "minimal risk" of harm to participants.

This is a retrospective study hence there will be no harm to the study participants._____

_____

2. The waiver or alteration will not adversely affect the rights and welfare of the participants.

The waiver will not affect the rights and welfare of the participants as the data collection process will be handled by the principal investigator and research analyst ensuring utmost confidentiality_____

_____

_____

3. The research could not practicably be carried out without the waiver or alteration.

The study could not practicably be carried out without the waiver as it involves analyzing already documented data prior to the time of collection of data and getting informed consent of the subjects is not feasible either from the fact that contact information may be missing, have changed and the subject may live too far from the site of the study.

_____

_____

4. Whenever appropriate, the participants will be provided with additional pertinent information after participation

___The study participants will be contacted in cases of unexpected relevant information obtained

_____

_____

5. Elements of informed consent for which a waiver or alteration is requested and the rationale for each:

___ a) INTRODUCTION - Use of heroin during pregnancy has been associated with high incidence of prematurity, low birth weight, higher number of neonates born experiencing Neonatal Abstinence Syndrome (NAS) and neonatal mortality. Globally, there has been marked improvement in the neonatal outcomes since the introduction of methadone as a gold

standard treatment of heroin addiction. This will provide information to help with better intervention and management in this population.

__b) PURPOSE OF THE STUDY – the purpose of the study is to determine the clinical outcomes of neonates born to mothers on Opioid Substitution Therapy (OST) with methadone in Kenya .It is a retrospective study hence data collected from the records of previously available patients.

_c) WHAT WILL BE DONE DURING THE STUDY –. It is a retrospective study that entails use of patients records for collection of data.Data will be obtained from study population through data collection forms checked for completeness and accuracy and entered into a password protected database and will not require the participants' physical presence during the study.

d) RISKS, HARMS AND DISCOMFORTS ASSOCIATED – The study has no foreseeable risks, harms and discomforts. This will be addressed by restricting access to collected data and coding of data to prevent the primary risk that is breach of confidentiality. The data will then be saved in a password protected computer.

e) STUDY BENEFITS- The study offers no direct benefit to the participants however this will be the first program evaluation of the newborn outcomes among babies of women on OST with methadone and will form the basis for future program planning and improvement of the current case-management plans. nformation obtained will enhance future patient care.

f) COST TO PARTICIPANTS- There will be no cost to the participants during the study.

g) REIMBURSEMENT FOR PARTICIPANTS- No reimbursements will be made to participants.

f) FURTHER QUESTIONS- If any problem or question about the study, you can contact the principal investigator, **Dr. Julliet Auma Omwoha 0725764062**

g) PARTICIPANT CHOICES- Participants will not be accessible to make voluntary decision to take part in the study.

h) CONSENT FORM (STATEMENT OF CONSENT)- Participants will not be available to apprehend a signature of written informed consent as this is a retrospective study.

_____

_____

_____

6. The research does not involve non-viable neonates:

_____The study does not involve non-viable neonates

_____

_____

____

7. The research is not subject to FDA and/or national research regulation:

___The study is not subject to FDA and /or national research regulation.

_____

_____

II. Request for waiver of parental permission (Not required for Exempt studies)

I believe that this protocol is eligible for waiver of parental permission because the protocol meets all of the following criteria: (Provide protocol-specific supporting information for each criterion that justifies the findings for one of the following two options :)

Option 1

1. The research presents no more than "minimal risk" of harm to participants.

_____

_____

_____

2. The waiver or alteration will not adversely affect the rights and welfare of the participants.

_____

_____

_____

3. The research could not practicably be carried out without the waiver or alteration.

_____

_____

_____

4. Whenever appropriate, the participants will be provided with additional pertinent information after participation.

_____

_____

_____

5. Elements of informed consent for which a waiver or alteration is requested and the rationale for each:

_____

_____

_____

6. The research does not involve non-viable neonates:

_____

_____

_____

7. The research is not subject to FDA and/or national research regulation:

Option 2:

1. The research protocol is designed for conditions or for a participant population for which parental or guardian permission is not a reasonable requirement to protect the participants (for example, neglected or abused children)

_____

_____

_____

2. An appropriate mechanism for protecting the children who will participate as participant in the research will be substituted

_____

_____

_____

3. The research is not subject to FDA and/or national research regulation:

_____

_____

_____

4. The waiver is consistent with international and national law:

_____

_____

_____

III. Request for waiver of written documentation of consent (Not required for Exempt studies and not required when the consent process is waived.)

I believe that this protocol is eligible for a waiver of written documentation of informed consent because the protocol meets one of the following criteria: (Provide protocol-specific supporting information for each criterion that justifies the findings for one of the following two options :) **(NOTE: Even when documentation of informed consent is waived, the**

investigator is required to give participants full consent information, and to obtain their voluntary consent orally.)

Option 1

(Example: Conducting interviews with street children engaged in drug abuse. The only record of the name or other identifying information of the participants would be the signed consent form and knowledge of an individual's participation or information provided could lead to potential legal, social, or physical harm.)

Explain*:*

1. The only record linking the participant and the research would be the consent document.

_____

_____

_____

2. The principle risk would be potential harm resulting from breach of confidentiality.

_____

_____

_____

3. Each participant will be asked whether the subject wants documentation linking the participant with the research and the participant's wishes will govern.

_____

_____

_____

4. The research is not subject to FDA and / national research regulation.

_____

_____

_____

Option 2

(Example: Using an anonymous survey consent or conducting telephone interviews with politicians about how constitutional provision for funding of political parties will affecting the campaign process of smaller parties

1. The research presents no more than minimal risk of harm to participants.

_____

_____

_____

2. The research involves no procedures for which written consent is normally required outside of the research context.

_____

_____

_____

Approval (KNH-UoN ERC Chairperson: Check all that apply to indicate that the waiver or alteration is approved and to indicate agreement with the investigators protocol specific findings justifying the waiver.)

☐ Waiver or Alteration of the Consent Process

☐ Waiver of parental permission

☐ Waiver of Written Documentation of Consent

NOTE: To approve a waiver of written documentation of informed consent the investigator must provide a written document describing the information to be disclosed. This document has to include all required and appropriate additional elements of consent disclosure, unless the consent process has been altered.

Choose one of the following when approving a waiver of written documentation:

☐ The investigator must provide a written description of the information provided orally to the participant.

☐ The investigator does not have to provide a written description of the information provided orally to the participant.

APPROVED BY CHAIR KNH-UoN ERC:

Name: _____

Signature _____

Date and Stamp: _____.