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Faculty of Health Sciences

School of Medicine

A DESCRIPTION OF PREGNANT WOMEN WITH ORGANOPHOSPHATE POISONING AT CHRIS HANI BARAGWANATH ACADEMIC HOSPITAL

MMED: OBSTETRICS AND GYNAECOLOGY

DR RAYMOND BVUMBI

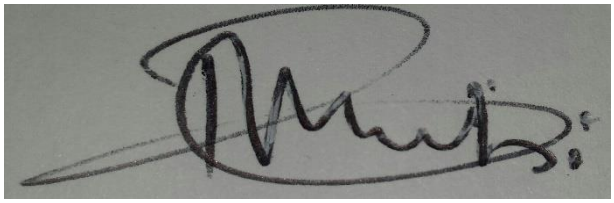
STUDENT NUMBER: 2184574

A research report submitted to the Faculty of Hearth Sciences, University of the Witwatersrand, Johannesburg, in partial fulfilment of the requirements for the degree of Master's in Medicine (MMed)

Johannesburg, 2022

DECLARATION

I, **Raymond Bvumbi**, declare that this research report is my own, unaided work. It is being submitted for the Degree of Master's in Medicine (MMed) in the department of Obstetrics and Gynaecology at the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at any other university.



Raymond Bvumbi

8th April 2022 in Johannesburg

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Lastly, I would like to thank my family.
To my wife, Esther, thank you for taking care of our family whilst I went through this journey. It could not have been possible without your sacrifice. To my children, (Mufaro, Piwanashe and Kutenda), thank you for giving me space and time to work on this project.

PRESENTATIONS ARISING FROM THIS PROJECT

Oral Presentations:

1. Wits School of Clinical Medicine Research Day: 30 September 2021

2. Rahima Moosa Mother and Children Hospital academic meeting: 23 September 2021

Poster Presentations:

1. Abstract accepted for a poster presentation at Federation of International Obstetrics and Gynaecologists Global Conference: 21 - 28 October 2021

ABSTRACT

Background: Organophosphate poisoning (OPP) is of public health importance as it poses a significant health risk that is associated with a high case fatality. Its severity in pregnancy is unknown due to limited studies.

Objective: To describe the socio-demographic characteristics, clinical features, maternal, fetal and early neonatal outcomes in pregnant women presenting with OPP at Chris Hani Baragwanath Academic Hospital (CHBAH), South Africa (SA).

Method: This was a retrospective descriptive study that reviewed 30 medical records of pregnant women who presented with OPP at CHBAH from 1st of January 2017 to 31st December 2019. Descriptive analyses were conducted. Fisher's exact test was used to explore the association between potential risk factors and maternal, fetal, and early neonatal outcomes. A p-value of $\leq$0.05 was statistically significant.

Results: Most women with OPP were between 18 - 35 years (n = 25; 83.3%), unemployed (n = 22; 73.3%), single (n = 26; 86.7%), and of the African race (n = 29; 96.7%). Eighty percent of these cases (n = 24) were intentional ingestion whilst one (3.3%) was accidental exposure. Majority were booked (n = 21; 70.0%), HIV negative (n = 27; 93.3%), rhesus positive (n = 29; 96.3%), rapid plasma reagin negative (100 %) with a median booking haemoglobin of 10.4g/dl (IQR 10.1 - 12.1, range 9.1 - 13.4) and median gestational age of 21 (IQR 18 - 24, range 16 - 34) weeks at booking and 30 (IQR 27 - 34, range 14 - 37) weeks on admission. There were 24 (81.2%) patients who were acidotic, with the worst median lactate of 2.85 (IQR 2.1 - 4.1, range 0.6 - 18.7) and worst median pH of 7.30 (IQR 7.21 - 7.30, range 6.9 - 7.52). The maternal fatality rate was 10% (n = 3) and half (n = 15; 50.0%) required ventilation, with median duration of ventilation being four days (IQR 1-3, range 1-19). All the women had delivered with 13 (43.3%) live births, four (13.3%) miscarriages, and 13 (43.3%) stillbirths. A loading dose of atropine >9.0mg was significantly associated with maternal death (p-value = 0.04). Poor fetal outcomes and early neonatal deaths were associated with unbooked status (p-value = 0.01), maternal pH $\leq$7.35 (p-value = 0.02), maternal ventilation (p-value = 0.01), maternal admission longer than 6.5 days in hospital (p-value = 0.02), maternal GCS $\leq$14 (p-value = 0.05).

Conclusion: Organophosphate poisoning in pregnancy is associated with significant morbidity and mortality in pregnant women and poor pregnancy outcomes.

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ABBREVIATIONS

AChe	Acetylcholinesterase
ALP	Alkaline phosphatase
ALT	Alanine transaminase
APACHE	Acute physiological assessment and chronic health evaluation
APGAR	Appearance, pulse, grimace, activity, and respiration
AST	Aspartate aminotransferase
BP	Blood pressure
CHBAH	Chris Hani Baragwanath Academic Hospital
COVID-19	Coronavirus disease – 2019
GCS	Glasgow coma scale
Hb	Haemoglobin
HCA	High care area
HIV	Human immunodeficiency virus
GGT	Gamma-glutamyl transferase
INR	International normalised ratio
MSL	Meconium-stained liquor
NICU	Neonatal intensive care unit
OPP	Organophosphate poisoning
OP	Organophosphate
RBC	Red blood cell
REDCap	Research electronic data capture
RPR	Rapid plasma reagin

SA	South Africa
SFH	Symphysis fundal height
TOP	Termination of pregnancy
WHO	World Health Organization

CHAPTER I: INTRODUCTION

1.1 Background

Acute pesticide poisoning is a global health concern, mostly in developing countries, resulting in significant morbidity and mortality (1, 2). Organophosphates (OP) and carbamates are some of the chemicals used in pesticides. Exposure to these compounds can have serious health effects (3). Cardiorespiratory failure and death may occur in severe acute pesticide poisoning (4). Pesticide exposure causes approximately one million unintentional and two million suicidal poisonings worldwide, leading to about 200 000 deaths per year (1, 5). Most cases are recorded in countries where there is increased use of pesticides in the agriculture industry (6). Accidental exposure is more common in agricultural areas whilst intentional exposure occurs more commonly in residential communities (3).

Countries in Africa that are most affected are the ones which are mainly agriculture based. This can be due to widespread use of pesticides which makes them easily accessible to the general community (4, 5). Lack of strict regulations regarding the selling and use of these dangerous chemicals also poses a great threat. South Africa (SA) is not immune to the effects of organophosphate poisoning (OPP). Studies have shown that there is an increase in OPP cases in farming communities, mainly in the Western Cape Province (4, 7). A study conducted in the Tshwane district, Gauteng Province, showed that OPP was mainly a result of intentional ingestion (2). In this Tshwane study, intentional poisoning with OP occurred in 51.7% of the cases, with 21.7% of cases being accidental and 26.6% of cases of unknown circumstances (2). A one-year review of Tygerberg Poison Information Centre consultations indicated that 61.0% of adult cases were due to intentional exposures (7).

Organophosphate poisoning is of public health importance as it poses a significant health risk that is associated a high case fatality. It is therefore a notifiable medical condition in SA. The condition falls under category two of agricultural or stock remedy poisoning and should be notified through a written or electronic notification within seven days of clinical or laboratory diagnosis (1, 8). This form collects the patient's demographic details and information regarding the onset, treatment, and outcome of the case (2, 7, 8). However, most clinicians who attend to these suspected or confirmed cases fail to notify them. Under-

reporting of cases can lead to inaccurate data on OPP as the situation might be worse than that recorded in the few studies that are published (2, 9). Most studies investigating OPP in pregnancy have been case series which do not provide a better understanding of the magnitude of the condition and its impact on the pregnant woman, fetus and early neonate (8, 10).

1.2 Problem Statement

Although OP, a term that is inclusive of carbamates, are freely available in SA, very few studies have been conducted around OPP in pregnancy. There has been a concern that there is an increase in the cases of pregnant women presenting with OPP at Chris Hani Baragwanath Academic Hospital (CHBAH) that has drawn the attention of clinicians in the department of obstetrics and gynaecology. In pregnancy, it is presumed that these OP compounds have effects on both the pregnant woman and the developing fetus, hence such cases are regarded as high-risk.

1.3 Justification

The findings from this study may assist in the development of a protocol for the management of OPP in pregnancy. It will also bring attention to the severity of OPP in pregnancy in our community.

CHAPTER II: LITERATURE REVIEW

2.1 History of organophosphate compounds

Since the first OP that inhibited acetylcholinesterase (AChe) activity was synthesized in 1854, research and development of OP compounds has progressed rapidly, with hundreds of OP formulations being available (3, 5, 6). Most of these substances have been used as insecticides and herbicides in the agricultural industry. The use of OP also extends to the plastics and oil industries, as well as to the pharmaceutical industry in the form of chemotherapeutic agents (2, 6, 7). OP containing compounds, such as pesticides and insecticides are readily available at marketplaces, hardware shops, and at informal street vendors without proper monitoring (1). This poses a great danger to the community and has a negative impact on the healthcare system (1, 2, 8).

There is increasing interest in OPs internationally due to their potential for use in acts of bioterrorism. However, in developing countries such as SA, the concern is still on exposure in the spheres of domestic and farming use, as well as their use in instances of self-harm, all of which have been noted to be on the rise in recent years (1, 2, 5, 9). This rise has been supported by increasing accessibility to OP compounds. These agents are often sold illegally as a cheaper option to the commercially available pesticides in urban areas (5, 8). Due to their acute toxicity, significant exposure to OP agents can result in severe effects, with the requirement for not only hospital admission, but possibly also admission into a critical care unit. This level of care is already under immense strain in our resource constrained setting, due to high levels of trauma and other acute infections such as coronavirus disease-2019 (COVID-19) and chronic diseases (4, 7, 11).

2.2 Epidemiology

Global trends have shown that pesticide poisoning, including OPP, is a significant problem in the developing world compared to the developed world (1, 2, 11). This is supported by studies which demonstrated that in 2001 alone, there were approximately 300 000 cases of non-accidental pesticide poisoning in the developing regions of China and South-East Asia, compared to a 10-year study from Western Australia which documented only 69 cases (1, 12, 13). Much of the data from the developing world arises from Asia, where there is still a large rural population that is dependent on farming practices that make use of OP-based

insecticides, which authors attribute as the major factor behind the high rates of poisonings in these areas (1, 13).

There are few studies from sub-Saharan Africa investigating OPP. Two of these studies were from Zimbabwe, that indicated remarkable increases in cases of OPP. The reported cases rose from 60 in 1995 to 192 in the year 2000 (9, 11). Furthermore, two articles from the Western Cape Province in SA demonstrated a rise in the incidence of OPP in the regions where the studies took place (1, 3, 4). The only study from the Gauteng Province in SA undertook a retrospective review of 207 cases reported to the surveillance office in the Tshwane district over a three-year period. This study included both adults and children (1, 2). The SA studies did not look specifically at the trend of OPP but presented significant demographic characteristic findings that showed a male predominance (58.9%) in the cases reported, with suicide as the main reason for ingestion (2, 5).

According to a review of six cases in a hospital in Pretoria, SA, OPP was a common cause of acute illness and death in pregnant teenagers (8). The study recommended that attending healthcare personnel must suspect OPP when attending to acutely ill young women who are unbooked or those who request termination of pregnancy (TOP) at advanced gestational age more than the legal 20 weeks (8).

Most reports on OPP indicate that the 25 to 30-year-old age group predominate, which is the young and economically active proportion of the population (1, 5). The South African study from the Western Cape Province showed that three in four of the cases were under 40 years of age and the study from Tshwane revealed that only 17.9% of their patients were over the age of 40 years (2, 4, 7). The only study found from SA giving a breakdown of ethnicity of patients with a diagnosis of OPP was a study published in 1976 and was a broader investigation of pesticide poisoning in general (1, 5). This study demonstrated a higher incidence of poisoning amongst the black African population group, with the lowest prevalence amongst the white population (1-3).

In a study of 21 cases conducted at a central hospital in West-Bangal, India, a fatality rate of 9.5% was recorded in pregnant women who presented with OPP (14, 15). A study from Sri

Lanka that included all OPP admissions found a fatality rate of 21.8% over a 11-year period (199 deaths from 914 hospital admissions). Explanation for this high fatality rate included the toxic nature of the OP consumed, the lack of readily available antidotes, long distances between hospitals, and over-stretched staff and resources (13). Further studies in Singapore, southern Taiwan, Nepal, Turkey, Jordan, SA, and Zimbabwe all showed fatality rates ranging from three to nine percent (2, 4, 11, 16). The study in the Western Cape Province which focussed on ICU admissions from OPP showed a fatality rate of 16.0% (1, 4).

2.3 Organophosphate exposure

In agricultural areas where a lot of pesticides and insecticides are used, majority of OPP cases that have been reported are from accidental exposure through ingestion, skin contact and inhalation (3, 5, 17, 18). However, in the urban settings, intentional exposure through ingestion has been reported in most cases (5, 19). Most cases are suicidal, TOP attempt, and intentional poisoning by another individual (1, 2, 18). Since these chemicals are readily available on the streets and shops, most people find it easy to use (3). In recent years, pregnant mothers have used illegal abortifacients such as pesticides to terminate unwanted pregnancies (8).

A recent World Health Organization (WHO) report stated that pesticides are now the most common method of suicide worldwide (2, 4). Studies have reported that suicide or parasuicide accounts for a large proportion of pesticide poisoning worldwide (1, 13). In one study from 1981 to 1986, 161 cases of OPP were found at Parirenyatwa Hospital in Zimbabwe, with 83.0% of them being coded as suicides or parasuicides and only 17.0% as accidents (5, 9). In SA, a study in the Eastern Cape Province, found that of all the patients admitted to ICU with a history of attempted suicide, 55.0% were secondary to OPP. A similar study in Gauteng Province, also found that half the patients had suicide-related poisonings (2, 4). These studies highlight the need for active enforcement of the relevant legislation and control of these substances, as well as the need for appropriate counselling and psychosocial services in the community (6, 7).

2.4 Mechanism of action in organophosphate compounds

Organophosphate poisoning results from the combination of OP or carbamate compounds with phosphorylate or carbamylate carboxylic esterase enzymes respectively (18, 20). Both

pathways result in the enzymes being unable to degrade the neurotransmitter acetylcholine at synapses. The accumulation of acetylcholine initially results in stimulatory effects on the skeletal and the autonomic nervous systems, which then later become inhibitory in nature (21). The effects are determined by the type of receptors affected, either muscarinic or nicotinic (16, 22).

2.5 Clinical effects of organophosphate poisoning

When there is overstimulation of muscarinic receptors, the clinical effects include vomiting, lacrimation, urination, salivation, diarrhoea, miosis, bradycardia and bronchospasms (16, 22, 23). Overstimulation of nicotinic receptors results in muscle paralysis and fasciculations, hypertension, hypoglycaemia, convulsions, respiratory distress, circulatory failure, and altered Glasgow Coma Scale (GCS) (16, 21, 24, 25). Patients with OPP commonly present with a combination of muscarinic and nicotinic effects, known as the cholinergic phase, with the clinical picture varying from little symptomatology to being moribund on admission (18, 25). Late findings of OPP may include personality changes, aggression, psychosis and deficits in memory and attention, and peripheral neuropathy which can lead to flaccid paralysis (6, 24, 26). Death commonly occurs due to respiratory failure from the combination of central and peripheral effects, and other complications like severe metabolic acidosis (25). A SA study from the Western Cape Province mentioned that 50.0% of patients presented with classical signs of OPP but did not comment on which of these signs were the most common presenting features (1, 4).

Signs and symptoms of OPP may become apparent from within 15 minutes (more commonly with carbamates) up to 24 hours after exposure (6, 25, 27). Another known complication is the OP intermediate syndrome that involves various combinations of muscle paralysis which may manifest one to four hours after the poisoning and generally after the resolution of the cholinergic phase. This often results in regression of the patient's improvement leading to unexpected mortality (21, 24, 28).

The diagnosis of OPP is made by a confirmed OP exposure and the clinical manifestation with muscarinic and cholinergic effects. Exposure to OP can also be confirmed by

measurements of the target enzyme levels in the patient's blood or urine (20, 23). These enzymes include butyryl-cholinesterase and AChe activity in red blood cells (RBCs) and plasma (20, 29). In SA, these laboratory tests are not readily available in public hospitals and management is mostly commenced on history of ingestion and clinical diagnosis (1, 4, 25). Different OP agents tend to result in different enzyme levels on presentation making interpretation of enzyme results difficult if the exact agent consumed is unknown. Due to these limitations, an AChe level of less than 50.0% of the minimum reference range is generally accepted to support the diagnosis of OPP in most studies (8, 19, 30).

Clinical experience suggests that transfer of OPs from the pregnant woman to the fetus via the placenta is probable (20, 31, 32). Although fetal plasma and RBC cholinesterase levels are lower than adults and fetal response to maternal OPP is hypothesised, a single acute overdose is unlikely to cause any physical deformities, hence a termination of pregnancy (TOP) may not be imperative (33). Previous research has postulated that increased levels of acetylcholine at the muscarinic and nicotinic receptors stimulates contraction of the uterus (33, 34). Pesticides have also been detected in amniotic fluid, umbilical cord blood, meconium, and infant urine, indicating exposure of the fetus to pesticides (35, 36). Spontaneous abortion has been reported in some pregnant women (15, 37).

2.6 Investigations

Many authors point out the need of performing thorough laboratory investigations when attending to patients presenting with suspected poisoning or drug overdose (21, 37). These tests include urinalysis, blood gas, full blood count, urea and electrolytes, and liver function tests. Other important tests include a urine and blood toxicology screen (15). A urine pregnancy test is recommended in any woman of childbearing age as this will guide in the medical management plan if the patient is found to be pregnant (8). Some medications used in acute management of poisons are contraindicated in pregnancy but in emergency cases, the health of the woman is prioritised to save her life (38). Enzyme levels are useful in confirming some poisoning cases and determining the severity of their effects. In case of OPP, AChe levels are tested to support the diagnosis of OPP and monitor response to treatment (21, 39).

2.7 Management of organophosphate poisoning in pregnancy

Organophosphate poisoning in pregnancy presents a critical situation for both the pregnant woman and the fetus. Previous research has shown that prompt diagnosis and management of OPP in pregnancy can reduce associated morbidity and mortality (10, 24, 25, 37). The mainstay of treatment in OPP is atropine, which blocks the action of acetylcholine at the muscarinic receptors. Atropine is only effective at the level of muscarinic receptors and does not influence the effects of acetylcholine on the nicotinic receptors (15, 16, 24). Negative effects of atropine on the fetus include tachycardia and reduced variability of heart rate (24, 38). Neonatal mydriasis has also been reported in some studies (24). Atropine has been shown to have no teratogenic effects according to surveillance studies and its use in pregnancy should not be withheld. A retrospective study of 15 pregnant women with OPP who received atropine showed no congenital nor neurological deficit in the babies (15, 24).

Oximes, which include pralidoximes, have been developed to reverse the effect of OP on nicotinic receptors. These oximes bind to the organophosphate-acetylcholinesterase complex, resulting in a conformational change, with the oxime binding to the OP and splitting off, leaving the AChe free and regenerated (21, 24, 38). Although promising in theory, with some impressive results in *in vivo* studies, the proposed benefits of oximes are not well-documented (24). There appears to be varied responses to oximes in the literature reviewed, with some small trials even demonstrating an increased mortality with oxime use (24, 40).

Several other agents have been investigated in the treatment of OPP. These include glycopyrrolate, benzodiazepine, ipratropium bromide and magnesium sulphate (21, 24). Glycopyrrolate has antimuscarinic properties, but it has no activity against the nicotinic effects of the OPs. In addition, glycopyrrolate does not cross the blood-brain barrier and therefore has minimal effect on the central nervous system symptoms. Glycopyrrolate is more expensive compared to atropine and therefore there is an economic consideration in resource limited environments (24, 37, 40). Ipratropium bromide is a nebulising anti-muscarinic agent that has been used in a limited context as an adjunct to intravenous atropine (6, 16, 41). Benzodiazepines are primarily used to reduce agitation and anxiety in patients with OPP and have been recommended as first line therapy in toxin induced

seizures (16, 21). Magnesium sulphate has been shown to decrease synaptic acetylcholine release by blocking calcium channels. Apart from that, there is some evidence that magnesium sulphate may help to prevent ventricular tachycardias that are associated with OPP (1, 6, 30).

A significant number of patients who present with OPP will require ventilatory support due to the toxidrome effects on the respiratory system. Organophosphate poisoning causes muscle paralysis, and the severe respiratory secretions will cause aspiration, hence the need to protect the airway (24, 28). Studies done in rural Asia have shown that the rates of intubation and ventilation approached 20.0 - 30.0% (24). Of these patients, two thirds needed ventilation on admission for a median duration of 45 hours. Extrapolation from these initial figures showed that 3140 to 6280 ventilators were required each year to ventilate poisoned patients in rural Asia, of which OPP accounted for 90.0% (24). The duration of ventilation is also associated with the length of HCA or ICU stay. A longer stay in ICU or HCA is associated with higher costs and an increased risk of complications, including nosocomial sepsis (1, 16, 42). Various studies from Singapore, Turkey and Saudi Arabia found that the average length of the ICU stay for patients exposed to OPs was between two to ten days, which is similar to an SA study in the Western Cape that reported the average length of ICU stay of eight days (4, 8, 42).

Severity of OPP can be assessed using the Acute Physiology and Chronic Health Evaluation II (APACHE II) score. Prediction scores indicating good outcomes following admission to ICU or HCA are attractive, especially for resource-limited countries. Several studies examining different scoring systems have been published to determine the most clinically accurate system (24, 27, 42). No studies were found regarding scoring system use in OPP in SA. As can be seen by the clinical manifestations, patients with worst APACHE II scores frequently need a significant amount of medical care on presentation and may have a protracted hospital stay, depending on the severity of poisoning and any associated complications (21, 28).

2.8 Effects of OPP on the fetus and early neonate

Few studies have been performed to ascertain the effects of OPP in the developing fetus. This could be because the priority is given to stabilising the pregnant woman as the index patient (19, 24). Toxins in the pregnant woman are delivered to the fetus through the

placenta, leading to detrimental effects on its homeostatic environment (33). Pregnant women who have passed viability stage should have their fetuses monitored only after the woman has been stabilised (19). If this monitoring is done when the patient is still being resuscitated, the fetus may also be in distress. Studies have shown that it is better to resuscitate the fetus in utero by resuscitating the pregnant woman as the communication through the placenta makes it better to improve the fetal condition (19, 37).

2.9 Suicide in pregnancy

According to the WHO global report on violence and health in 2002, suicide, a worldwide phenomenon on the rise, occurs every 40 seconds and an attempt occurs every one to three seconds (38, 43). Suicide is the fourth leading cause of death of women of reproductive age, causing 8.0% – 9.0% of deaths in this age group and accounts for 1.0 – 2.0% of maternal deaths in low- and middle-income countries (43). Suicide is also believed to be an important cause of maternal death during the perinatal period. The most common method is intentional self-poisoning. Self-poisoning is not only for the purpose of suicide, but also employed to gain attention, express distress or to get revenge (38, 44).

Stigma, misreporting and inaccurate recording of cause of death contribute to inaccuracy of data, and the true proportion of deaths attributable to suicide in pregnant women living in developing countries may not be represented in available data. Risk factors for suicide in pregnancy include adverse economic and socio-demographic factors, discrimination against women and inappropriate and unresponsive healthcare services (43).

CHAPTER III: RESEARCH METHODS

3.1 Aim

The aim of the study was to assess the socio-demographic characteristics, maternal and pregnancy outcomes of pregnant women with OPP at CHBAH from 1 January 2017 to 31 December 2019.

3.2 Objectives

The main objectives of the study were:

1. To describe the socio-demographic characteristics of pregnant women presenting with OPP at CHBAH.

2. To describe the clinical features and maternal outcomes of OPP cases.

3. To describe the fetal and early neonatal outcomes in pregnant women presenting with OPP at CHBAH.

3.3 Methodology

3.3.1 Study setting

The study was conducted at CHBAH in Soweto, Johannesburg, SA. Chris Hani Baragwanath Academic Hospital is a tertiary teaching hospital which is affiliated to the University of Witwatersrand. The maternity department at CHBAH is the largest in the country and serves several community health centres and hospitals in the greater Soweto area of Gauteng Province. The hospital serves about two million people, mainly of low income, and the maternity unit delivers approximately 22 000 babies each year (44).

The unit has an admission area, an observation area for monitoring pregnant women in latent phase of labour, and a delivery area. It also has a high care area (HCA) for managing high risk unstable patients and antenatal and postnatal wards. Patients requiring intensive care are managed in the general adult intensive care unit (ICU).

3.3.2 Study design

This was a retrospective, descriptive, analytical, cross-sectional study.

3.3.3 Study population

The study enrolled pregnant women who presented with features of OPP at CHBAH between 1 January 2017 and 31 December 2019.

Inclusion criteria

The study included pregnant women who presented at CHBAH with a clinical diagnosis of OPP. These were divided into probable and definitive cases. Probable cases were suspected OPP with suggestive clinical features whilst definitive cases were confirmed history of OPP ingestion with clinical features and reduced AChe levels.

Exclusion criteria

Pregnant women with multiple chemical or drug ingestion were excluded from the study.

Estimated sample size

This was a descriptive exploratory study and therefore a sample size calculation was not performed. However, a description of OPP in pregnant women reported in literature had sample sizes ranging from six to twenty-one. The assumption was that the study would target at least 30 records for review as a purposive sampling strategy.

3.3.4 Data collection and tools

Details of pregnant women admitted for OPP were retrieved from registers in the HCA, ICU, and maternity admissions. All cases of OPP in pregnancy are treated as high risk and are admitted to HCA or ICU, depending on the severity of symptoms. Medical records were accessed from the records department. The National Health Laboratory Services (NHLS) provided data on female patients who had AChe levels tested during the study period. The NHLS data was matched with that from the CHBAH records to identify any additional patients' files from CHBAH records and the ones meeting the study inclusion criteria were used for data collection.

The following information was collected from patient medical records using a data collection tool (Annexure 1): socio-demographic factors (age, parity, gestational age, marital status, employment status) and circumstances of ingestion (i.e., reason for ingestion). Examination

findings on presentation and the worst readings during admission: blood pressure, pulse, respiratory rate, level of consciousness, pupillary light reflex, salivation, fasciculations, seizures, diarrhoea were collected. This information was also obtained from the paramedics' charts that they use when transporting patients to hospital. The amount (loading dose given in incremental boluses until toxidrome features subside) and duration of atropine administration was also captured from the patients' records.

Results from the investigations done on the patients were obtained from the patients' files. These included blood gases on admission and the worst recorded parameters during the duration of stay in hospital, full blood count, urea and electrolytes, liver function tests, and AChe levels. Maternal outcomes were also captured which included ventilation requirement, duration of ventilation and length hospital stay, mode of delivery, and discharge status. Fetal and early neonatal outcomes [live births, still births, birth weight, APGAR score, any malformations, duration of hospital stay, and discharge status] were captured in the last section of the data collection tool. The data collection tool was piloted using five files.

3.3.5 Data Analysis

The de-identified information recorded in the data sheet was entered into REDCap data management system (version 4.8.6) and was exported into STATA (version 15) for analysis. Categorical variables were summarised by frequency and percentage tabulations. Continuous variables were assessed for normality using the Shapiro-Wilk test and where applicable, data was summarised using means and standard deviations or medians interquartile ranges and ranges.

Age was categorised into <18, 18-35 and >35 years, as less than 18 years is considered high risk teenage pregnancy whilst >35 years is high risk advanced maternal age. Maternal pH was categorised into $\leq$7.35 and >7.35 (i.e., acidosis versus normal pH), whilst GCS was categorised into $\leq$ 14 and 15 (i.e., abnormal versus normal). Lactate was converted into two categories $<$2 and $\geq$2 (i.e., normal versus abnormal). Acetylcholinesterase levels were converted into a binary variable using 3930 U/L cut-off that is used by NHLS as evidence of OPP. Fisher's exact test was used to explore the associations between potential predictor variables and maternal and fetal outcomes (i.e., dependent variables). A p-value of $\leq$0.05 was considered to be statistically significant.

3.4 Ethical requirements and permission to conduct research

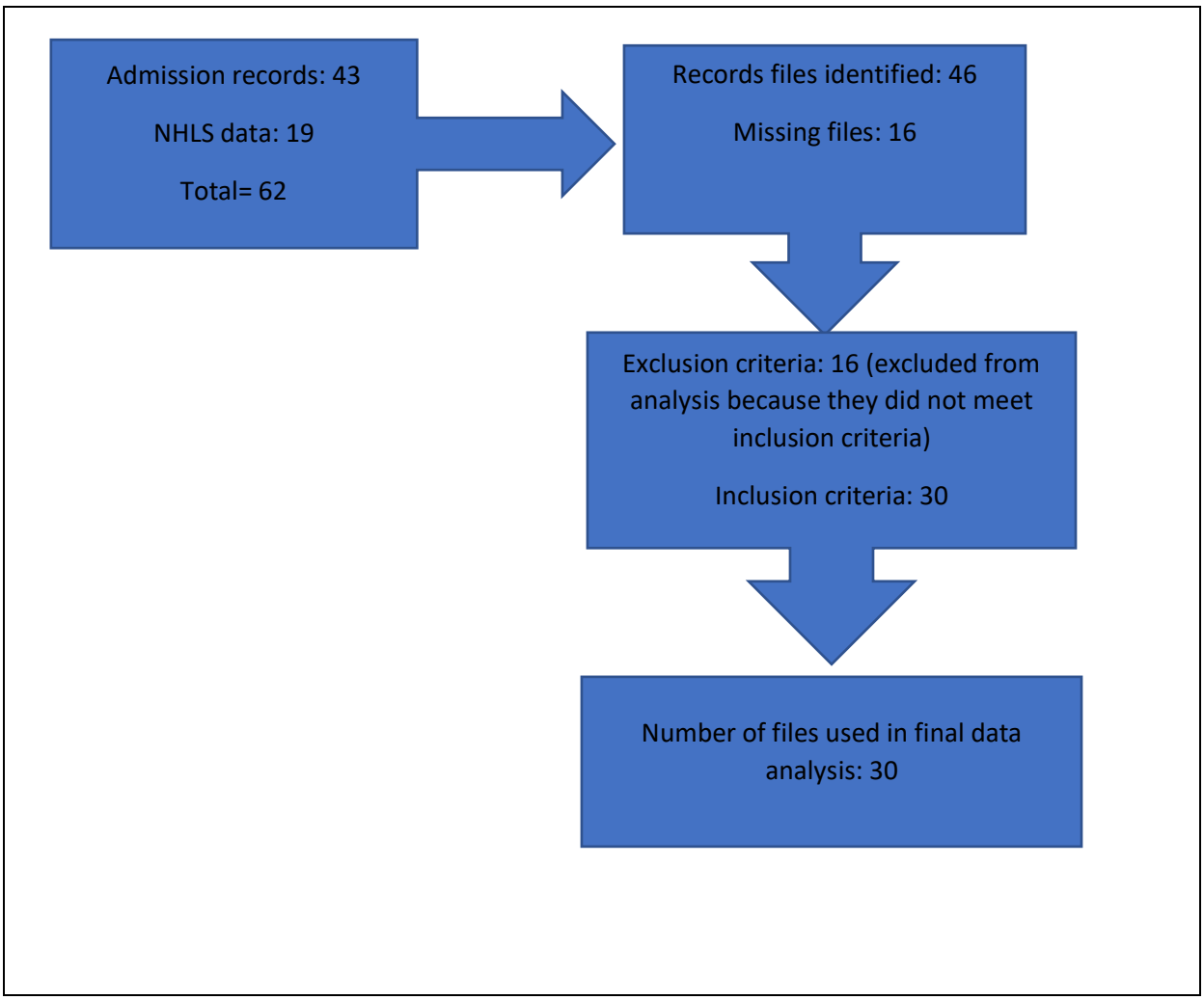
Ethics approval to conduct the study was obtained from the University of Witwatersrand Human Research Ethics Committee (Number M200335). It was granted after the protocol approval by the post-graduate research committee (Annexure 2). Permission was also obtained from the Chief Executive Officer at CHBAH (Annexure 3) and the Obstetrics and Gynaecology Head of Department (Annexure 4).

CHAPTER IV: RESULTS

4.1 Study Population

A total of 62 patient details were identified. These included 43 patients from the admission registers in the maternity section at CHBAH and 19 from the NHLS Database. Forty-six files were retrieved from the records department, and we could not get 16 of the remaining files. Out of the 46 files, a total of 30 files were included in the analysis and 16 files were excluded because they did not meet the inclusion criteria (see Figure 1 below for more details).

Figure 1: Study flow chart



4.2 Baseline characteristics

Most of the pregnant women with OPP, 83.3% (n = 25), were between the ages of 18-35 years, with 13.3% (n = 4) being less than 18 years whilst 3.3% (n = 1) were greater than 35 years as shown in Table 1. Almost all patients (n = 29; 96.7%) were black African patients and only one patient was coloured. Thirteen percent of the women (n = 4) were married whilst 26.7% (n = 8) were employed. Patients who required ICU were 13.3% (n = 4) whilst 86.7% (n = 26) were admitted to HCA as shown in Table 1.

Median parity was one (IQR 0 - 1, range 0 - 3) and median gravidity was two (IQR 1 - 2, range 1 - 4). Seventy percent (n = 21) of the patients were booked. Median gestational age on admission was 21 weeks (IQR 18 - 24, range 14 - 37). Seven percent of the patients (n = 2) were HIV positive, 100.0% were RPR negative and 3.7% (n = 1) were Rhesus negative. The median haemoglobin was 10.4g/dl (IQR 10.1 - 12.1, range 9 - 13.4). Intentional ingestion of OPP was recorded in 80.0% (n = 24) of patients, whilst 3.3% (n = 1) was accidental and 16.7% (n = 5) was unknown (Table 1).

Table 1: A description of baseline characteristics

Description	n (%) or median (IQR, range)
Age in years (n = 30)	
<18	4 (13.3)
18-35	25 (83.3)
> 35	1 (3.3)
Race	
African	29 (96.7)
Coloured	1 (1.3)
Marital Status	
Single	26 (86.7)
Married	4 (13.3)
Employment Status	
Employed	8 (26.7)
Unemployed	22 (73.3)
Ward of admission	
HCA	26 (86.7)
ICU	4 (13.3)
Median parity (IQR)	1 (0 - 1, 0 - 3)
Median gravidity (IQR)	2 (1 - 2, 1 - 4)
Booking status	
Booked	21 (70.0)
Unbooked	9 (30.0)
Median gestational age on admission in weeks	21 (18 - 24, 14 - 37)
Booking bloods	
HIV positive	2 (6.7)
RPR positive	0 (0)
Rhesus negative	1 (3.7)
Median Hb (g/dl) (IQR)	10.4 (10.1 - 12.1, 9.0 - 13.4)
Exposure to OPP	
Intentional	24 (80.0)
Accidental	1 (3.3)
Not stated	5 (16.7)

4.3 Clinical features of women with OPP

Eighteen percent of women with OPP had hypovolaemic shock. The median lowest systolic blood pressure (BP) during hospital stay was 98 (IQR 94 - 105, range 55 - 172) mmHg whilst the median lowest diastolic BP was 52 (IQR 47 - 66, range 35 - 111) mmHg. The median worst pulse during admission was 120 (IQR 109 - 130, range 49 - 154) beats per minute. The respiratory rate had a median of 18 (IQR 14 - 24, range 8 - 41) breaths per minute on admission, with a median worst respiratory rate of 26 (IQR 18 - 32, range 8 - 41) breaths per minute as shown in Table 2.

The median GCS on presentation was 14 (IQR 11 - 15, range 3 - 15) whilst the median worst GCS during hospital stay was 12 (IQR 8 - 14, range 3 - 15). All patients (n = 30) presented with an increase in respiratory secretions on admission, 96.4% (n = 27) presented with pin-point pupils, 92.6% (n = 25) had salivation, 54.2% (n = 13) had fasciculations whilst 43.5% (n = 10) had diarrhoea (Table 2). Fifteen (51.7%) of the women with OPP had live fetuses on admission whilst 14 (48.3%) had confirmed intrauterine deaths. Five (38.4%) out of the 13 patients who had a cardiotocograph done had pathological traces, whilst four (30.8%) were normal and four (30.8%) of the traces were suspicious (Table 2)

Table 2: Clinical features of women presenting with organophosphate poisoning

Description	n (%) or median (IQR, range)
Blood Pressure in mmHg	
Median systolic BP on admission	103 (98 – 126, 58 - 165)
Median worst systolic BP**	98 (94 - 105, 55 - 172)
Median diastolic BP on admission	67 (51 – 78, 41 - 108)
Median lowest diastolic BP**	52 (47 - 66, 35 - 111)
Systolic BP <90mmHg (Shock)	6 (17.9%)
Pulse (beats per min)	
Median pulse rate on admission	79 (63 – 95, 49 - 154)
Median worst pulse rate **	120 (109 - 130, 49 - 154)
Respiratory Rate (breaths per min)	
Median respiratory rate on admission	18 (14 - 24, 8 - 41)
Median worst respiratory rate**	26 (18 - 32, 8 - 41)
Respiratory secretions (n* = 30)	30 (100.0)
Median Glasgow Comma Scale (GCS) admission	14 (11 - 15, 3 - 15)
Median worst GCS **	12 (8 - 14, 3 - 15)
Pupils on admission (n* = 28)	
Normal	1 (3.6)
Pinpoint	27 (96.4)
Dilated	0 (0)
Salivation (n* = 27)	25 (92.6)
Fasciculations/Seizures (n* = 24)	13 (54.2)
Diarrhea (n* = 23)	10 (43.5)
Pregnancy status on admission (n* = 29)	
Live fetus	15 (51.7)
Intrauterine death	14 (48.3)
CTG findings on admission (n* = 13)	
Normal	4 (30.8)
Suspicious	4 (30.8)
Pathological	5 (38.4)

* Number of records from which the variable was captured

** Worst reading during the period of admission

4.4 Maternal haematological and biochemical findings

Seventeen (56.6%) patients had AChe levels tested and 15 (88.2%) were less than 3930 U/L. Most patients (81.2%) showed a general picture of metabolic acidosis both on admission and worst readings during hospital stay as shown by median pH <7.35, base excess >2.0, and lactate >2.0. (Table 3). Bloods done during admission showed normal haematological and biochemical results for the pregnant women who presented with OPP as shown in Table 3 below.

Table 3: Maternal haematological and biochemical findings

Description	n (%) or median (IQR, range)
Number of AChe tests done	17 (56.6)
Women with AChe levels (U/L) (n = 17)	
≤3930	15 (88.2)
Blood gas on admission (n = 30)	
Median pH	7.30 (7.21 - 7.39, 6.90 - 7.53)
Median pO_2 mmHg	74.5 (53.7 - 88.0, 27 - 171)
Median pCO_2 mmHg	47.0 (34.6 - 52.0, 22.7 - 53.6)
Median base excess mEq/L	6.1 (3.2 - 7.9, 2.3 - 15.2)
Median HCO_3 mmol/L	17.8 (14.2 - 19.2, 11.5 - 21.9)
Median lactate	2.2 (1.1 - 3.8, 0.6 - 10.2)
Metabolic acidosis	24 (81.2%)
Blood gas worst reading	
Median pH	7.27 (7.15 - 7.32, 6.90 - 7.52)
Median pO_2 mmHg	57.1 (48.0 - 86.0, 48.0 - 86.0)
Median pCO_2 mmHg	47.3 (42.4 - 54.0, 28.9 - 72.4)
Median base excess mEq/L	6.7 (3.7 - 8.5, 2.3 - 15.2)
Median HCO_3 mmol/L	16.7 (14.2 - 19.2, 8.1 - 21.9)
Median lactate	2.9 (2.1 - 4.1, 0.6 - 18.7)
Median hematological and biochemical parameters	
WCC $x10^9$/L	11.4 (8.5 - 14.8)
Hemoglobin (g/dL)	10.7 (9.2 - 11.9)
Plateletsx10^9/L	220.0 (158.0 - 264.0)
Potassium(mmol/L)	3.9 (3.2 - 4.2)
Sodium (mmol/L)	138.0 (137.0 - 139.0)
Urea(mmol/L)	2.5 (1.6 - 3.6)
Creatinine(um/L)	52.0 (45.0 - 62.0)
Albumin(g/L)	36.0 (32.0 - 37.5)
Alanine transaminase(U/L)	15.0 (11.0 - 22.0)
Aspartate amino transaminase (U/L)	24.0 (18.0 - 37.0)
GGT (U/L)	16.5 (9.5 - 43.5)
ALP (U/L)	102.0 (74.5 - 166.0)
INR	1.0 (1.0 - 1.1)
Calcium (mmol/L)	2.1 (1.9 - 2.2)
Magnesium(mmol/L)	0.8 (0.7 - 0.9)
Phosphate (mmol/L)	1.0 (0.8 - 1.4)

4.5 Maternal outcomes

The fatality rate was 10% (n = 3). Median loading dose of atropine was 9mg (IQR 6.0 - 14.0, range 3-60) whilst the median duration of atropine infusion was 2 days (IQR 1 - 3, range 1 - 7). Ventilation was required in 15 (50.0%) of the admitted patients with a median duration on ventilation of 4 days (IQR 1 - 3, range 1 - 29). The median duration of hospital stay was 6.5 days (IQR 4 - 10, range 3 - 45) (Table 4.1).

Nineteen patients (63.3%) delivered vaginally whilst 11 (36.7%) had a caesarean section. Of the caesarean deliveries, nine (81.8%) were due to fetal distress, one (9.1%) previous caesarean section, and 9.1% due to other reasons. Eight patients had meconium-stained liquor (Table 4.1).

Table 4.1: Maternal outcomes

Description	n (%) or median (IQR, range)
Maternal deaths (n = 30)	3 (10)
Atropine administration (n = 30)	
Median loading dose in mg	9 (6 - 14, 3 - 60)
Median days on atropine	2 (1 - 3, 1 - 7)
Ventilation (n = 30)	15 (50.0)
Median duration of ventilation in days (n = 15)	4 (1 - 3, 1 - 29)
Median duration of hospital stay in days (n = 30)	6.5 (4 - 10, 3 - 45)
Delivery mode (n = 30)	
Vaginal	19 (63.3)
Caesarean section	11 (36.7)
Indication for caesarean section (n = 11)	
Fetal distress	9 (81.8)
Previous caesarean delivery	1 (9.1)
Unknown	1 (9.1)
Meconium-stained liquor (n = 8)	
Thick MSL	4 (50.0)
Thin MSL	4 (50.0)

Table 4.2 below shows that the maternal deaths from OPP were generally young patients, unbooked, required ventilation, had low AChe levels, low pH, high lactate, and had poor fetal outcomes. Organophosphate poisoning was identified as the cause of death of the three deaths at the morbidity and mortality meetings.

Table 4.2: Maternal deaths description

Case #	Age in years	Ventilation, Number of days	Worst pH	Worst lactate	Fetal Outcome	AChe levels IU/L	Worst GCS	Booking Status
1	23	Yes, 7 days	7.19	8.1	MSB	<200	8	Booked
2	21	Yes, 4 days	6.90	12.6	MSB	305	3	Unbooked
3	24	Yes, 3 days	7.05	18.7	Miscarriage	313	5	Unbooked

4.6 Fetal outcomes

All pregnant women with OPP had delivered on discharge with 13 (43.3%) live births, four (13.3%) miscarriages, and 13 (43.3%) stillbirths. Of the stillbirths, five (38.5%) were macerated whilst eight (61.5%) were fresh stillbirths (Table 5).

The median birth weight was 1815 grams (IQR 1100 - 2575, range 325 - 3905) and 11 (36.7%) were alive on discharge. The median APGAR score of the live births was six (IQR 5 - 8, range 2 - 9) at 1 minute and nine (IQR 7 - 10, range 6 - 10) at 5 minutes of life, with six (46.2%) requiring admission to Neonatal Intensive Care Unit (NICU). Median duration of hospital stay for the neonates was two days (IQR 1 - 3, range 0 - 10).

Table 5.1: Fetal outcomes

Description	n (%) or median (IQR, range)
Fetal outcome at delivery (n* = 30)	
Miscarriage	4 (13.3)
Live birth	13 (43.3)
Stillbirth	13 (43.3)
Stillborn status (n* = 13)	
Macerated still birth	5 (38.5)
Fresh still birth	8 (61.5)
Median birth weight in grams (n* = 27)	1815 (1100 - 2575, 325 - 3905)
APGAR score (n* = 13)	
Median score at 1 minute	6 (5 - 8, 2 - 9)
Median score at 5 minutes	9 (7 - 10, 6 - 10)
Congenital abnormalities (n* = 19)	0 (0)
Admission to NICU (n* = 13)	6 (46.2)
Median duration hospital stay in days (n* =13)	2 (1 - 3, 0 - 10)
Discharge status (n* = 30)	
Alive	11 (36.7)
Fetal loss	17 (56.7)
Early neonatal death	2 (6.7)

*Number of files from which variable was captured

Table 5.2 below shows that the two early neonatal deaths were both preterm, delivered via caesarean section due to fetal distress and thick MSL, had low APGAR scores at one and five minutes, and required admission to NICU.

Table 5.2: Early neonatal deaths description

Case #	Gestational Age in wks	Birth weight	MSL	Reason for C/S	1 min APGAR	5 min APGAR	Days in NICU
1	35	2640 grams	Thick	Fetal distress	2	4	3
2	28	1180 grams	Thick	Fetal distress	3	4	5

4.7 Factors associated with maternal outcomes

An atropine dose of more than 9.0mg was significantly associated with maternal fatality. All the deaths occurred in patients who had a loading dose of more than 9mg and none of the patients with a loading dose of less than 9mg died (p-value of 0.04) as shown in Table 6.

Other variables which included the worst pH, ventilation status, length of hospital stay, AChe levels, GCS, worst lactate and booking status were not significantly associated with maternal fatality (Table 6).

Table 6: Factors associated with maternal outcomes

Variable	N	Alive	Dead	p-value*
Worst pH	N = 27	(n = 24)	(n = 3)	1.00
≤7.35	21 (77.8)	18 (75.0)	3 (100.0)	
>7.35	6 (2.2)	6 (25.0)	0 (0.0)	
Ventilation	N = 30	(n = 27)	(n = 3)	0.22
Yes	15 (50.0)	12 (44.4)	3 (100.0)	
No	15 (50.0)	15 (55.6)	0 (0.0)	
Length of stay	N = 30	(n = 27)	(n = 3)	1.00
<6.5days	15 (50.0)	14 (51.8)	1 (33.3)	
>6.5days	15 (50.0)	13 (48.2)	2 (66.7)	
AChe levels U/L	N = 17	(n = 14)	(n = 3)	1.00
≤3930	15 (88.2)	12 (85.7)	3 (100.0)	
>3930	2 (11.8)	2 (14.3)	0 (0.0)	
GCS	N = 28	(n = 25)	(n = 3)	1.00
≤14	23 (82.1)	20 (80.0)	3 (100.0)	
>14	5 (17.9)	5 (20.0)	0 (0.0)	
Worst lactate	N = 27	(n = 24)	(n = 3)	0.47
≤2.0	5 (18.5)	4 (16.7)	1 (33.3)	
>2.0	22 (81.5)	20 (83.3)	2 (66.7)	
Atropine dose	N = 26	(n = 23)	(n = 3)	**0.04**
≤9.0mg	16 (61.5)	16 (69.5)	0 (0.0)	
>9.0mg	10 (38.5)	7 (30.5)	3 (100.0)	
Booking status	N = 30	(n = 27)	(n = 3)	0.21
Booked	21 (90.0)	20 (74.5)	1 (33.3)	
Unbooked	9 (10.0)	7 (24.5)	2 (66.9)	

*P-values obtained from Fisher's exact test

4.8 Factors associated with fetal outcomes

Fetal mortality was significantly associated with unbooked status (p = 0.01), worst maternal pH ≤7.35 (p = 0.02), maternal ventilation (p = 0.01), hospital stay ≥6.5 days (p = 0.02), worst maternal GCS of ≤14 (p = 0.05) (Table 7). There was no significant association of poor fetal outcomes with AChe level ≤3930 (p = 0.13), lactate level >1.0 (p = 1.00) and atropine >9.0mg (p = 0.23) as shown in Table 7.

Table 7: Factors associated with fetal outcomes

Variable	N	Alive	Fetal loss/END	p-value*
Booking status	N = 29	(n = 11)	(n = 18)	**0.01**
Booked	21 (72.4)	11 (100.0)	10 (55.6)	
Unbooked	8 (27.6)	0 (0.0)	8 (44.4)	
AChe level U/L	N = 16	(n = 5)	(n = 11)	0.13
≤3930	15 (93.8)	4 (80.0)	11 (100.0)	
>3930	1 (6.2)	1 (20.0)	0 (0.0)	
Worst pH	N = 26	(n = 10)	(n = 16)	**0.02**
≤7.35	20 (76.9)	5 (50.0)	15 (93.8)	
>7.35	6 (23.1)	5 (50.0)	1 (6.2)	
Ventilation	N = 29	(n = 11)	(n = 18)	**0.01**
Yes	15 (51.7)	2 (18.2)	13 (72.2)	
No	14 (48.3)	9 (81.8)	5 (27.8)	
Length of stay	N = 29	(n = 11)	(n = 18)	**0.02**
<6.5days	15 (51.7)	9 (81.8)	6 (33.3)	
>6.5days	14 (48.3)	2 (18.2)	12 (66.7)	
Maternal GCS	N = 27	(n = 10)	(n = 17)	**0.05**
≤14	22 (81.5)	6 (60.0)	16 (94.1)	
>14	5 (18.5)	4 (40.0)	1 (5.9)	
Lactate	N = 26	(n = 10)	(n = 16)	0.34
≤2.0	5 (19.2)	3 (30.0)	2 (12.5)	
>2.0	21 (80.2)	7 (70.0)	14 (87.5)	
Atropine dose	N = 25	(n = 9)	(n = 16)	0.23
≤9.0mg	15 (60.0)	7 (77.8)	8 (50.0)	
>9.0mg	10 (40.0)	2 (22.2)	8 (50.0)	

*P-values obtained from Fisher's exact test

CHAPTER V: DISCUSSION

This study sought to describe the socio-demographic profile, characterise the clinical features, maternal outcomes as well as determine the fetal and early neonatal outcomes amongst pregnant women presenting with OPP at CHBAH.

5.1 Baseline sociodemographic characteristics

The majority of patients in this study, 83.3% (n = 25), were between the ages of 18 - 35 years. These findings are comparable to previous reports on OPP which indicate that the 25 to 30-year-old age group predominate. A study from the Western Cape Province of SA showed that 75% of the cases were under 40 years of age. Similarly, a study from Tshwane, Gauteng Province of SA revealed that 82.1% of their patients were aged 40 years and less (2, 4). The under 40 age-group is the relatively young and economically active proportion of the population. Therefore, this implies a huge economic burden from OPP resulting from hours of lost productivity as these patients will not go to work and in most cases fail to earn income.

The majority (96.7%) of the pregnant women with OPP were black African. This is in keeping with the demographics of the catchment area covered by CHBAH. There were four (13.3%) women with OPP who were married and eight (26.7%) were employed. The unemployment rate in our study was much higher (63.7%) as compared to the women unemployment rate in SA of 32.5% according to statistics SA as of December 2020 (45).

Median parity was one (IQR 0 - 1, range 0 - 3) and median gravidity was two (IQR 1 - 2, range 1 - 4). These are in keeping with our predominantly younger study population. HIV prevalence was 6.7%, which is very low as compared to the average prevalence of 21.0% amongst pregnant women in SA (8, 46).

Majority of the OPP cases in our study were a result of intentional ingestion. This is in keeping with published literature, as most studies have shown that intentional exposure through oral ingestion is the most recorded route of exposure in urban, non-farming areas. Most of these cases tend to be suicidal or parasuicidal, an intention to cause termination of pregnancy, and intentional poisoning by another individual (2, 4, 11). In SA, a study

undertaken in the Eastern Cape province, found that 55.0% of the patients admitted to ICU with attempted suicide were secondary to OPP (4). This was also demonstrated by the findings of a study done in Tshwane, Gauteng, SA which reports that 50.2% of their patients had suicide-related poisoning (1, 2).

5.2 Clinical features of women with OPP

In this study it was found that the most common clinical effects were muscarinic. All patients in this study presented with increased respiratory secretions on admission, more than 90% presented with pin-point pupils and salivation, at least half had fasciculations whilst more than two-thirds had diarrhoea. This is consistent with previous studies that showed a predominance of muscarinic effects over nicotinic effects (6, 11, 21, 25). According to literature, when there is overstimulation of muscarinic receptors and the observed clinical effects include vomiting, lacrimation, urination, salivation, diarrhoea, miosis, bradycardia and bronchospasm (1, 16, 23).

Overstimulation of nicotinic receptors results in muscle paralysis and fasciculation, hypertension, hypoglycaemia, convulsions, respiratory distress, circulatory failure, and altered GCS (9, 18, 38). This means clinicians should be on the lookout for these features of muscarinic and nicotinic toxicity and be quick to institute management without waiting for laboratory AChe confirmation. This is more so if the clinical features are supported by a history of OP exposure. The Western Cape Province study, in SA, mentioned that half of their patients presented with classical signs of OPP. The authors, however, did not comment on which of these signs were the most common presenting features (4).

A low GCS occurred in 82.1% of patients in this study. Literature has shown that a low GCS is poor prognostic factor as it is associated with higher doses of OP ingestion, respiratory depression, and other organ failures (6, 16, 28). There were 17.9% of patients who had a low BP (worst systolic $\leq$90mmHg). This is in keeping with literature findings which showed that in severe cases, OPP patients present with hypotension (25, 27). Most patients in this study had a normal pulse rate on admission [79 (IQR 63 - 95), range 49 - 154]. This was somewhat unexpected as the effects of OPP is usually bradycardia on presentation (6, 25). This finding could be because patients were started on atropine either by the paramedic team at the scene or at the referring healthcare facility. Tachycardia is one of the side effects of atropine and this explains the median worst pulse rate of 120 (IQR 109 – 130, range 49 - 154) beats

per minute. The respiratory rate showed a wide range from eight to forty-one. This could be due to the mixed picture on presentation as some patients will be tachypnoeic due to acidosis or severely bradypnoeic due to depressed GCS. Studies have reported that severe cases of OPP will present in respiratory depression with deep laboured breathing which can be tachypnoeic or bradypnoeic (5, 21, 38).

There were poor pregnancy outcomes in this study, with 11 (37.9%) of women delivering live babies and this was comparable to published studies which have reported high fetal loses (8, 15, 39). This could be explained by the gestational age at which the OPP was taken and the severity of the OPP on the mother (37, 39).

5.3 Maternal haematological and biochemical findings

Most patients (88.2%), who had enzyme levels tested, had AChe levels less than 3930 U/L. This is in agreement with literature, which notes that exposure to OP can be confirmed by measurements of the target enzyme levels in the patient's blood or urine (20, 23, 40). However, since these tests are not readily available in public hospitals, management can be commenced on clinical diagnosis and history of ingestion, as in our study 43.4% of patients were managed based on clinical findings alone (1, 25).

The overall picture of the blood gas tests showed that most of the patients in this study had some metabolic acidosis which is in keeping with other findings in literature (15, 21). Full blood count, urea and electrolytes, and liver function test results were within the normal reference ranges. This is in contrary to findings in existing literature, which have shown that patients with severe OPP present with metabolic derangements, renal impairment, high INR, liver derangements (21, 25).

5.4 Interventions

There were four (13.3%) patients who required ICU whilst 26 (86.7%) were admitted to HCA. Other studies on OPP have also shown a high rate of admission into high care and intensive care areas as these patients need close monitoring and depending on the severity, they will need supportive care (19, 28, 37). It has also been shown that some of the patients have recrudescence of symptoms as the OP is released from fat tissue into the systemic circulation, hence the need of monitoring in a high care setting (6, 30). This situation is

worse in obstetric practice as there will be two patients involved (pregnant woman and fetus) and this requires more intense monitoring (15, 19, 36).

All the pregnant women with OPP in this study were treated with intravenous atropine. Ventilation was required in 15 (50.0%) of the admitted patients with a median duration on ventilation of four days (IQR 1 – 3, range 1 - 29). The duration reported in our study is similar to ranges described in literature. Various studies from SA, Singapore, Turkey, and Saudi Arabia found that the average length of the ICU stay for patients who had been exposed to OPs was between two to ten days (1, 4, 13).

Nineteen patients (63.3%) delivered vaginally whilst 11 (36.7%) had caesarean section done mainly due to fetal distress. Four patients had spontaneous miscarriages, 13 had stillbirths, and 13 delivered live babies. According to literature, negative effects of atropine on the fetus include tachycardia and reduced variability of heart rate (19, 36). Clinicians should be aware that atropine may make it difficult to interpret the CTG, leading to a high caesarean section rate as compared to the general rate of 15.0%, according to WHO (44).

5.5 Maternal outcomes and their associated factors

The fatality rate in this study was 10.0% (n = 3). This is comparable to studies in literature. In a study of 21 cases done at a central hospital in West-Bangal, India, a fatality rate of 9.5% was recorded in pregnant mothers who presented with OPP (34). Studies specifically focussing on ICU included the study undertaken in the Western Cape province of SA which showed a fatality rate of 16.0% (4). Variable fatality rates for OPP are reported in the literature, from as high as above 40.0% to as low as 2.4%. Reasons suggested for the higher fatality rates include variation in the toxic nature of the OP consumed, the lack of readily available antidotes, long distances between hospitals and over-stretched staff and resources (1, 7, 28).

In our study, a loading dose of atropine >9mg was associated with maternal fatality and this was statistically significant (p-value = 0.04). The need for a higher atropine dose has been correlated to a higher OP toxin load as it has been reported in literature (21, 25). This will cause severe muscarinic and nicotinic effects on the women with OPP hence leading to multiorgan failure, causing death (25). Other variables such as the worst pH, ventilation

status, length of hospital stay, AChe levels, GCS, worst lactate and booking status were not significant predictors of maternal fatality as reported by studies in literature (15, 34, 42). The reason for this divergence could be related to the small sample size of our study.

5.6 Fetal outcomes and associated factors

Our findings of poor fetal outcomes are in keeping with the literature, which reports spontaneous abortions and intrauterine fetal demise as common outcomes among pregnant women with OPP (12, 15). In the literature, it is postulated that increased levels of acetylcholine at the muscarinic and nicotinic receptors stimulates contraction of the uterus (33, 41). In our study a third of the fetuses were alive upon discharge/death of the women who presented with OPP whilst two-thirds had either died *in utero* or were early neonatal deaths. The two early neonatal deaths were delivered via caesarean section due to severe fetal distress with thick MSL, had very low APGAR scores, and required NICU admission. This is much different from what has been found in literature which showed a fetal loss rate of 22.0% (37).

In our study, unbooked status, maternal ventilation, maternal length of hospital stay >6.5 days, maternal pH $\leq$7.35, and maternal GCS $\leq$14 were associated with poor fetal outcomes. These were all statistically significant. This is in keeping with the literature which has shown that most patients with severe OPP need ventilation and they have metabolic derangements which negatively affects the fetus (8, 39).

5.7 Limitations of the study

The major limitation in this study was the small sample size of 30 patients done at one tertiary care. It is therefore difficult to generalise our findings to the greater population. The small sample size also made it difficult to use logistic regression to evaluate the predictors of maternal and fetal outcomes. Cases included in this study were based on clinical diagnosis of OPP, with some of the cases being confirmed with laboratory AChe levels. This may have resulted in some patients being missed. Examples include patients who were minimally symptomatic or with atypical presentation. Some patients who could have died before reaching hospital were also missed from this study. This was a cross-sectional study thus it

was not possible to look at the long-term outcomes of the effects of OPP on the mothers. In this study, we did not test for the direct evidence of fetal exposure to OPP. It was also limited to the immediate early neonatal effects and due to its cross-sectional nature, long-term effects on the babies who survived in utero OP exposure could not be assessed.

5.8 Strengths of the study

Despite the aforementioned limitations, this study makes a meaningful contribution to our knowledge of OPP in pregnancy. Our study looked at a broad number of variables and this makes it more informative. This study also linked the CHBAH database to the NHLS database on AChe levels which identified cases that could have been missed if we had used the hospital records only.

CHAPTER VI: CONCLUSION

6.1 Summary of main findings

From this study, most mothers who presented with OPP in pregnancy were in the age group 18 - 35 years, unemployed, not married, and were of the African race. Most of them were booked and they were HIV negative, Rhesus positive, RPR negative with a median booking haemoglobin of 10.4g/dL and median gestation age of 21 weeks at booking. On presentation most pregnant women with OPP had features of the toxidrome syndrome which included respiratory secretions, pin-point pupils, salivation, fasciculations and diarrhoea.

The blood gases done on pregnant women with OPP showed a general picture of metabolic acidosis. Maternal fatality rate was 10.0% with 50.0% requiring ventilation and median duration of ventilation was two days. All the patients had delivered on discharge with 13 (43.3%) live births, four (13.3%) miscarriages, and 13 (43.3%) stillbirths. An atropine dose of >9mg was significantly associated with poor maternal outcome. Poor fetal outcomes were associated with maternal ventilation, mothers who stayed longer than one week in hospital, and maternal pH$\leq$7.35.

6.2 Recommendations

The findings from this study are a significant groundwork for future studies in OPP in pregnancy. These future studies should have a bigger sample size or alternatively be systematic reviews with meta-analyses to get more precise estimates of measures of effects such as odd or hazard ratios. Future studies should investigate the long-term effects of OPP on both the mothers and the babies who survived in-utero exposure. Future studies should also evaluate the use of the APACHE II score in identifying women who are at risk of complications.

A high index of suspicion is required especially for patients presenting with symptoms that are consistent with the toxidrome of OPP. Arterial blood gases and AChe levels are critical investigations for patients with suspected OPP. Extra care should be taken with patients who have a deranged blood gas picture, low AChe levels, or those who require ventilatory support as these are poor prognostic factors. These actions will go a long way in significantly reducing the maternal mortality, negative foetal and early neonatal outcomes due to OPP.

Organophosphate poisoning in pregnancy should be discussed in near-miss meetings as it is a notifiable condition associated with high mortality. These regular discussions will help raise awareness and knowledge of managing of OPP in pregnancy amongst clinicians. Mental health issues affecting women should recognised and appropriately managed with the help of psychologists, psychiatrists, and social workers. A protocol or standard operating procedure for the management of OPP in pregnancy should be put in place to help manage such patients. Our study highlights the need for active enforcement of the relevant legislation and control of accessibility of OP compounds.

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ANNEXTURE 1: DATA COLLECTION TOOL

Confidential

A DESCRIPTION OF PREGNANT WOMEN PRESENTING WITH ORGANOPHOSPHATE POISONING AT CHRIS HANI BARAGWANATH ACADEMIC HOSPITAL

OPP BARA

1 record id	_____
hospital number	_____
2 age of patient	_____
3 race	○ african ○ indian ○ white ○ coloured
4 marital status	○ single ○ married ○ cohabitating ○ widowed ○ divorced
5 employment status	○ employed ○ unemployed
6 ward(s) of admission	☐ hca ☐ icu ☐ both hca and icu
7 date of admission	_____
8 date of discharge	_____
9 length of hospital stay in days	_____
10 discharge status	○ alive ○ dead
11 gravidity	_____
12 parity	_____
13a booking status on admission	○ booked ○ unbooked
13b booking bloods hiv status	○ negative ○ positive ○ unkown
13c booking bloods cd4 count	_____
13d booking bloods viral load	_____
13e booking bloods rhesus status	○ negative ○ positive ○ unknown

13f booking bloods rpr status
○ negative ○ positive
○ unknown

13g booking blood haemoglobin

_____

14a gestational age at booking

_____

14b gestational age on admission

_____

14c gestational age at delivery

_____

15a ventilation required
○ yes ○ no

15b number of days ventilated

_____

16a how was opp ingested

○ intentional
○ accidental
○ not stated

16b where was opp sourced

○ house
○ street
○ shop
○ not stated

17a clinical findings systolic blood pressure on admission

_____

17b worst systolic blood pressure

_____

17c clinical findings diastolic blood pressure on admission

_____

17d worst diastolic blood pressure

_____

17e pulse rate on admission

_____

17f worst pulse rate

_____

17g respiratory rate on admission

_____

17h worst respiratory rate

_____

17i secretions on examination

- ○ yes
- ○ no
- ○ not stated

17j pupils status on examination

- ○ pin-point
- ○ normal
- ○ dilated
- ○ not stated

17k salivation on examination

- ○ yes
- ○ no
- ○ not stated

17l fasciculations/seizures on examination

- ○ yes
- ○ no
- ○ not stated

17m diarrhoea

- ○ yes
- ○ no
- ○ not stated

17n gcs on admission

_____

17o worst gcs

_____

17p sfh on admission

_____

17q fetal heart on admission ○ present ○ absent ○ not stated	
17r ctg report on admission	○ reactive ○ suspicious ○ pathological ○ not stated
18a apache II score	○ yes ○ no
18b apache II score on admission	
18c worst apache II score	
19a acetylcholinesterase levels	○ yes ○ no
19b ache on admission	
19c worst ache levels	
20a blood gas ph at admission	
20b worst blood gas ph	
20c blood gas po2 at admission	
20d worst blood gas po2	
20e blood gas pco2 at admission	
20f worst blood gas pco2	
20g blood gas base excess on admission	
20h worst blood gas be	
20i blood gas hco3 on admissiom	
20j worst blood gas hco3	

20k blood gas lactate on admission

20l worst blood gas lactate level

20m blood gas glucose on admission

20n worst blood gas glucose

20o blood gas potassium on admission

20p worst blood gas potassium

20q blood gas haemoglobin on admission

20r worst blood gas haemoglobin

20s blood gas chloride on admission

20t worst blood gas chloride

20u sodium admission

20v worst blood gas sodium

21a blood results white cell count

21b blood results haemoglobin

21c blood results haematocrit

21d blood results mcv

21e blood results platelets

21f blood results sodium

21g blood results potassium	
21h blood results chloride	
21i blood results urea	
21j blood results creatinine	
21k blood results albumin	
21l blood results alanine transaminase	
21m blood results aspartate transaminase	
21n blood results alkaline phosphatase	
21o blood results gamma-glutamyl transferase	
21p blood results calcium	
21q blood results magnesium	
21r blood results phosphate	
21s blood results inr	
22a atropine total loading dose	
22b number of days on atropine	
23a pregnancy status at discharge or death	○ delivered ○ undelivered
23b mode of delivery	○ vaginal ○ cesarean section
23c indication for cesarean section	○ Fetal distress ○ Poor progress ○ maternal resuscitation ○ previous cesarean delivery ○ other

23d meconium stained liquor	○ Yes ○ No
23e description of msl	○ thin ○ thick
24a fetal outcome at delivery	○ miscarriage ○ live birth ○ stillborn
24b fetal outcome still born status	○ fresh still born ○ macerated still born
24c fetal outcome birth weight	_____
24d fetal outcome apgar score at 1min	_____
24e fetal outcome apgar score 5min	_____
24f fetal outcome congenital abnormalities	○ yes ○ no ○ not stated
24g fetal outcome nicu admission	○ yes ○ no
24h fetal outcome days spent in hospital	_____
24i fetal outcome status at discharge	○ alive ○ dead

ANNEXURE 2: University of Witwatersrand Human Research Ethics Committee - Certificate

UNIVERSITY OF THE WITWATERSRAND JOHANNESBURG

R14/49 Dr R Bvumbi

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
CLEARANCE CERTIFICATE NO. M200335

NAME: (Principal Investigator)	Dr R Bvumbi
DEPARTMENT:	School of Clinical Medicine Department of Obstetrics and Gynaecology Medical School University
PROJECT TITLE:	A description of pregnant women with organophosphate poisoning at Chris Hani Baragwanath Academic Hospital
DATE CONSIDERED:	2020/03/27
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Professor Y Adam and Dr A Chikandiwa
APPROVED BY:	CB Penny Dr CB Penny, Chairperson, HREC (Medical)
DATE OF APPROVAL:	2020/08/07

This clearance certificate is valid for 5 years from the date of approval. Extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Research Office Secretary on the 3rd Floor, Phillip Tobias Building, Parktown, University of the Witwatersrand, Johannesburg.
I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated, from the research protocol as approved, I/we undertake to submit details to the Committee. **I agree to submit a yearly progress report**. When a funder requires annual re-certification, the application date will be one year after the date when the study was initially reviewed. In this case, the study was initially reviewed in **March** and will therefore reports and re-certification will be due early in the month of **March** each year. Unreported changes to the application may invalidate the clearance given by the HREC (Medical).

Principal Investigator Signature

12/08/2020
Date

ANNEXURE 3: Permission to conduct research: Chris Hani Baragwanath Academic Hospital

GAUTENG PROVINCE
HEALTH
REPUBLIC OF SOUTH AFRICA

MEDICAL ADVISORY COMMITTEE

CHRIS HANI BARAGWANATH ACADEMIC HOSPITAL

PERMISSION TO CONDUCT RESEARCH

Date: 3 February 2020

TITLE OF PROJECT:

A description of pregnant women with organophosphate poisoning at CHBAH

UNIVERSITY: Witwatersrand

Principal Investigator: Raymond Bvumbi

Department: Obstetrics and Gynaecology

Supervisor : Prof Y Adam, Dr AT Chikandiwa

Permission Head Department (where research conducted): Yes

The Medical Advisory Committee recommends that the said research be conducted at Chris Hani Baragwanath Academic Hospital. The CEO / management of Chris Hani Baragwanath Academic Hospital is accordingly informed and the study is subject to:-

- Permission having been granted by the Committee for Research on Human Subjects of the University of the Witwatersrand.
- The Hospital will not incur extra costs as a result of the research being conducted on its patients within the hospital
- The MAC will be informed of any serious adverse events as soon as they occur
- Permission is granted for the duration of the Ethics Committee Approval.

.....
Recommended
(On behalf of the MAC)
2020/02/03

.....
Approved/~~Not Approved~~
Hospital Management Date:
Date: 04/02/2020

ANNEXURE 4: Permission to conduct research: Department of Obs & Gynae CHBAH

GAUTENG PROVINCE
HEALTH
REPUBLIC OF SOUTH AFRICA

PERMISSION TO CONDUCT RESEARCH AT CHRIS HANI BARAGWANATH ACADEMIC HOSPITAL

PRINCIPAL RESEACHER:

FULL NAME: RAYMOND BVUMBI

DESIGNATION: REGISTRAR

CONTACT NUMBER: 083 249 7829

EMAIL: RCBVUMBI@GMAIL.COM

NAME OF SUPERVISOR: PROF. Y. ADAM

TITLE OF RESEARCH
A DESCRIPTION OF PREGNANT WOMEN WITH ORGANOPHOSPHATE POISONING AT CHRIS HANI BARAGWANATH ACADEMIC HOSPITAL

STUDY SITE/S: CHRIS HANI BARAGWANATH ACADEMIC HOSPITAL

BRIEF OUTLINE OF METHODOLOGY

THIS WILL BE A DESCRIPTIVE, RETROSPECTIVE CROSS SECTIONAL STUDY SUBJECTS / CASES WILL BE OBTAINED FROM REGISTERS IN MATERNITY ADMISSIONS, INTENSIVE CARE AND HIGH CARE UNITS. INFORMATION WILL THEN BE EXTRACTED FROM PATIENTS' FILES IN RECORDS USING A DATA COLLECTION SHEET.

PROTOCOL: YES

DATA SHEET: YES

EXPECTED START DATE: 1ST APRIL 2020 EXPECTED DURATION: FIVE MONTHS

ETHICS CLEARANCE? Y / N / DEPENDING

CONFLICT OF INTEREST? Y / (N) / DETAILS

COST TO HOSPITAL ANND OR PATIENTS Y / (N)

SOURCE OF FUNDING: SELF

APPROVAL OF HOD Y / N

SIGNATURE	NAME IN PRINT + DESIGNATION	OFFICIAL STAMP+ DATE
	Yadam	