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UTERINE FIBROIDS AND OBSTETRIC OUTCOMES AMONG WOMEN LIVING IN SUB-SAHARAN AFRICA: SYSTEMATIC REVIEW AND META-ANALYSIS

BY

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DECLARATION

I, Eric Senam Atta Komla Ablormeti, declare that except for other people's investigations which have been duly acknowledged, this research is the result of my original research undertaken under the supervision of Dr. Anthony Danso-Appiah and that it has neither in whole nor in part been presented for another degree in this university or elsewhere.

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(Supervisor)

DEDICATION

This dissertation is dedicated to the Almighty God for his immense grace and mercies that has brought me this far and to my family and friends.

ACKNOWLEDGEMENTS

I wish to express my sincere gratitude, first and foremost to the Almighty God for seeing me through this project work.

To my supervisor Dr. Anthony Danso-Appiah, I am extremely grateful for the guidance and support. My profound appreciation also goes to Mr. David Oweridu, and Mr. Morrison Asiamah, for their contributions to various aspects of this work. A special appreciation to the authors whose articles and books I reviewed and everyone who in diverse ways contributed to making this project a success. God bless you all.

This systematic review was supported by the capacity building initiative of the UG Centre for Evidence Synthesis and Policy (UGCESP) and Africa Communities of Evidence Synthesis and Translation (ACEST) that are jointly providing mentoring/training in evidence synthesis and translation across Low and Middle-Income Countries (LMICs).

ABSTRACT

Introduction: Uterine fibroid is a serious public health problem affecting about 80% of women globally. Apart from adverse pregnancy outcomes, it affects quality of life of women. This thesis investigated uterine fibroids and obstetric outcomes among women living in Sub-Saharan Africa through a systematic review and meta-analysis. The study specifically, assessed the risk factors of uterine fibroids such as; age, parity menarche, body mass index and family history. It further assessed fibroid types, number of fibroids, fibroid location, and the maternal and foetal outcome of pregnancy among women with fibroid in Sub-Saharan Africa.

Method: This study employed a systematic review to synthesize empirical evidence on uterine fibroid. Several relevant databases such as PubMed, Google Scholar, Lilacs, Cochrane Library, Hinari and African Journals online were searched for studies without language restriction. The search retrieved 909 articles electronically from the data bases and 6 articles from gray literature. Overall, 898 articles were screened for eligibility. In all, 18 articles met the eligibility criteria and were included in the review. Data were extracted using the Critical Appraisal Skills Programme form and Risk of bias assessment of the included studies was done using Hoy et al Risk of bias assessment tool for observational studies. A meta-analysis of the data was done using the Review manager software. Heterogeneity was assessed.

Results: A total of 909 articles were retrieved, and 898 were screened for eligibility after duplicates were removed. Forty-two (42) full-text articles were assessed for eligibility; of which 18 were eligible for systematic review. Findings from the review has established that the prevalence of uterine fibroid is highest among women aged 30 – 39 years, **51.0%** (**95% CI: 47.0 – 56.0**). Nulliparous women had the highest prevalence of fibroids, **50%** (**95% CI: 36.0 – 64.0**).

Intramural fibroids were the commonest type of fibroids seen among SSA women, **49.12%**. However, fibroid sizes were poorly assessed. We have also found a statistically significant association between fibroids and postpartum haemorrhage (PPH), vaginal bleeding, Caesarean section (C/S), abdominal pain, placenta previa/abruptio, and low APGAR score as compared with women without uterine fibroids. However, the study has shown no significant association between UF and fetal malpresentation, miscarriage/abortion, preterm, intrauterine growth restriction (IUGR), premature rapture of membrane (PROM), stillbirth and low birth weight.

Conclusion: Uterine fibroids are associated with adverse pregnancy outcomes such as antepartum haemorrhage, postpartum haemorrhage, increased caesarean section rate, low APGAR score and abdominal pain. However, the information included in this study are insufficient.

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LIST OF ABBREVIATIONS

ART	Assisted Reproductive Technology
ANC	Antenatal Care
BMI	Body Mass Index
CS	Caesarean Section
DIC	Disseminated Intravascular Coagulation
GnRHa	Gonadotropin Releasing Hormone agonist
IUGR	Intrauterine Growth Restriction
LBW	Low Birth Weight
LMICs	Low Middle-Income Countries
PROM	Premature Rapture of Membrane
PPH	Postpartum Haemorrhage
SSA	Sub-Saharan Africa
UF	Uterine fibroids

CHAPTER ONE

1.0 INTRODUCTION

1.1 Background

Uterine fibroid (UF), also called myoma, leiomyofibroma, fibroleiomyoma or leiomyoma (Munro et al., 2011). It is a serious public health problem as it stands as the commonest pelvic tumour in women (Parker, 2007). UF is a "discrete, rounded, firm, white to pale pink, benign myometrial tumour composed mostly of smooth muscle with varying amounts of fibrous connective tissues" (Pernoll, 2001). It affects about 80% of women worldwide (Laughlin & Stewart, 2011). Although there is scanty information on uterine fibroids in Sub-Saharan Africa, a prevalence of 36% was reported in Ghana(Sarkodie, Botwe, Adjei, et al., 2016), and 29.3% in Nigeria. In Eastern Africa a prevalence of 28.2% was reported (Adawe et al., 2022)

1.1.1 Types of Uterine fibroids

There are three main types of fibroids, namely Subserous fibroids, Intramural fibroids and Submucosal fibroids, classified according to the layers of the uterus in which the nodules are found (Munro et al., 2011).

Subserous fibroids, as any other fibroids starts from the myometrium (the middle layer of the uterus). They grow and extend into the outer surface of the uterus called the subserous. In the subserous they can be said to be lying just below covering of the abdominal cavity called peritoneum. Characteristically, they are asymptomatic, but common. Where they grow large, they may exhibit symptoms(Pernoll, 2001)

Intramural fibroids develop within the middle layer of the uterus (myometrium). They may distort the shape of the endometrial cavity or the outer surface of the uterus (Munro et al., 2011). They may manifest with swelling of the abdomen, menorrhagia and infertility (Ivanova et al., 2016).

Submucosal fibroids develop from the myometrium and grow towards the endometrial cavity exerting pressure on the endometrial surface and its blood vessels. This pressure impact on the

endometrial surface results in irregular uterine bleeding, a common characteristic of submucosal fibroids as they grow into the endometrial cavity (Viswanathan et al., 2007).

Submucosal fibroids are further classified as, Type 0, Type I and Type II. A submucosal fibroid that is pedunculated and does not extend into the intramural space is classified as type 0. Type I do not have a stalk as it is in the case of type 0 and are therefore attached at the base with less than 50% intramural extension. Type II submucosal fibroids also do not have a peduncle however, approximately 50% of the fibroid nodules are found in the intramural region (Bajekal & Li, 2000)

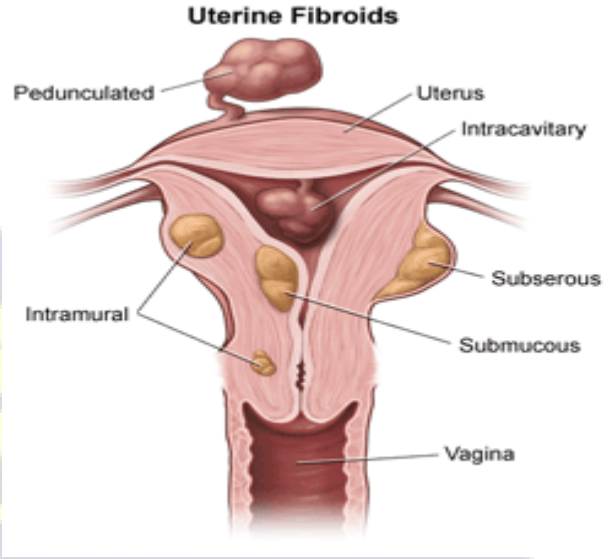

Figure 1: Types of uterine fibroids by anatomical positions in uterus

1.1.2 Characteristics of Fibroid

Uterine fibroids vary in sizes. The size can be very tiny and undetectable to as small as seedling, and to bulky mass or size of grapefruit (Emmanuel et al., 2021) which can increase uterine size and distortions of the uterine cavity. Some fibroids may grow large enough to fill the pelvis or to block the passage of foetus (when located within the cavity especially pedunculated large fibroids) during delivery (Stewart, 2001). Fibroids may be located in the body also called corpus uteri or in the lower

segment (cervix), or in the fundus. Each of the above locations has been researched and found to have adverse effects on pregnancy outcomes (Klatsky et al., 2008).

Furthermore, a UF may be classified as either posteriorly, anteriorly or laterally located. Deveer et al. (2012) in their quest to understand effects of fibroid location on pregnancy outcome followed 84 pregnant women till they deliver. Sixty-four of the 84 women were noted to have fibroids anteriorly located and the remaining 20 were posterior. It emerged that posteriorly located fibroids are likely associated with miscarriage (Deveer et al., 2012)

Fibroids may be single or multiple. Lam et al. (2014) conducted a study and observed that multiple fibroids were associated with adverse pregnancy outcome(Lam et al., 2014).

1.1.3 Risk factors

The cause of uterine fibroids remains unclear (Okolo, 2008). However, there are hypothesis of likely causes of fibroids. Oestrogen and progesterone were hypothesized to influence uterine fibroids development (Goodwin et al., 2008). As such, reported risk factors consistent with this theory are younger age at menarche and premenopausal status (Jacobson et al., 2007). In respect of the later many holds the view that fibroid will adversely affect maternal and foetal outcome because of high level of these hormones in pregnancy. Other widely explored risk factors associated with uterine fibroid include race accounting for 2 to 3 folds of increased risk among the black race compared with the white race (Stewart et al., 2017).

A study conducted among Ghanaian women has also identified the risk to be associated with increasing age. The study further compared women who has never given birth to those who have ever given birth and concluded that nulliparous were at increased risk compared to parous women. Additionally, the study found that obesity and late age of last delivery also increases the risk of fibroid development (Sarkodie, Botwe, & Ofori, 2016). Family history of uterine fibroid also predisposes one to uterine fibroid development (Ciebiera et al., 2016).

1.1.4 Signs and symptoms

Though most women present asymptomatic (Al-Hendy et al., 2017) about half of women do present with symptoms such as abnormal pain, uterine bleeding, feelings of heaviness in the

pelvis, abdominal protrusion and urine frequency among others. Furthermore, a quarter of women affected have symptoms that affects activities of daily living or are serious enough to require surgery or medical management (Borah et al., 2013). Sometimes women who experience heavy bleeding as a result of having fibroid located submucosally do presents with grave anaemia (Fasubaa et al., 2019) . Severe abdominal pain may result from twisting of a stalk of fibroid and also when fibroids outgrow their blood supply causing it to become ischemic and necrosed (called red degeneration)(Gupta et al., 2008). This pain can necessitate laparotomy or myomectomy in pregnancy which ideally is not recommended because of risk of hemorrhage and loss of the foetus (Baird et al., 2003).

1.1.5 Fibroids in pregnancy

Uterine fibroid is common among women in their reproductive age and as such, does co-exist with pregnancy. In most women the fibroids were in situ before they conceived. Although difficulty to diagnose in pregnancy the prevalence varies between 10.7% to 16.7% (Laughlin et al., 2009). African American women are noted to have highest prevalence followed by the Caucasians, Hispanic and Asian women (Laughlin et al., 2009). Egbe et al. in 2018 conducted a study among women attending antenatal care in Cameroon and reported a prevalence of 12.5% (Egbe et al., 2018).

However, many women with uterine fibroid may conceive and deliver healthy baby at term, but some women do have challenges resulting from the presence of uterine fibroid. These adverse effects of UF in pregnancy can be deleterious to both mother and foetus. As such Klatsky et al. (2008) conducted a study and has found that uterine fibroid in pregnancy does have effect on mother and foetus. The study identified, acute abdominal pain, preterm labour and miscarriage as well as first trimester bleeding as adverse effects of fibroids in pregnancy. Other equally important adverse effects were intrauterine growth restriction (IUGR), preterm delivery placenta previa and abruptio (Klatsky et al., 2008). In the same study, post-partum complications such as caesarean delivery, postpartum hemorrhage (PPH), peripartum

hysterectomy and retained placenta were observed as adverse effects (Klatsky et al., 2008). An adverse effect such as placenta abruptio is a well-known and an important cause of maternal and fetal mortality in the world (Haeri & Dildy, 2012). Studies have suggested a 3–fold increase in cases of abruption placentae in pregnant women with uterine fibroids, especially if the fibroid nodules are submucous, retroplacental or have a volume greater than 200 cm3 (Klatsky et al., 2008; Lev-Toaff et al., 1987).

1.1.6 Diagnosis

Most UF are diagnosed clinically and are confirm by imaging techniques (Noutakdie Tochie et al., 2021). The commonest and widely available confirmatory test is pelvic ultrasound scan and is the test of first choice in the developing world. It is non-invasive and can be perform right in the consulting rooms by clinicians with little training (Sarkodie, et al., 2016). Hysterosalpingography, laparoscopy, laparotomy magnetic resonance imaging, computerized tomography, and endoscopic diagnostic methods can also be used (Okunade & Gbadegesin, 2014).

1.1.7 Management of uterine fibroids

A symptomatic uterine fibroid may be managed medically or surgically taking into consideration the state of the woman (Noutakdie Tochie et al., 2021). Medically, narcotics and tocolytics are successful in managing symptomatic uterine fibroids in pregnant women (Ciavattini et al., 2015b).

Myomectomy is rarely performed in pregnancy (Ciavattini et al., 2015a). Furthermore, there is still a controversy on myomectomy during caesarean section(C/S). Yellamareddygari et al. (2010), concluded that leaving the myoma during C/S will avert hemorrhage and disseminated intravascular coagulation (DIC) (Yellamareddygari et al., 2010). As technology advances, Magnetic Resonance Imagery-guided focused ultrasound surgeries are performed. And also other newer surgeries like artery embolization, and robot-assisted myomectomy are available (Parazzini et al., 2016).

Although the presence of fibroid is almost never associated with death, fibroid may cause morbidity and affect quality of life of women including negative effect on academic achievements (Parker, 2007). In addition, fibroids may negatively affect pregnancy outcome, but the impact in quantitative terms, is unclear(Parazzini et al., 2016).

1.2 Problem Statement

In the United States alone, it was estimated that 1.4 million cases of Abnormal Uterine Bleeding (AUB) commonly caused by UF are reported each year (Matteson et al., 2013). This number of cases accounts for an estimated cost of about 34.4 billion dollars per year (Cardozo et al., 2012). A study conducted in University of Benin Teaching Hospital, Benin City, Nigeria reported uterine fibroid as contributing 10.3% and 17.6% of new gynecological admissions and surgeries respectively (Osaikhuwuomwan & Kehinde, 2015). Even with the above it is believed that the prevalence of uterine fibroid is underestimated because majority of the women diagnosed were the symptomatic in search for hospital service whilst the remaining asymptomatic are not diagnosed but may be living with the disease across the globe. A study conducted among women receiving care for gynaecological condition in Nigeria has established a rise in the prevalence of UF from 0% below 20 years to a maximum of 40.3% among age group 30-39 years. Again, the study reported a reduction in incidence thereafter to 32.9% among women aged 40-49 and to the overall lowest 0.42% among women aged 60 and above (Okogbo et al., 2011). This seems to suggest that women in their youthful age are worse affected, whiles they are the working cohort of the sub region.

Improvement in fertility even at old age as a result of assisted reproductive techniques (ART) has led to women delaying pregnancy. This phenomenon has contributed to a rise in fibroid complicating pregnancies in recent time(Yu et al., 2018). Furthermore, the disorder has been associated with poor pregnancy outcomes, including spontaneous abortion, and preterm birth (Klatsky et al., 2008). In addition, black women are diagnosed earlier in life with fibroids. Their fibroids are mainly multiple and large, sometimes equivalent to term baby (>= 2500grams). In accordance they do experience severe symptoms comparing to other race (Wise et al., 2004).

Pregnant women with co-existing UF are generally scared about the outcome of pregnancy and labour, although some studies have established that most women go through cyesis uneventful (Giovanni et al., 2013). However, UF are also estimated to complicate about 10%–40% of pregnancies before delivery (Eze et al., 2013). On the other hand, some studies have reported inconsistent relationships between uterine fibroids and adverse obstetric outcomes (Lee et al., 2010)

Lethaby & Vollenhoven, (2007) observed that uterine fibroids, especially multiple, intramural or submucous, were associated with increased risk of early miscarriage when compared with control subjects (Lethaby & Vollenhoven, 2007). Lev-Toaff et al., (1987) also observed an increased risk of miscarriage among women with fibroids situated in the uterine corpus compared to women with uterine fibroids in the lower portion of the uterus (Lev-Toaff et al., 1987). Surgeries are hardly performed in pregnancy because of exposure of the foetus in utero to anaesthetics drugs but, degenerating uterine fibroid in cyesis can cause severe acute abdomen which can warrant surgical intervention (Cook et al., 2010). This surgery required specialized skills which may not be available in our setting, SSA (Igboeli et al., 2019). Most health facilities in the region may not have the capacity to secure fresh frozen plasma or platelet concentrate to rescue a woman in disseminated intravascular coagulation (DIC). In view of this, Yellamareddygari et al. in 2010 concluded that caesarean myomectomy should not be done, instead women should be scanned and myomectomy performed before pregnancy (Yellamareddygari et al., 2010).

Adverse effects of UF in pregnancy is never limited to the first two trimesters. In the third trimester uterine fibroids are associated with an increased risk of preterm labour and delivery (Klatsky et al., 2008). Preterm birth has remained the main contributor of neonatal morbidity and mortality (Ciavattini et al., 2015b) and management of preterm or premature babies is another challenge in low resource setting like SSA (Igboeli et al., 2019).

Where there are no contraindications, women are expected to deliver per vaginum. In recent times caesarean section rate has increased and some of the indications were abnormal presentations, Malpresentation and malposition are known to cause difficult labour and delivery and therefore may necessitate caesarean section (Klatsky et al., 2008). A study carried out by Vergani et al, in 2007 observed that women with big uterine fibroids had higher rates of cesarean delivery prior onset of labour (Vergani et al., 2007). Caesarean section is a minor surgical procedure, but in our part of the world (SSA) because of human resource and healthcare infrastructure gap the case is not the same (Igboeli et al., 2019).

Investigating uterine fibroid and therefore management of uterine fibroid has improved in recent times as technology has evolved (Stewart et al., 2017). Additionally, knowledge on the disease, its management and preventions has improved the life of women in the developed world (Igboeli et al., 2019). Despite advancement in the diagnosis and management of uterine fibroids, the health system challenges in some developing countries pose a threat to uterine fibroid group of women. Additionally, there is paucity of scientific evidence on the effects of uterine fibroids on mother and foetus (Igboeli et al., 2019; Ivanova et al., 2016).

1.3 Justification

The debate on the impact of fibroids on pregnancy and adverse obstetric outcome is still inconclusive as some studies suggest increased risk of miscarriage, preterm delivery and haemorrhage, but others say otherwise (Klatsky et al., 2008). This phenomenon is likely to create confusion and uncertainty among clinicians managing uterine fibroid in pregnancy especially when considering the effect of fibroid size, location and fibroid types on pregnancy, and obstetric outcomes. Knowledge of such characteristics can influence care and management of pregnant women. Similarly, literature on risk factors or the sociodemographic factors have been studied extensively. Some studies report early menarche, parity and age of mother as significant whilst others do not find such relationship (Klatsky et al., 2008). It has become imperative to conduct a systematic review and meta-analysis to determine the effects of uterine fibroids on pregnancy and obstetric outcomes (mother and child) Furthermore, this is the first

systematic review and meta-analysis to summarize obstetric and foetal outcomes associated with uterine fibroid in pregnancy in sub-Saharan Africa. In general, this study aimed at providing clinically useful data that will inform recommendation in educating and managing pregnant women with uterine fibroids throughout antenatal, intrapartum and postpartum periods.

1.4 Conceptual Framework

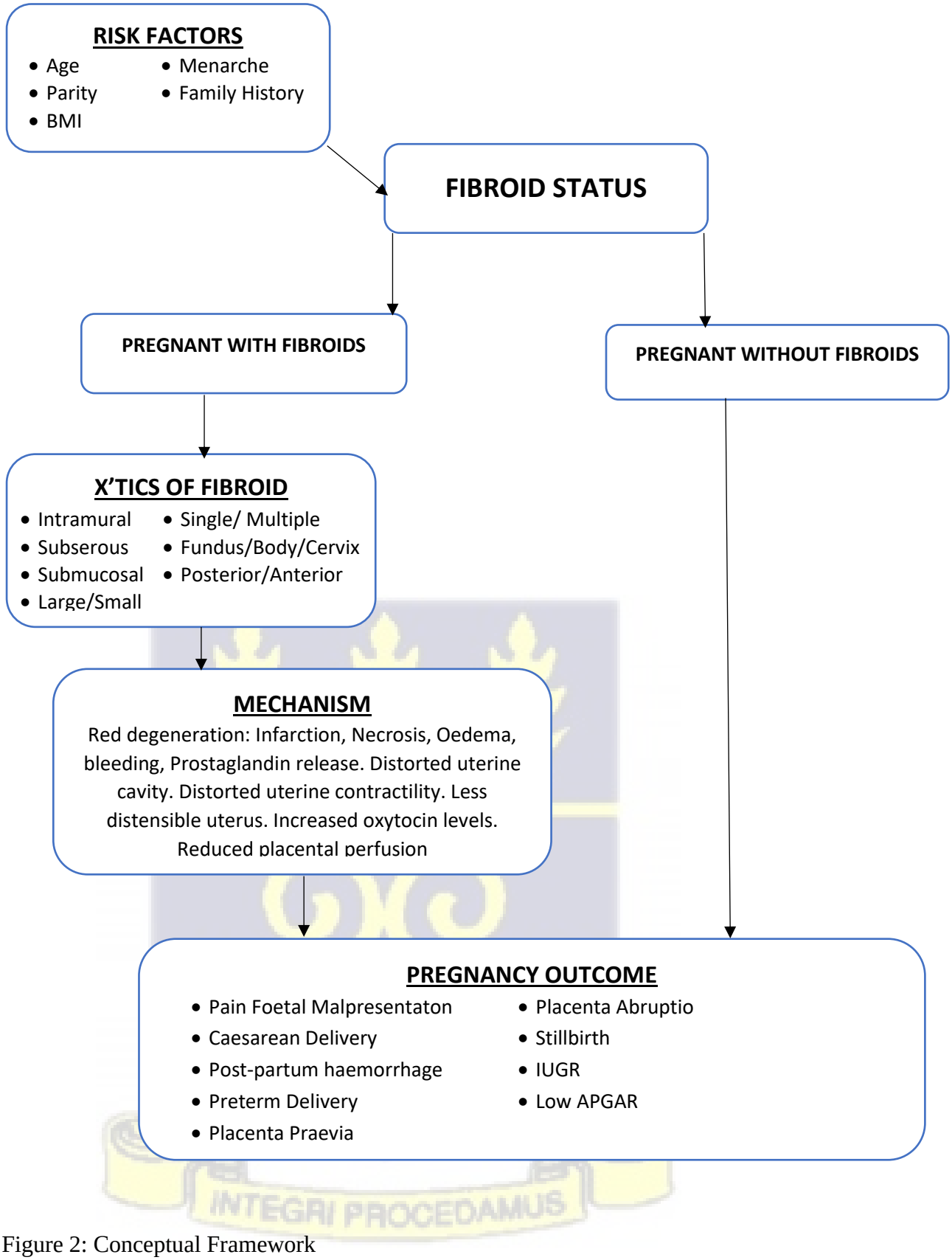

Figure 2: Conceptual Framework

1.4.1 Narrative

The age of a woman, parity, BMI, family history and menarche are factors known to influence uterine fibroids development (Stewart et al., 2017) and these were explained either through hormonal mechanisms or genetics(Okolo, 2008).Pregnancy may be more complicated if associated with uterine fibroids. Pregnancy without fibroids can also result in adverse outcomes but the risk may be lower. Occasionally, the presence of uterine fibroids can cause severe abdominal pain mimicking acute abdomen and therefore surgical intervention. This pain is due to red degeneration, a condition where fibroid outgrown its blood supply, become ischaemic and infarcted. The oedema and prostaglandin released (from the damaged cells) are thought to be responsible for the severe pain(Gupta & Manyonda, 2009).

The location of fibroids, such as retroplacental is noted to cause intrauterine growth restriction (IUGR), abruption placenta, placenta previa, small for date, low birth weight, and stillbirth. These retroplacental fibroids causes reduced blood flow to the placenta and thereby reducing placenta perfusion. This in turn will lead to decreased oxygen and nutrients supply to the growing foetus leading to the aforementioned effects. Similarly lower uterine segment located fibroids can also increase the risk of caesarean section as they may obstruct the cervical canal.

Large uterine fibroids may deform the uterine cavity. This can lead to malpresentation of foetus and also increasing the rate of caesarian sections among those with uterine fibroids. Presence of large fibroids can also result in uterine atony. Thus, large fibroid nodules will not allow for effective uterine contraction leading to dysfunctional labour intrapartum, and postpartum haemorrhage (PPH). As labour delays the foetus is at risk of asphyxia (for that matter low APGAR score) and possibly stillbirth. systematic review would provide evidence to ascertain the effects of pregnancy outcome among women with fibroids and without fibroids in pregnancy.

1.5 Review Questions

1. What is the effect of sociodemographic factors and obstetric histories on the development of uterine fibroids in SSA?
2. What are the sub-types of uterine fibroid in relation to obstetric outcomes in SSA?
3. What are the effects of uterine fibroid size location and number in relation to obstetric outcomes in SSA?
4. What are the main obstetric outcomes among pregnant women with uterine fibroid living in SSA?

1.6 Objectives

1.6.1 Main objective

The overall objective of this systematic review and Meta-analysis is to assess maternal and foetal (obstetric) outcomes of birth among women with uterine fibroid in Sub-Sahara Africa.

1.6.2 Specific Objectives

1. To estimate the sociodemographic factors and obstetric histories as risk factors of uterine fibroids in SSA.
2. To estimate the sub-types of uterine fibroids among women in SSA
3. To assess the size, location and number of uterine fibroids in relation to obstetric outcomes among SSA women
4. To compare the effects of uterine fibroids on obstetric outcomes (Feto-maternal) among women living in SSA

CHAPTER TWO

2.0 LITERATURE REVIEW

2E.1 Risk factors for Uterine Fibroid (sociodemographic and obstetric factors)

2.1.1 Age

A prospective cross-sectional study conducted in Ghana showed that uterine fibroid was mainly associated with women of older age group of the reproductive age than the younger age (Sarkodie et al.., 2016). Also, an international internet-based study indicated that women at fertile age are more concerned about the adverse effects of uterine fibroids such as intermenstrual bleeding (bleeding in between menses) and pain symptoms which can affect all aspect of women health (Zimmermann et al., 2012). Furthermore, a cross sectional survey analysis conducted in the United States indicated that as women aged prevalence of uterine fibroids increase as was seen in the age group 50-54 (Fuldeore & Soliman, 2017). Additionally, a research in the antenatal department in Cameroon (three hospitals) observed that respondents with uterine fibroids were older than those without leiomyoma (Egbe et al., 2018). Okezie & Ezegwui, 2006 in a review of management of uterine fibroids a pick incidence of uterine fibroids among women aged 31-35 years (Okezie & Ezegwui, 2006). A case control longitudinal study conducted in Nigeria showed that uterine fibroids was commoner with increasing maternal age (Charles Ugwoke Eze et al., 2013).

Additionally, systematic review extracted from 60 publications showed that age increased uterine fibroids risk (Stewart et al., 2017). A cohort study conducted in Kenyatta showed that presence of fibroids was associated with advanced maternal age (Mutua, 2014). A retrospective study conducted in south east Nigeria showed that uterine fibroids were predominantly during the third and fourth decades of women life (Obuna et al., 2008). Moreover, a retrospective study conducted in Nigeria showed that uterine fibromyoma was majorly between women who were 30-44 years. (Aboyeji & Ijaiya, 2002). Also, a quantitative prospective cross-sectional quasi-experimental study conducted in Ghana showed that the highest of cases was found among

women less than 35 years and the lowest recorded among women aged greater than 45 years (Sarkodie et al., 2016). A study conducted in Israel showed that uterine myoma increased with age until the fifth decade and decreased afterwards (Lurie et al., 2005). A retrospective study conducted in Benin Teaching Hospital showed that women with uterine fibroid ranged from 20 to 55 years (Omu et al., 1984)

Tchente et al. in 2009 observed that advanced maternal age is associated with fibroids development (Tchente Nguefack et al., 2009). Likewise, Eze et al. has found in his study (C U Eze et al., 2013). Similarly, Vergani et al. in 2007 has observed that increasing maternal age is associated large uterine fibroid in pregnancy (Vergani et al., 2007).

2.1.2 Parity

Another prospective cross-sectional study conducted in Ghana indicated that uterine fibroid was associated more with nullips compared to parous women and also with patient with late age at last delivery (Sarkodie, Botwe, Adjei, et al., 2016). In contrast a study conducted in Cameroon indicated that respondents with uterine fibroids were of low parity (Egbe et al., 2018). A five-year review in management of uterine fibroid at Enugu showed that majority of women with uterine fibroids were nulliparous (Okezie & Ezegwui, 2006). A cross sectional study conducted in Nigeria showed that being nulliparous predisposes women to having uterine fibroid (Ugburo et al., 2012). Obuna et al., in 2008 observed higher frequency of uterine fibroids occurrence among nulliparous women of the higher socio-economic class (Obuna et al., 2008).

Moreover, a retrospective study conducted in Nigeria showed that uterine fibromyoma was more common among women of low parity (0-2) (Aboyeji & Ijaiya, 2002). Furthermore, a study carried out in a University Teaching Hospital in Nnewi indicated that most of the patients with uterine leiomyoma were nulliparous (Co et al., 2012). Similarly, we have also observed that women with large uterine fibroid were mainly nulliparous (Vergani et al., 2007)

Egbe et al. reported low parity as a factor associated uterine fibroid among pregnant women with fibroid in his study (Egbe et al., 2018). In addition, the same study confirms that women who have given birth multiple times were at low risk of developing uterine fibroids.

2.1.3 Family History

A systematic review extracted from 60 publications showed that family history increased uterine fibroids risk (Stewart et al., 2017). A study conducted in a Nigerian population showed that positive family history of uterine fibroids was significantly associated with recurrence of uterine fibroids after myomectomy (Obed et al., 2011). A cross sectional study conducted in Nigeria indicated that women believed having a positive family history predisposes one to having uterine fibroids. (Ugburo et al., 2012)

Templeman et al., (2009) also observed similar finding as women with UF were at increased risk of having a sister or mother with uterine fibroids (RR 1.42, 95% CI 1.25-1.61) (Templeman et al., 2009). In a multicenter hospital-based case-control study conducted in Thailand the result showed a strong association between family history and presence of uterine fibroid with an odd ratio of 3.47 which is statistically significant (Ikomi & Singer, 1997)

2.1.4 Menarche

Menarche simply refers to onset of menstruation for the first time in a girl's life. It is characterized by physical development which occurs under the influence of the ovarian hormones' oestrogen and progesterone. Uterine fibroids are known to develop only in women who have reached reproductive age. And similarly growth of UF nodules reduced during states of low oestrogen such us menopause and use of gonadotrophin-releasing hormone agonist (GnRHa) (Okolo, 2008). When a woman starts menstruation early, the likelihood of undergoing several cyclical myometrial cell divisions is high. As these cyclical cell division continuous the chances of mutation in the gene which controls cell proliferation are also high. Mutation in the myometrial cell may result into the development of uterine fibroids (Flake et al., 2003).

A cohort study conducted by Edwards et al., in 2013 has observed increased risk of fibroids among women who had their first menses earlier or on the eleventh birthday relative to women who had their first menses between age 12-13. He further reported that participants whose menarche were after 13 years has reduced incidence of fibroids compared to 12-13years. Their result further shows that participants with early menarche (≤11 years) were at increased risk of developing multiple fibroids relative to those with a mean age at menarche of 12–13 years (Edwards et al., 2013). Similarly, Wise et al., (2004) in The Black Women's Health Study, an ongoing prospective cohort study has found age at menarche to be inversely proportional (Wise et al., 2004). Several studies reported similar findings (Faerstein et al., 2001; Lumbiganon et al., 1996).

2.1.5 Obesity/ Body Mass Index (BMI)

Obesity plays a role as a risk factor for UF development by either through hormonal or inflammatory mechanisms (Pavone et al., 2018). In the study of women who underwent surgical management of fibroids, it was observed that women who gained weight more than 20kg were at increased risk of developing UF when compared with those who gained weight <10kg (Templeman et al., 2009). Sun et al. (2019) conducted a cohort study from 2016 to 2018 and found that overweight and obesity were risk factors for uterine fibroids (Sun et al., 2019). Their result was also consistent with studies conducted by C. R. Chen et al and Ciavattini et al (C. R. Chen et al., 2001; Ciavattini et al., 2013). However, Sulaimani et al.(2021) reported no statistically significant association between Body Mass Index (BMI) and uterine fibroid in their study (Sulaimani et al., 2021).

2.2 Types of fibroids/ Anatomical classification of uterine fibroids

The location, size and number of UF nodules varies. These characteristics can negatively impact female reproduction in many ways including fecundity and adverse pregnancy outcomes (Klatsky et al., 2008).

Several studies have reported that early miscarriages are common with women with submucosal and intramural types of fibroids (Bernard et al., 2000; Casini et al., 2006). Additionally , a study

has found that cases of submucosal fibroid and miscarriage seem different as submucosal fibroids were identified to increase the trend of miscarriage from 22% to 47%(Klatsky et al., 2008).

Lam et al., (2014), concluded that there was no statistical significance relationship between fibroid types and effects on preterm delivery, C/S and mean birth weight. However, the study reported that women with intramural fibroids had significantly higher rates of caesarean sections relative to women in whom the UF were only subserosal (Lam et al., 2014). He further compared subserous fibroids with intramural fibroids and reported that there was low blood loss among women with subserous compared to women with intramural fibroids. However, this increased blood loss was not statistically significant. Similarly, Saleh et al. reported that fibroid type has no significant importance with occurrence of adverse obstetric outcomes (Saleh et al., 2018).

2.3 Characteristics of uterine fibroids

2.3.1 Number of fibroids

In an observational study it was found that number of UFs had no significant importance with occurrence of adverse obstetric outcomes (Saleh et al., 2018). Meanwhile, a study by Lam et al. (2014) has found that patients with multiple UF were substantially more likely to have a preterm birth compared to women with a solitary UF (Lam et al., 2014). However, the difference in caesarean section(C/S) rate is not statistically significant despite higher C/S rate (55% v 45%) in women with multiple fibroids relative to those with a solitary fibroid (Lam et al., 2014). Similarly, Ciavattini et al. (2015). observed raised preterm delivery, cesarean delivery, and malpresentation (breech) presentation rates among participants with multiple fibroids compared with single fibroids or no fibroids (Ciavattini et al., 2015b). The findings from Lev-Toaff et al also supported lam et al. findings of increased risk of preterm associated with multiple fibroids (Lev-Toaff et al., 1987). Comparing the effect of multiple and single fibroid on the birth weight of babies, Lam et al.(2014), found that, there were no statistically significant difference in the birth weights (Lam et al., 2014).

Lai et al. reported no correlation between increased numbers of fibroids and adverse obstetric outcomes and also no relationship between preterm delivery and fibroid number (Lai et al., 2012)

2.3.2 Location of fibroids within the uterus

According to Lam et al (2014), women who had UF in the lower uterine segment, were significantly more likely to have a C/S (86% v 40%, p=0.01). Six (6) out of 26 and 2/26 women with lower uterine segment fibroid had C/S on account of malpresentation and placenta previa respectively. Furthermore, lower uterine segment located fibroids have increased risk of postpartum haemorrhage which is statistically significant. However, there were no relationship between fibroid location and preterm delivery as well as mean birth weight of babies (Lam et al., 2014).

Several other studies have also reported that uterine fibroids in the lower uterine segment are significantly more likely to end up with C/S(Lev-Toaff et al., 1987; Vergani et al., 2007).

2.3.3 Size of fibroid

Lam et al. (2014), categorized fibroid size into three groups; 4-7 cm, 7 -10 cm and >10 cm. The result has shown no association between UF size and mean birthweight, rate of preterm delivery or the mode of delivery. However, they found that the rates of PPH were higher; 11% vs. 13% vs. 36% for 4-7 cm, 7-10 cm, and >10 cm respectively and was statistically significant (Lam et al., 2014). A prospective observational study conducted in Kenya has found no significant association between fibroid size and bad obstetric outcome (Saleh et al., 2018).

In a retrospective cohort study it was found that preterm delivery was also significantly more frequent in the large fibroid group (Shavell et al., 2012)

A study has reported a statistically significant relationship between postpartum haemorrhage and presence of large uterine fibroid (Shavell et al., 2012). However, another study has observed no statistically significance difference in the rate of caesarean section among the cases and the controls (Lai et al., 2012). Recent study conducted by Sulaimani et al. (2021), concluded

that large uterine fibroid is associated with increased C/S, postpartum haemorrhage and is statistically significant (Sulaimani et al., 2021). However, he observed that there were increased rate of preterm labour, intrauterine growth restriction and malpresentations but were not statistically significant (Sulaimani et al., 2021).

2.4 Obstetric outcomes

2.4.1 Maternal outcomes

2.4.1.1 Abdominal pain.

Lower abdominal pain may be considered normal when all other etiologies are excluded. Occasionally pain especially associated with degenerating uterine fibroids in pregnancy may be severe and will also warrant admission (Cook et al., 2010). Several studies have found a higher rate of severe abdominal pain among women with fibroid in pregnancy compared with women without fibroids in pregnancy (Deveer et al., 2012; Ezzedine & Norwitz, 2016; Katz et al., 1989). The pain is as a result of red degeneration of UF characterized by infarction and necrosis secondary to tissue anoxia resulting from fibroids overgrowing their blood supply. Two studies have found that fibroids in pregnancy do not demonstrate significant rapid growth and therefore the proposed theory of rapid growth of fibroid causing pain is likely not to be the case (Morgan Ortiz et al., 2011; Ouyang et al., 2006). However, pain may be associated with location of fibroids and not size of fibroids (Katz et al., 1989)

2.4.1.2 Premature rapture of membrane

The study by Coronado et al. (2000). has observed an increased risk of premature rapture of membrane among women with uterine fibroid (Coronado et al., 2000). However, Lai et al.(2012), had reported no association between fibroid and premature rapture of membrane (Lai et al., 2012). Similarly, Sulaimani et al. (2021), observed no statistical significance difference between women with fibroid and without fibroid on premature rapture of membrane (Sulaimani et al., 2021).

2.4.1.3 Bleeding in early pregnancy

Early pregnancy bleeding refers to vaginal bleeding before 24 weeks of gestational age or bleeding occurring within first and second trimester (Muram et al., 1980). Several studies have

observed that bleeding in early pregnancy occurs most with fibroid implanted close to the placenta than pregnancies where fibroids are not in contact with the placenta (Exacoustòs & Rosati, 1993; Muram et al., 1980)).

2.4.1.4 Placenta previa

Placenta previa is an obstetric complication in which the placenta partially or completely occludes the internal orifice of the cervix, with an incidence of 0.3% to 2% (Faiz & Ananth, 2003). Coronado et al. (2000), in their study compared women with uterine fibroid and without fibroid. He observed that women with fibroid have an increased risk of placenta previa compared to women without (Coronado et al., 2000). Likewise, the study by Lai et al.(2012), Stout et al.(2010), and Vergani et al.(2007) have all reported an increased risk of placenta previa among women with uterine fibroid (Lai et al., 2012; Stout et al., 2010; Vergani et al., 2007).

2.4.1.5 Placenta abruptio

Placenta Abruptio results from a cascade of pathophysiological processes that lead to placental separation prior to delivery, complicating about 1% of births (Ananth et al., 1999). Significant retroplacental haemorrhage from placenta abruption is an important cause of maternal and foetal (Klatsky et al., 2008; Lev-Toaff et al., 1987) mortality in the world (Haeri & Dildy, 2012) Several other studies have reported three folds increase in cases of abruptio placentae among pregnant women with UF, especially if the UF nodules are situated submucosally or rightly beneath or have a volume > 200 (Klatsky et al., 2008; Lev-Toaff et al., 1987).

In another study conducted in the US it was found that there was an increased risk of placenta abruptio among women with uterine fibroid compared to women without fibroid (Coronado et al., 2000). Furthermore, Stout et al.(2010), also reported an increased risk of placenta abruptio among women with uterine fibroid and without fibroid (Stout et al., 2010).

2.4.1.6 Cesarean delivery

The risk of Cesarean delivery has increased up to about 6 times among women with uterine UF compared to women without UF in a retrospective study conducted between 1987 – 1993 in the US (Coronado et al., 2000).

In an observational study conducted in Africa (Egypt), vaginal delivery was less than cesarean section among 46 women who were followed with diagnosis of uterine fibroid in pregnancy (Saleh et al., 2018). More so, Klatsky et al. recorded that woman with fibroids were at a 3.7-fold increased risk of cesarean delivery (Klatsky et al., 2008). Vergani et al. (2007) reported that multiple fibroids, large fibroids, and fibroids in the lower uterine segment are predisposing factors for cesarean delivery (Vergani et al., 2007). Furthermore, Lai et al. in their study have reported that the presence of leiomyomata was associated with increased risks for cesarean delivery (Lai et al., 2012). Stout et al.(2010) have also reported an association of increased caesarean section among women with fibroid (Stout et al., 2010).

In contrast, Vergani et al(2007) reported high incidence of spontaneous vaginal deliveries among participants with uterine fibroids and further recommended women (with large uterine fibroids) are given the opportunity for trial of labour (Vergani et al., 2007).

Although studies have reported higher incidence of operative deliveries among women with large uterine fibroid, Exacoustòs & Rosati (1993), has found lower incidence of approximately 13% compared to 48% (Exacoustòs & Rosati, 1993). In most of the cases, malpresentation seem to be the main indicator for caesarean section (Coronado et al., 2000; Vergani et al., 2007).

2.4.1.7 Miscarriage

In a systematic review by Klatsky et at (2008), they have observed an increased risk of miscarriages among cases (women with UF) than the controls (Klatsky et al., 2008). Similarly, in a meta-analysis conducted by Pritts et al (2009), even after adjusting for locations of UF a significant association was found between miscarriage and UF (Pritts et al., 2009). Furthermore, a study by Stout et al, has found a significant association between miscarriage and presence of uterine fibroid (Stout et al., 2010). The case of uterine fibroid associated with miscarriage was not different in the study conducted by Chen et al., as it was found that there is a statistically significant association between miscarriage and presence of UF (Y.-H. Chen et al., 2009).

Benson et al. (2001), in their study had similar finding of increased miscarriage among pregnant women with fibroid compared to pregnant women without fibroids (14% vrs 7.5% respectively). He however observed that multiple fibroids increased the miscarriage rate and not the size of the fibroid (Benson et al., 2001).

2.4.1.8 Malpresentation

In a study it was found that there was 4-fold increased risk of malpresentation among women with uterine fibroid (Coronado et al., 2000). Similarly, a study observed that the presence of UF was associated with increased risk of malpresentation (Lai et al., 2012). Furthermore, malpresentation was found to be significantly associated with presence of UF in a study conducted in the US (Stout et al., 2010). Additionally, Vergani et al. (2007) also observed a higher rate of malpresentation in their study (Vergani et al., 2007). However recent study reported no statistical significance difference between women with uterine fibroid and without fibroid on malpresentation (Sulaimani et al., 2021).

2.4.1.9 Intrauterine growth restriction (IUGR)

Literally, fibroid co-existing with foetus in utero will be expected to restrict foetal development. However, literature available has shown that women having fibroids co-existing with foetus in utero are not at increased risk compared to those without (Exacoustòs & Rosati, 1993; Rice et al., 1989; Vergani et al., 1995). On the contrary, a study has shown that uterine fibroid is associated with IUGR and was statistically significant (Y.-H. Chen et al., 2009). Furthermore, several other studies have reported fetal deformity arising from compression especially by a large submucosal fibroids (Graham & Miller, 1980; Lee et al., 2010).

2.4.1.10 Postpartum haemorrhage (PPH)

Applying univariate and multiple variables analyses, the result of increased association between UF and PPH remained same (Lai et al., 2012). The study conducted by Egbe et al. has also found an association between uterine fibroid and primary haemorrhage which is statistically significant (Egbe et al., 2018). Navid et al. in 2012 conducted a prospective study in which he has observed an association between fibroid and postpartum haemorrhage (Navid et al., 2012).

A recent study concluded that fibroid is statistically and significantly associated with postpartum haemorrhage (Sulaimani et al., 2021). A retrospective cohort study based on a database of all women with singleton pregnancies and ultrasound diagnosis of uterine leiomyomata in pregnancy from January 1996 to December 2004 concluded an increased odds of postpartum haemorrhage among women with uterine fibroid compared to women without fibroid (Vergani et al., 2007). However, three studies have all not reported increased risk of PPH(Coronado et al., 2000; Sulaimani et al., 2021).

2.5 Foetal outcomes

2.5.1 Stillbirth

Washington state retrospective population-based study conducted between 1987–1993 has observed that cases were more likely than controls to have increased foetal death (Coronado et al., 2000), and similar conclusion was arrived at in another study (Stout et al., 2010). However, s systematic review reveals no association between uterine fibroid in cyesis and stillbirth (Klatsky et al., 2008). Similarly, a study also reported that there is no association between uterine fibroid in cyesis and stillbirth (Rice et al., 1989).

2.5.2 APGAR scores

In a retrospective population-based study conducted in the Washington state between 1987–1993 it was found that cases were more likely than controls to have newborns with 5-minute APGAR scores of less than 7 (Coronado et al., 2000). Similarly, Egbe et al.(2018) has reported low APGAR after 5minutes among babies delivered to women with fibroid(Egbe et al., 2018). A retrospective cohort study conducted recently reported a statistically significant association between uterine fibroid and APGAR score (Sulaimani et al., 2021). Vergani et al. (2007),has also observed an increased odds of low APGAR score (< 7 in the first 5 minute) among women with uterine fibroid compared to their counterpart women without fibroid (Vergani et al., 2007).

2.5.3 Birthweight

In the study conducted by Coronado et al.(2000) Coronado et al. it was observed that cases (pregnant women with uterine fibroids) were more likely to have low birth weight (LBW) (Coronado et al., 2000). Sulaimani et al. (2021), in their current study reported no association

between uterine fibroid and birth weight (Sulaimani et al., 2021). Similarly, a retrospective cohort study conducted in 2007 reported no statistical significance difference between birthweights of babies delivered to women with fibroid and without fibroid (Ezzedine & Norwitz, 2016)

2.5.4 Preterm delivery

A study comparing pregnancy outcomes in women with and without UF has reported an increased risk of preterm deliveries among women with UF (Lai et al., 2012). Likewise, Stout et al. have also observed an increased risk of preterm deliveries among participants with UF (Stout et al., 2010). Furthermore, Ciavattini et al (2015) also observed an association between multiple fibroid and preterm delivery and was statistically significant (Ciavattini et al., 2015). However, the same study has seen no significant association between large fibroid and preterm delivery. Shavell et al. (2012), observed a higher rate of preterm delivery in 42 women with sonographically detected large uterine myoma (Shavell et al., 2012). However, in another study there was no association with fibroid size (Vergani et al., 2007). Similarly stout et al.(2010) have not found significant association between large uterine fibroid and preterm delivery (Stout et al., 2010),

Uterine fibroids affect the female reproductive system and several of the studies conducted have assessed the effects of UF on reproduction. The findings varied from one study to the other. No single study was able to conclude quantitatively the effects of UF on maternal and foetal outcomes of pregnancy.

CHAPTER THREE

3.0 METHODS

3.1 Protocol and registration

This systematic review and meta- analysis protocol has not been published but was registered on Prospective Register of Systematic Reviews (PROSPERO) with registration number: CRD42021285098**.** It follows a pre- specified protocol in accordance with the Meta- analysis Of Observational Studies in Epidemiology (MOOSE) consensus statement. The PICOS framework was adopted to describe the Population, Intervention, Comparators, Outcomes and types of Studies included in the review (P-Patients, I-intervention, C-control, O-Outcomes, and S-Study).

3.2 Criteria for considering studies for this review

Population

Women diagnosed with fibroid living in a sub-Saharan African country were eligible for inclusion in this systematic review.

Study

All studies conducted in Sub-Saharan Africa such as cross-sectional studies, longitudinal, and cohort studies which reported UF were included in the study. Randomized controlled trials and quasi- experimental trials were excluded. In addition, abstracts with no follow- up report of findings, ongoing clinical studies, review papers, case report, letters to the editor, and editorials were excluded.

Exposure(s)

Pregnant women with co-existing uterine fibroids

Comparator

Pregnant women without uterine fibroids.

Outcome

Primary outcomes

The primary outcome of this study were effects of uterine fibroid on foetal and maternal outcomes of pregnancy and risk factors of uterine fibroids.

Secondary outcomes

Secondary outcomes examined were;

i) Types of fibroids - intramural, submucous and subserosal

ii) Number of fibroid nodules- multiple or single

iii) Location – cervix, body, fundus

3.3. Search strategy

3.3.1 Electronic database searches

Two authors conducted the search independently. Potentially eligible studies were searched from PubMed, Google Scholar, Hinari and African Journals Online from inception of database to April 2022. The key search terms used were “Uterine fibroid”, “Leiomyoma”, “Myoma”, “Fibromyoma”, “Risk factors”, “Obstetric outcome”, “Sub-Saharan Africa”, “SSA”, “LMICs”. The search was done without language restriction. Search strategies at PUBMED, Google Scholar, Hinari and African Journals Online were attached (Appendix 1)

3.3.2 Other sources

The reference lists of all relevant studies were searched manually to retrieve potentially eligible studies. Past systematic reviews’ reference lists were also searched to identify relevant studies for inclusion. Unpublished articles were reviewed for eligibility. Experts were contacted for additional studies that could have been missed from electronic searches.

3.4 Study selection

Two researchers (EA and DO) independently examined the titles and abstracts of all identified papers using pre-tested study selection flowchart. The full texts of the potentially relevant studies were retrieved and screened against the inclusion/exclusion criterion. Discrepancies that emerged during the screening were settled by discussion with a third researcher (supervisor, ADA). At the screening stage some articles were excluded and the reasons for exclusions were recorded.

3.5 Data extraction

Relevant data were extracted from the selected articles by two investigators (EA and ADA) using a pretested data extraction template developed from Microsoft Excel. Relevant variables and characteristics such as country where the study was carried out, year the study was conducted, title, author, year of publication, study area, study design, number and type of participants were collected. Information on socio-demographic characteristics, obstetric variables and history were also collected. The primary outcome variables collected and meta-analysed were preterm birth (live baby delivered before 37 weeks of gestation); LBW(<2500 g irrespective of gestational age); APGAR score (where a score of 7 or higher is considered normal and below 7 is abnormal in the first 5 minute after birth); stillbirth (death or loss of baby before or during delivery); postpartum haemorrhage (blood loss of >=500ml and 1000ml or more after 24 hours delivery via spontaneous vaginal delivery and caesarean section respectively); foetal malpresentation; miscarriage/spontaneous abortion (loss of pregnancy before 20weeks of gestation or viability); Cesarean delivery (delivery by incision into abdomen); placenta abruptio (the separation the placenta partially or completely from the inner wall of the uterus before delivery); placenta previa (low lying placenta in the uterus and either covers all or part of the cervix) and premature rapture of membrane (rapture of membrane before labour begins). Data extracted was checked again by the two researchers to ensure accuracy and consistency.

3.6 Quality assessment (risk of bias assessment)

Two researchers independently assessed the risk of bias in the selected studies using the checklist developed by Hoy et al (Hoy et al., 2012). The checklist allowed researchers to assess domains such as the sampling technique and sample size, outcome measurement, response rate, and statistical reporting. Under these 4 domains are 10 items which we have assessed as either low risk or high risk. We again total the low and high risk and finally rated an article as low, moderate or high risk. In situations where data from the included study were unclear, the reviewer contacted other reviewer for second opinion of the included study for explanation. Discrepancies between reviewers were resolved through discussion with supervisor. Risk of

bias and quality results was presented in a table and explanations to the risk assigned to each domain was provided in the appendix section of the review (appendix 3).

3.8 Data management and analyses

Characteristics of the included studies were narratively synthesized- study design, the magnitude of the outcome of interest, population characteristics, geographical location where the included studies were conducted. The data extracted were entered into Microsoft excel and then exported to RevMan v5.4 and Stata version 16.0 (StataCorp LLC. Texas, USA). For binary outcomes, odds ratio (OR) and their 95% Confidence Interval (CI) were calculated. For continuous outcomes, mean difference (MD) with their standard deviation, and also presented with their 95% CI.

To generate the overall pooled estimate, random-effects model recommended to adjust for variability in the presence of heterogeneity among studies (Barth et al., 2010; White et al., 2008) was used. And we checked heterogeneity across studies with I^2 test statistics. I^2 test statistics provides a more reliable test to measure the variability or heterogeneity across the studies. I^2 ranges between 0 and 100%, I^2 less than 25% indicates low heterogeneity whereas I^2 greater than or equal to 75% indicates very high heterogeneity across studies (Ried, 2006).

3.9 Investigation of heterogeneity

The I^2 statistics, which measures the variation across studies due to heterogeneity rather than chance was employed to assess the level of heterogeneity in the analysis (Higgins & Thompson, 2002). The level of heterogeneity was classified as substantial heterogeneity if I^2 >50%. Cochrane's Q statistics and Tau was presented and $p<0.05$ was used as the cut-off for significant heterogeneity.

3.10 Missing data

Some studies had missing data and, in our quest, to collect sufficient data we contacted the original researchers through the links provided. Articles with missing data whose original researchers were not reachable, their impact on the research findings were addressed in the discussion section.

3.11 Ethical issues

This study is based on published data, and therefore ethical approval is not a requirement.

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CHAPTER FOUR

4.0 RESULTS

4.1 Eligible studies

The studies varied widely regarding the categorization of maternal age and parity. Ages were categorised with different intervals and for the extreme of age some were categorised as greater than and less than. We finally chose the age range 20 – 29 which caters for age range with short intervals such as 20- 25 and others. We have also ignored the age range 60 years and above because it was reported in only one study with a single respondent aged 60 years and above (Chama et al., 2009). Parity was also poorly reported. As such we have decided to group parity as nulliparity, primiparity, multiparity, and grand multiparity. Ingela et al, for example reported parity as; Para 0 = 262, and Para 1 and above = 382. This implies the study actually considered parity as no or yes rather than the degree of parity. We were unable to perform sensitivity analysis after we have detected high levels of heterogeneity as a result of few studies available for meta-analysis.

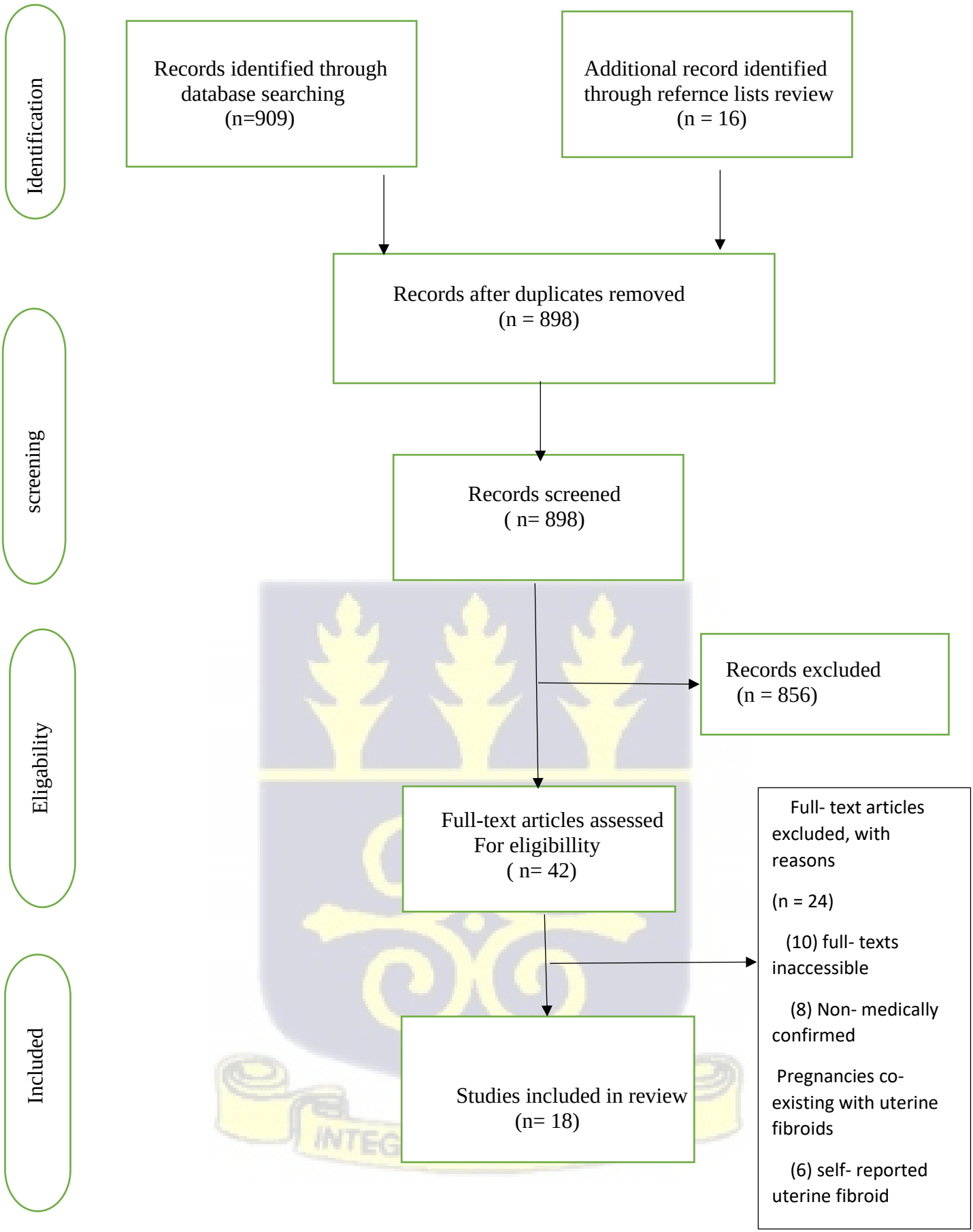


Figure 3: Flow diagram showing sources of studies and the selection process

4.2 Characteristics of included studies

Table 1 below shows the characteristics of the studies included in the systematic review and meta-analysis. The included studies were conducted in five different countries of SSA. Again, these five countries are from 3 sub-regions of SSA, namely; West Africa, Middle Africa and East Africa. West Africa contributed 83.33% (15/18) of the total included articles and the majority of these articles are from Nigeria 93.33% (14/15). Mali contributed one article giving us a percentage of 6.67. Middle Africa contributed two articles giving us a percentage of 11.11% (2/18). These articles are from Cameroon and DR Congo. About 6% of the included articles were conducted in East Africa, specifically Kenya.

Ultrasound scan and histopathology were the two main diagnostic tests used in the confirmation of uterine fibroids among the participants. Ultrasound scan form the majority of diagnostic criteria, with about 72.2% verses histopathology 27.7%. All the included studies were conducted between 2005 and 2021. The ages of the participants ranged from 15 to 65 years. However, two studies did not comment on the age range of participants. Four of the 18 studies reported on maternal and foetal outcomes. The sample size of studies ranges from 13 to 1460 participants

Table 1: Characteristics of included studies

STUDY ID	YEAR	COUNTRY	STUDY DESIGN	AGE	FIBROID CASE	NO FIBROIDS CASES	SAMPLE SIZE	METHODS OF DIAGNOSIS	REPORTED OUTCOME
Chama et al., 2009	2009	Nigeria	Retrospective cross-sectional	22 - 65	331	N/R	331	Histopathology	Risk factors and characteristics of fibroids
Ingala et al., 2017	2013	DR. Congo	Retrospective cross-sectional	N/R	6440	23955	644	ultrasonography	Risk factors, characteristics of fibroids and sub-types
Owolabi et al., 2010	2010	Nigeria	Retrospective cross-sectional	23 - 55	320	4121	320	Histopathology	Risk factors, characteristics of fibroids and sub-types
Obuna et al., 2008	2008	Nigeria	retrospective cross-sectional	19 - 55	180	1142	170	ultrasonography	Risk factors, characteristics of fibroids and sub-types
Ezeama et al., 2012	2012	Nigeria	Retrospective cross-sectional	24 - 51	117	N/R	103	Histopathology	Risk factors, characteristics of fibroids and sub-types
Muhammad et al., 2013	2013	Nigeria	Retrospective cross-sectional	21 - 51	386	12094	316	ultrasonography	Risk factors and characteristics of fibroids
Osaikhuwuomwan et al., 2015	2015	Nigeria	Retrospective cross-sectional	15 -54	420	3683	420	ultrasonography	Risk factors and characteristics of fibroids
Fasubaa et al., 2019	2018	Nigeria	Retrospective cross-sectional	29 - 59	106	314	106	ultrasonography	Risk factors and characteristics of fibroids
Okon et al., 2020	2020	Nigeria	Retrospective cross-sectional	N/R	320	1600	280	ultrasonography	Risk factors and characteristics of fibroids
Ijeruh et al., 2021	2018	Nigeria	Prospective cross-sectional descriptive study	18 - 56	1460	N/R	1460	ultrasonography	Risk factors, characteristics of fibroids and sub-types
Okunade & Gbadegesin, 2014	2014	Nigeria	Prospective cross-sectional descriptive study	20 - 49	300	N/R	300	ultrasonography	Risk factors, characteristics of fibroids and sub-types
Mohammed et al., 2005	2005	Nigeria	Retrospective cross-sectional	25 - 50	209	9082	209	Histopathology	Risk factors and characteristics of fibroids
Okezie & Ezegwui, 2006	2006	Nigeria	Retrospective cross-sectional	18 - 55	203	1865	190	Histopathology	Risk factors, characteristics of fibroids and sub-types
Coulibaly et al., 2021	2021	Mali	Retro-prospective descriptive study	20 - 55	180	770	180	ultrasonography	Risk factors, characteristics of fibroids and sub-types
Egbe et al., 2018	2018	Cameroon	Prospective cross-sectional	20 - 40	38	188	266	ultrasonography	PPH,CS, PPH, Previa, Abruption, malpresentation, Miscarriage, Vaginal bleeding, abdominal pain,stillbirth, preterm, birth weight, APGAR score

Eze et al., 2013	2013	Nigeria	Longitudinal study	15 - 44	100	716	200	ultrasonography	PPH,CS, PPH, Previa, Abruption, malpresentation, Miscarriage, Vaginal bleeding, abdominal pain, stillbirth, preterm, birthweight, APGAR score
Ago, 2017	2017	Nigeria	Prospective cross-sectional	20 - 42	72	817	889	ultrasonography	PPH,CS, PPH, Previa, Abruption, malpresentation, Miscarriage, Vaginal bleeding, abdominal pain, stillbirth, preterm, APGAR score
Mutua, 2014	2014	kenya	Prospective cohort	18 - 45	71	72	143	ultrasonography	PPH,CS, PPH, Previa, Abruption, malpresentation, Miscarriage, Vaginal bleeding, stillbirth, preterm, birth weight, APGAR score

4.3 Risk of bias of included studies

The risk of bias in the included observational studies were assessed using the Hoy et al (2012) risk of bias tool which presents a guide to assessing the methodological quality of observational studies. Across the four key domains, the scale and interpretation of total risk scores are; 0-3 (low risk), 4-6 (moderate risk) and 7-9 (high risk). All the studies (18) were scored as having low risk of bias as they reported detailed methods regarding the target population, sampling frame, sampling, validity of outcome measurements, response rate and data analysis. Though the study population were not representative of national population.

Table 2: Risk of Bias Assessment

Ser #	STUDIES	1	2	3	4	5	6	7	8	9	10
1	Chama et al., 2009	High risk	High risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
2	Ingala et al., 2017	High risk	High risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	High risk	Low risk
3	Owolabi et al., 2010	High risk	High risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
4	Obuna et al., 2008	High risk	High risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
5	Ezeama et al., 2012	High risk	High risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	High risk	Low risk
6	Muhammad et al., 2013	High risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
7	Osaikhuwuomwan et al., 2015	High risk	High risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
8	Fasubaa et al., 2019	High risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
9	Okon et al., 2020	High risk	High risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
10	Ijeruh et al., 2021	High risk	High risk	High risk	High risk	Low risk	Low risk	Low risk	Low risk	High risk	Low risk
11	Okunade & Gbadegesin, 2014	High risk	High risk	High risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
12	Mohammed et al., 2005	High risk	High risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
13	Okezie & Ezegwui, 2006	High risk	High risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
14	Coulibaly et al., 2021	High risk	High risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
15	Egbe et al., 2018	High risk	High risk	High risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
16	Eze et al., 2013	High risk	High risk	High risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
17	Ago, 2017	High risk	High risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
18	Mutua, 2014	High risk	High risk	High risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk

4.4 Demographic (risk) factors

4.4.1 Age

Overall, 9 studies were included in the meta-analysis of age as a risk factor in uterine fibroid development. The results shows that age group 30 – 39 has the highest prevalence of fibroids 51.0% (CI= 47.0 – 56.0; I^2=85%) followed by age group 40 – 49 years with a prevalence of 28.0% (CI= 23.0 – 33.0; I^2=90%) (Figure 4). The age group 20 – 29 and 50-59 years had prevalence of 17% (CI= 11.0 – 23.0; I^2=96%) and 4% (CI= 2.0 – 6.0; I^2=99%) respectively. The overall pooled prevalence was 26% (20.0 – 32.0; I^2=99.2%).

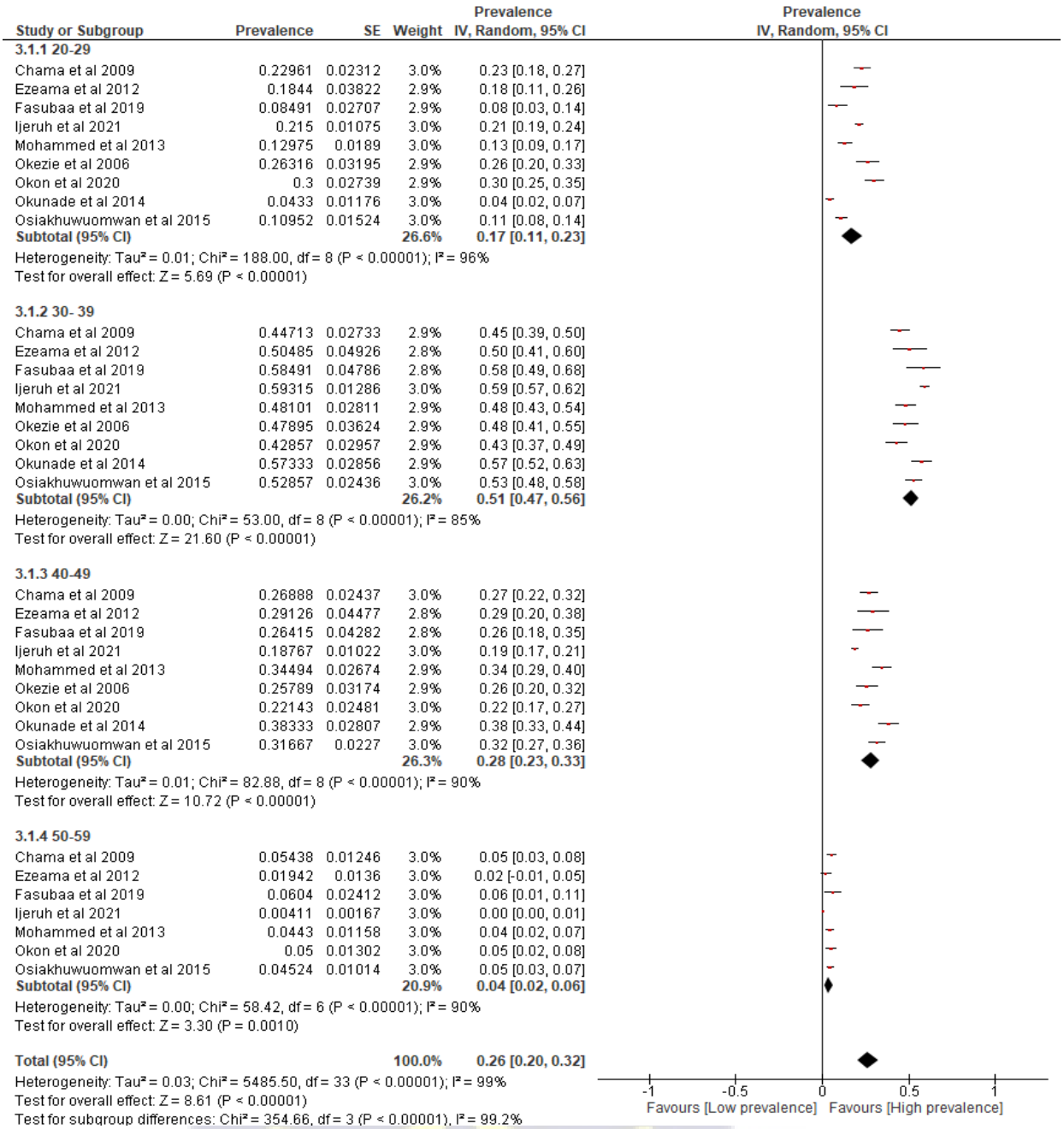
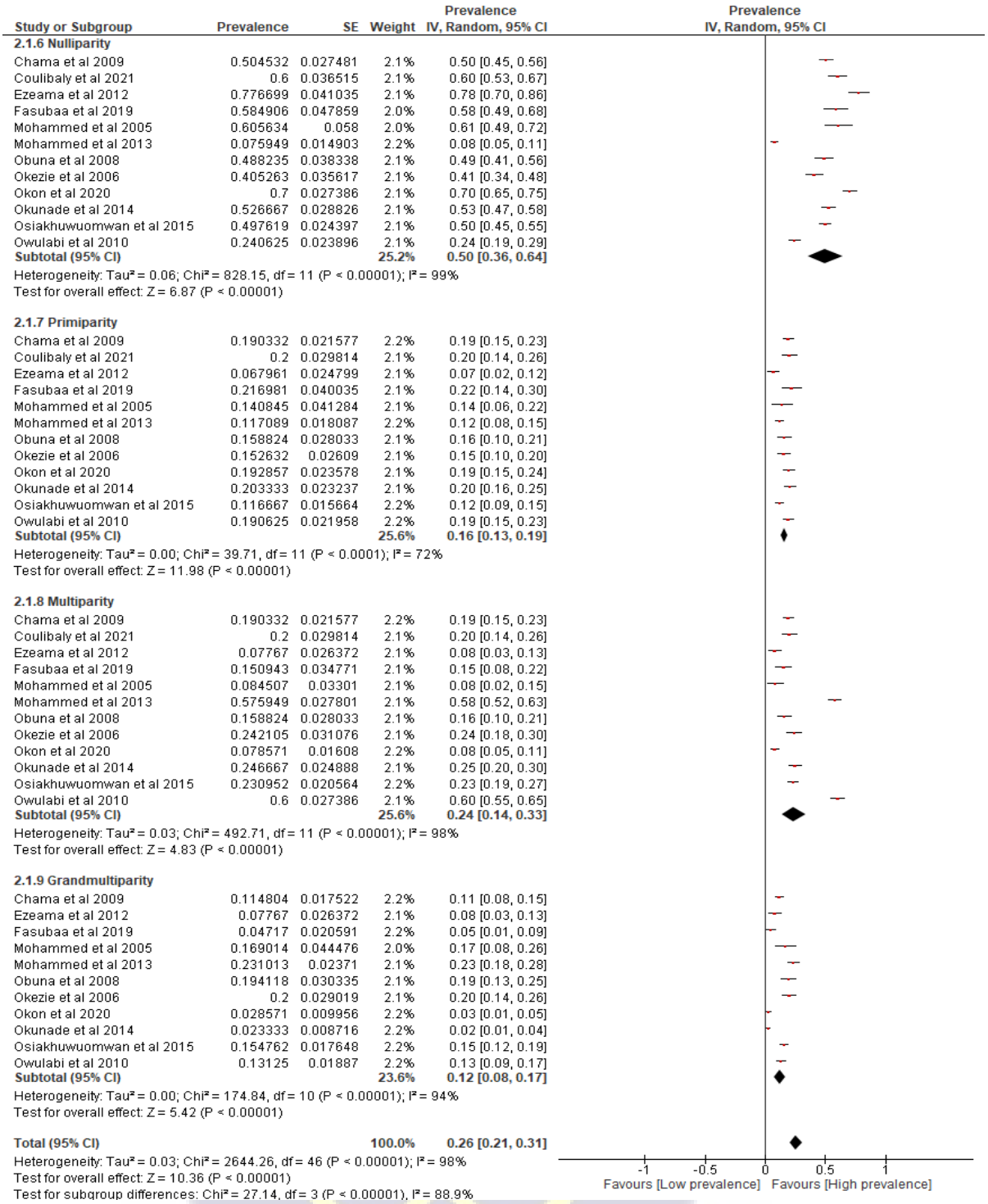


Figure 4: Forest plot showing the effect of Age on the risk of developing uterine fibroid.

4.4.2 Parity

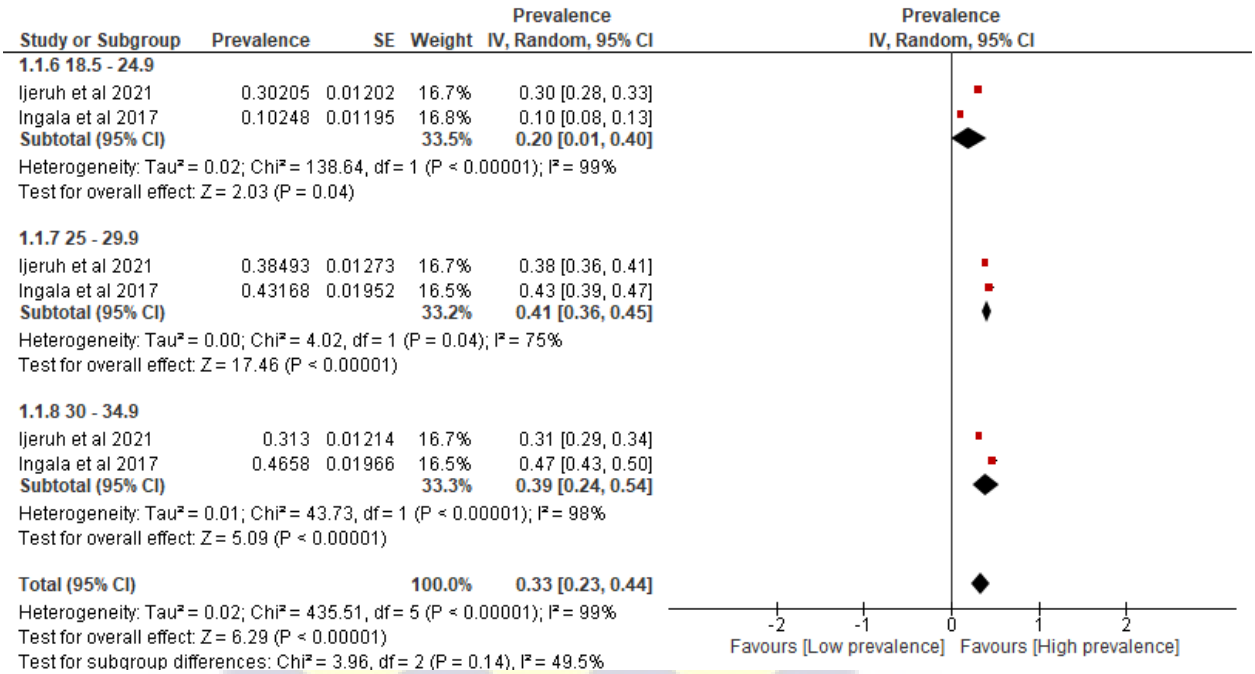
Twelve studies assessed parity of women with uterine fibroids. Nulliparity, primiparity, multiparity and grand multiparity were the strata (Figure 5). The result from figure 5 below shows the pooled prevalence of parity on development of uterine fibroids, 26% (CI= 21.0 – 31.0; I^2 = 98.0%) with a substantial heterogeneity. Prevalence of fibroids is highest among the nulliparous women with a frequency 50.0% (CI=36 – 64; I^2 = 98.0%). The result also showed that multiparous women were the second group with the next highest frequency of 24.0% (CI= 14.0 – 33.0; I^2 = 98.0%). The prevalence was lower among the primiparity 16.0% (CI= 13.0 – 19.0; I^2 = 72.0%) and grand multiparity 12.0% (CI= 8.0 – 17.0; I^2 = 94.0%) respectively.



4.4.3 Body mass index

Figure 5: Pooled prevalence of the effect of parity on developing uterine fibroid In this review BMI was estimated for normal, overweight and obese (figure 6). There were not enough data to

estimate for morbid obesity (>35kg/m2). The pooled prevalence was 33% (CI= 23.0% - 44.0%; $I^{2\,=}$ 99.0%) shown in figure 6 below. From the result, the prevalence of fibroid is highest among the overweight 41% (CI= 36.0 – 45.0; $I^{2\,=}$ 75.0%). The prevalence (39%) is higher among the obese compared to the normal (20%).



4.4.4 Menarche

Two studies (Egbe et al., 2018, and Ingala et al., 2017) out of the total 18 studies included the variable menarche in the outcomes assessed. The first study was a descriptive cross-sectional

Figure 6: Forest plot of BMI (normal, overweight, and obese) showing the prevalence of fibroids

study (Ingala et al., 2017). In this study majority of the participants, 462 out of 644 had their menarche on or after age 12. One-hundred and eighty-two (182) of the remaining respondents had menarche before 12 years. In the second study (Egbe et al., 2018….) the mean age at menarche between women with fibroid and without fibroid is 14.0 and 14.7 respectively. And this was statistically insignificant (p =0.11).

4.4.5 Family history of fibroids

Table 1: Comparism of with and without Familial Predisposition of uterine fibroids

Only two studies have reported on the risk of family history on developing uterine fibroid. Four-hundred and thirty-four, a percentage of 52.7 said they have no family history of fibroids and 390 (47.3%) of the respondents admitted to familial predisposition as shown in table 3 below.

Study id	**Family history of fibroids**	
	Yes	**No**
Ingala et al., 2017	366 (56.83%)	278(43.17%)
Coulibaly et al., 2021	24 (13.33%)	156 (86.66%)
Total	**390 (47.33%)**	**434 (52.67%)**

4.5. TYPES OF FIBROIDS

From the results table below table 4, intramural fibroids were the predominant types 49.2% (1474). Submucous fibroids were the second most prevalent types 26% (783/3001) in this review and the least been the subserous 24.7% (744/3001).

Table 4: Comparism of types of uterine fibroids in SSA

Study ID	**Types of fibroids**		
	Submucous	**Intramural**	**Subserous**
Ingala et al, 2017	270	274	100
Owolabi et al, 2010	58	174	78
Ezeama et al, 2012	8	32	6
Ijeruh et al, 2021	347	695	419
Okezie & Ezegwui, 2006	26	109	55
Coulibaly et al, 2021	43	116	12
Egbe et al, 2018	9	5	24
Eze et al, 2013	18	24	38
Mutua, 2014	4	45	13

Total	**783 (26.09%)**	**1474 (49.12%)**	**744 (24.79%)**

CHARACTERISTICS OF FIROIDS

4.6.1 Number of fibroids

A total of 6 studies were included in the meta-analysis of number of fibroids shown in figure 8. The result shows that multiple fibroids are prevalent in SSA, 61.0% (CI= 56.0 – 66.0; I^2=61%) when compared with single fibroids 39.0% (CI= 34.0 – 44.0; I^2=61%).

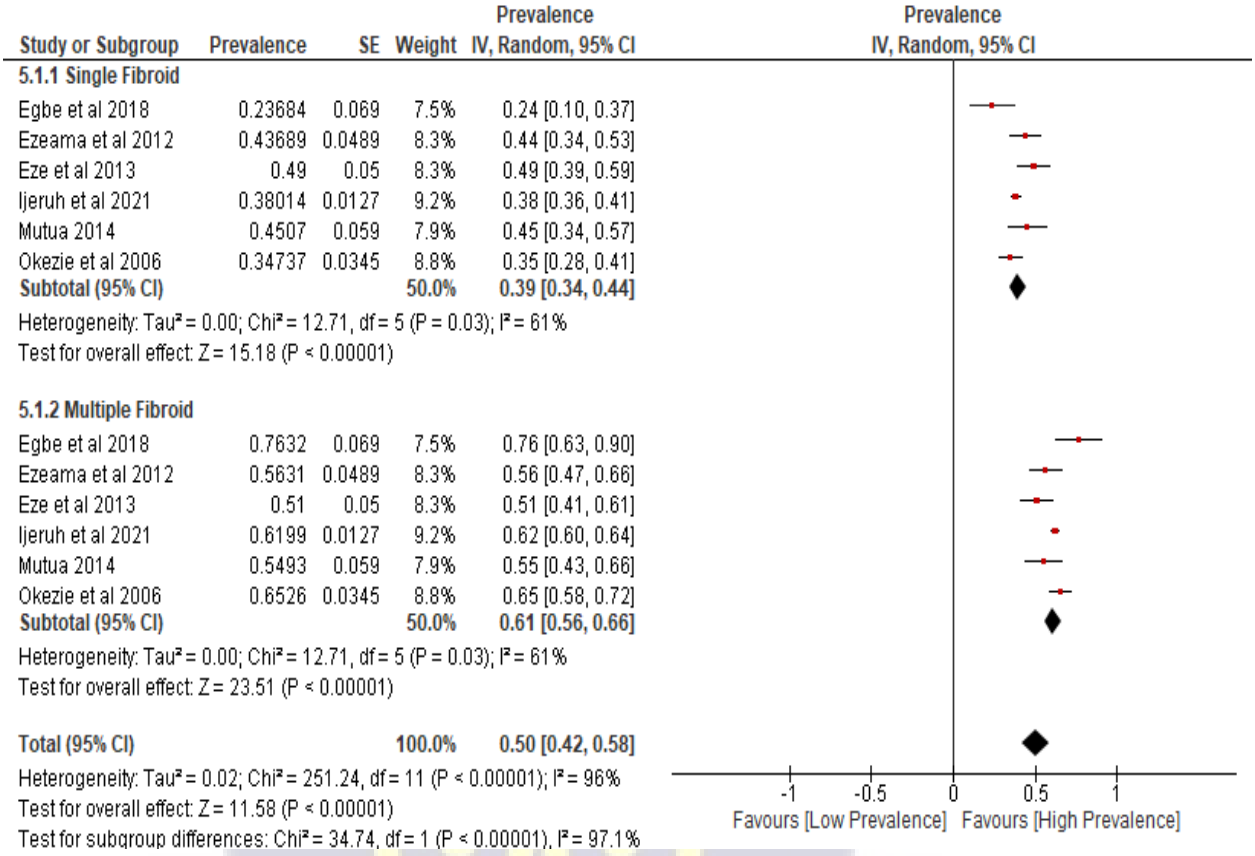


Figure 8: Forest plot of pooled prevalence of fibroid sub grouped according to number of fibroids

4.6.2 Location of fibroids

Out of the 18 studies included only three studies reported on fibroid locations. From the result, (table 5) majority, 72.9%, of fibroids were found in the body of the uterus. Others were found at the fundus and the cervix with percentages, 24.4% and 2.8% respectively.

Table 2:Comparing Location of Fibroid among women

Study	**Fibroid location**		
	Fundus	**Cervix**	**Body**
Ingala et al, 2017	0	26	534
Ijeruh et al, 2021	482	29	949
Mutua, 2014	23	2	28
Total	**505 (24.36%)**	**58 (2.75%)**	**1511 (72.89%)**

4.7 Effects of fibroids on pregnancy outcomes

From the meta-analysis obtained on effects of fibroids, it was realized that individuals with fibroids were 3.9 times more likely to experience postpartum haemorrhage compared to without Fibroid (OR= 3.93;CI= 1.28 – 12.05; I^2= 17%), bleeding per vaginum (OR= 4.51;CI= 1.96 – 10.38; I^2= 18%), caesarean section (OR= 2.82;CI= 1.01 – 7.92; I^2= 74%), miscarriage (OR= 1.38; CI= 0.73 – 2.63; I^2= 0%), preterm (OR= 1.58; CI= 0.80 – 3.11; I^2= 0%), malpresentation (OR= 1.92; CI= 0.74 – 4.95; I^2= 0%), abdominal pain (OR= 3.09;CI= 1.73 – 5.54; I^2= 0%), intrauterine growth restriction (OR= 1.70; CI= 0.60 – 4.78; I^2= 0%) and premature rapture of membrane (OR= 0.99; CI= 0.31 – 3.15; I^2= 0%).

Table 3: Summary of the results of meta-analysis

Outcome	Studies	OR	95% CI	T^2	I^2	P-value
PPH	2	3.93	1.28 - 12.05	0.23	17	0.02
Vaginal bleeding	2	4.51	1.96 – 10.38	0.07	18	0.0004
C/S	2	2.82	1.01 – 7.92	0.41	74	0.048
Miscarriage	2	1.38	0.73 – 2.63	0.00	0	0.32
Preterm	3	1.58	0.80 – 3.11	0.00	0	0.18
Malpresentation	2	1.92	0.74 – 4.95	0.00	0	0.18
Abdominal pain	2	3.09	1.73 – 5.54	0.00	0	0.0001
IUGR	2	1.7	0.60 – 4.78	0.00	0	0.32
PROM	2	0.99	0.31 – 3.15	0.00	0	0.99

Placenta Previa/Abruptio

The study by Egbe et al. (2018) has reported on late bleeding per vaginum (PV) among the study participants (38 cases and 188 controls) but was not able to differentiate if this was abruption or previa. However, the study has found that the likelihood of experiencing bleeding pv is high among pregnant women with fibroids compared to those without and was statistically significant (OR 5.2; CI: 1.6 – 16.3; P= 0.004)

Stillbirth

One study reported on stillbirth (Mutua, 2014). Out of a total of 143 participants (71 case and 72 controls) only a stillbirth was recorded among the cases giving a percentage of 1.4 %.

APGAR score

Two studies have assessed APGAR scores of babies delivered to pregnant women with co-existing fibroids and without fibroids (Egbe et al., 2018; Mutua, 2014). In the first study (Egbe et

al. 2018) a total of 226 participants were followed up (38 cases and 188 controls). Twelve out of 38 (12/38) cases had babies with APGAR's <= 7 in the first 5 minutes. The controls also recorded 14 (14/188) cases of babies with APGAR's <=7 in the first 5 minutes. Overall, the odds of delivering babies with low APGAR has increased by 6.0 among pregnant women with fibroids compared to those without fibroids and was statistically significant (CI: 1.9 – 19.1; P = 0.002).

In the second study (Mutua, 2014) 143 participants were enrolled comprising 71 cases and 72 controls. The APGAR scores for the cases and controls were compared after the average was calculated. The study however, did not compare the APGAR score on the scale of good and bad (> 7 as good and <= 7 as poor APGAR in the first 5 minutes). The median APGAR for the cases and controls were 9 and 10 respectively with a risk ratio of 0.92. This has reached statistical significance (P= 0.044; CI: 0.86 – 0.998).

Birth weight

The variable birth weight was assessed by two studies on different scale of measurement (Egbe et al., 2018; Mutua, 2014).

Egbe et al assessed the birth weight on ratio scale. Five (5) of the cases (5/38) had babies with birthweight < 2500g and 9 out of 188 controls also had babies with birthweight < 2500g. women with fibroids were 3 times more likely to deliver babies with birth weight < 2500g compared to women without fibroids (OR =3.3; CI: 0.6–14.7). However, this difference has not reached statistical significance (p = 0.12).

The second study Mutua, has reported the mean and standard deviation of the birth weights between women with fibroids and without fibroids. With a sample of 71 cases the mean birth weight was 3067.7 (± 608.5) and 3212.5 (± 618.6) for the controls (72). The result has shown that there was equal risk among the two groups but that has also not reached statistical significance (OR= 1.0; CI: 1.0 – 1.0001; P = 0.144).

CHAPTER 5

5.0 DISCUSSION

5.1 Introduction

The sub-Saharan African region is predominantly made up of black race. Studies have also found that black race is significantly associated with UF (Huyck et al., 2008; Okolo, 2008; Stewart et al., 2017). Although fibroids may be asymptomatic it has been implicated in adverse effects of pregnancy and foetal outcomes. As such a study has recommended myomectomy before conception (Yellamareddygari et al., 2010). Equally, some socio-gynaecological factors are known to influence UF development. Additionally, fibroids characteristics such as types, location and size are also known to influence fibroids severity and outcome of pregnancies and foetuses.

To the best of our knowledge this is the first systematic review in SSA to answer the foeto-maternal outcomes of pregnancies co-existing with UF as well as the characteristics and risk factors of UF in SSA.

5.2 Sociodemographic and obstetric factors

5.2.1Effect of age on fibroid development.

A total of 18 studies were included in this systematic review. Nine (9) articles contributed to the effect of age on uterine fibroid development and as such, relevant data to calculate the effect of age was extracted. The pooled prevalence of age in this study was 26% (CI: 20.0% - 32.0%) and was statistically significant. However, the heterogeneity is significant, I^2=99.2%. In this review increasing age seem to be associated with fibroid development as depicted by the result in figure 3. However, women in their late age have the lowest prevalence. The later may be explained by the theory of the protective effect of post- menopausal status (Templeman et al., 2009). Age has

consistently been a risk factor for fibroid development as it is known that fibroid do not occur before menarche and their frequency decreases with menopause (Marshall et al., 1997). Comparing the age groups, the prevalence is highest among 30 – 39years group. This however may be attributed to delayed childbirth as a result of pursuit of academic ladder by women or better still these group may be well educated with high income and presents themselves for early treatment (Ukwenya et al., 2015). A quasi experimental study conducted in Ghana, by Sarkodie et al also found that fibroids are common among the age group 30 – 40 and has explained that fibroid detection by sonography is very common among women in their late 30's and 40's and usually shrink after menopause (Sarkodie et al., 2016) . However, this result is in contrast to findings by Stewart et al (2017) which says fibroids are more common among women in their 5th and 6th decades but not beyond. They also found that fibroid can increased to about 10 times in women in their 5th and 6th decades when compared with those in the 3rd decades (Stewart et al., 2017). The studies included in this review were mainly cross-sectional studies and whilst they confirm the incidence at point in time, they do not offer much insight into the trends of diagnosis with age, in contrast with longitudinal studies. Another limitation of this review was inadequate data for age group beyond 59 to compute for older age groups. Although the data is insufficient the findings of this study is useful.

5.2.2 Effects of parity on fibroids development.

Twelve studies assessed parity of women with uterine fibroids. The overall prevalence was 26% (21.0 – 31.0) and was statistically significant ($p < 0.01$) with significant heterogeneity, I^2=98.0%. Parity was grouped into four and the result is suggestive of protective effect by parity. This result is consistent with other studies by Chen et (2001) and Sato et al (2002), which have found parity to be protective (Chen et al., 2001; Sato et al., 2002). During pregnancy there is a sharp rise in estrogen and progesterone levels (hormones implicated in fibroid development). On the other hand, postpartum is associated with sharp decline of progesterone and estrogen. This dramatic

effect of sharp rise and decline can affect fibroid growth. Accordingly, Laughlin et al (2010), in their study have observed that about 36% of fibroids seen on ultrasound during first trimester of pregnancy have all disappeared within 3 – 6 months postpartum. And those that remained were reduced in diameter by 0.5 cm (Laughlin et al., 2010)

In this study participants who are nulliparous have the highest prevalence of UF 50% (fig.5). This increased risk may be explained by the theory that nulliparous turn to have more menstrual cycles compared to parous women whose cycles were reduced by pregnancy and postpartum (Okolo, 2008). However, it is also known that the presence of fibroids may compromise fertility and therefore reduce parity (Payson et al., 2006; Somigliana et al., 2007). This implies adjusting for confounders such as infertility is important.

The trend in prevalence was however different in this current study as multiparous women have a higher prevalence compared to primiparous (fig. 5). Two studies (Owolabi et al., 2010 and Muhammad et al., 2013) contributed to this higher incidence and were justified as studies conducted in settings of Nigeria (north east and west) where early child marriage is high (Muhammad et al., 2013). The sample size of the studies included in this review were small and furthermore, the studies were cross-sectional. This calls for further studies (of cause well designed studies) to investigate this hypothesis.

5.2.4 Effect of Menarche on fibroid development.

Overall, two studies reported on menarche. The first study, (Ingala et al., 2017) a descriptive study has found that 28.3% (182) participants with fibroids have their menses before age 12. Majority 71.7% (462) had their menses at 12 years and above. According to literature women who had their menarche earlier are at increased risk of developing uterine fibroids compared to those with late menarche. The theory supporting this state that early menarche is associated with increased

menstrual cycles and for that matter significant exposure to ovarian hormone estrogen and progesterone which are responsible for fibroid growth (Schwartz, 2001)..

A single prospective cross-sectional study (Egbe et al., 2018) has reported the mean age at menarche of participants was 14.0 versus 14.7 years among pregnant women with and without fibroids respectively. Though women with fibroids turn to have their menarche earlier per the result in table 5, the test statistics is insignificant ($p = 0.11$). This finding contrast the findings by Edwards et al 2013 where their results showed that age at menarche ≤11 years is associated with an increased risk of fibroids when compared with the mean age at menarche (12–13 years) and that age at menarche >13 years is associated with reduced risk (Edwards et al., 2013). However, it is important to know that this is an observational study and this may only reflect a point estimate. Additionally, the sample size of the study is very small. Furthermore, the confounders of menarche such as BMI and lifestyle were not taking into consideration.

5.2.5 Family history

Generally, chronic diseases are linked to familial predisposition. Uterine fibroids are hypothesized to be common among families with history of fibroids. In a study conducted by Winkler and Hoffmann in 1938 it was reported that fibroids were 4.2 times more common in first-degree relatives of women with fibroids than those without (Winkler and Hoffmann 1938).

A more recent study by Schwartz et al. 2000b which studied 638 fibroid patients and 617 controls in the Puget Sound area of Washington reported that fibroid patients were more likely than the controls to report a history of fibroids in a mother or sister (33.2% vs. 17.6%). And again, the odds ratio increased to 5.7 in cases of early-onset fibroids, as might be expected for a genetically influenced trait (Schwartz et al. 2000b). In this current review the first study by Ingala et al, 2017 has reported that women with family history of fibroids were more compared to those without (366 verses 278) and this was statistically significant. However, this study is a descriptive study

and can only report point incidence. Furthermore, it could not adjust for confounders such as body weight and lifestyles as well as age.

The second study (Coulibaly et al., 2021) has rather reported lower incidence of fibroids among women who have family history of fibroids. This contradicts literature which says fibroids are common among women who have family history of fibroids (Vikhlyaeva et al. 1995). Furthermore, this study was actually comparing reasons for reporting for fibroids consultations and not to ascertain how many patients have family history of fibroids and without fibroids. This may contribute to the bias of recording increasing number of patients without family history of fibroids. More studies may be needed to confirm the hypothesis.

Effect of obesity on fibroids development.

The effect of obesity has been studied and found to have increased risk of fibroid development compared to normal weight. A large prospective study of registered nurses in the United States found an increased fibroid risk with increasing adult BMI, as well as an increased risk associated with weight gain since age 18 years (Marshall et al. 1998b). In this review the prevalence of fibroids is highest among the overweight's 41% (36.0 – 45.0). This was followed closely by the obese group with a prevalence of 39% (24.0 – 54.0). The result corroborates with the findings of a study conducted in the United State of America comparing incidence of fibroids among black women and white women. It was observed that the prevalence of fibroid is highest among overweight blacks compared to normal and obese women. The result also shows that the obese women were the second highest in terms of prevalence of fibroids. Another important observation in this study was that whilst the blacks have the highest prevalence, 29% (239/813) of fibroids among the overweight's, the white race has recorded the highest prevalence, 50% (254/504) among the normal BMI group (Baird et al., 2003). This therefore implies that among the blacks and for that SSA overweight women turn to have higher prevalence of fibroids.

5.3 Types of fibroids

The result of our review (table 4) suggests that intramural fibroids were the commonest fibroids identified within the sub-Saharan African region (49.12%). About 70% of fibroids remained intramural because uterine fibroids are known to start as intramural tumours. They are usually asymptomatic; however, they may cause infertility due to compression of the fallopian tubes (Vitiello & McCarthy, 2006). This type of fibroids is also known to impair uterine contractility during and after labour and therefore the increased risk of PPH. This implies physician should anticipate PPH in women with intramural fibroids.

This current study result is also consistent with literature that submucosal fibroids are the second commonest fibroids (26.09%). Submucosal fibroids can occasionally become pedunculated and prolapse into the cervical canal or vagina leading to obstruction during labour and delivery. With this type of myomas, there are high possibilities of the uterus becoming infected and submucosally pedunculated (Gross et al., 1983).

The least fibroid type in our study is the subserous fibroids. Subserosal fibroids are found in the outer layer of the uterus and may project into the abdomen or pelvis. This type of fibroids may also become pedunculated and undergo torsion and consequent infarction and thus be a cause of severe abdominal pain (Roy et al., 2005). In view of these physicians should anticipate for acute abdomen in women with pedunculated fibroids. With respect to diagnostic criteria (ultrasound and histopathology) used this evidence is also useful. However further studies may be useful.

We also conclude that women in SSA should be encouraged to do ultrasound scan prior conception to understand the type of fibroids they have. This will also help in counselling by the physician during ANC and labour. Again, counselling on the need for myomectomy for submucous and intramural fibroids can also be done whilst women with sub-serosal fibroids can be reassured.

5.4 Fibroid characteristics

5.4.1 Number of fibroids

This current review has meta-analyzed 5 studies that reported on number of fibroids. The result in figure 8 suggests that multiple fibroids were the commonest among SSA women. This finding is consistent with literature that says black women are at increased risk of developing multiple fibroids with increased severity of symptoms and also at an earlier age (Baird et al., 2003; Marshall et al., 1997; Wise et al., 2004). Studies have found that, there is an increased risk of pregnancy loss, caesarean section and malpresentations in women with multiple fibroids (Benson et al., 2001; Ciavattini et al., 2015b). Bearing in mind the above effects women with multiple fibroids should be counselled accordingly by physicians attending to them during ANC and delivery.

5.4.2 Location of fibroids within the uterus

Majority of the fibroids in this study were located in the body of the uterus. This implies SSA women are most- likely to have their fibroids in the body of the uterus. Fibroids are mainly seen in the body of the uterus, which forms the bulk of the organ. However, this estimate may not be precise because multiple fibroids may not be found in one particular location. The effect of fibroid located in the body includes PPH resulting from ineffective uterine contraction during labour and postpartum (Klatsky et al., 2008). In this review we observed that 24.36% of fibroids are located in the fundal region of the uterus. The least been fibroids located in the cervical region 2.75%. It is also important to say that physician should look out for these features as they are crucial in management decision making. Although fibroids located in the cervical regions are few, they are associated with acute urine retention among pregnant women (Wu et al., 2015). However, the studies included in this review are observational studies with methodological constraints and also minimal sample size, for which further well-designed studies must be conducted to evaluate this characteristic in SSA.

5.4.3 Fibroid's size.

Sub-Saharan African women are noted to report late with large fibroids and its associated complications such as obstructions, severe anaemia and hydronephrosis (Igboeli et al., 2019). Many of the included studies did not include fibroid size in the study. However, a study by Egbe et al. has found that the mean fibroid size among the participants was 2.82 cm (sd + - 1.64). Large uterine fibroid is associated with increased C/S, and postpartum haemorrhage (Klatsky et al., 2008; Sulaimani et al., 2021). We cannot conclude on fibroid size since the available studies are scanty. We are also encouraging the scientific community to come out with more studies on the fibroid sizes estimation with ultrasound scans.

5.5 Effects of fibroids on maternal and foetal outcomes (Obstetric outcomes)

The present systematic review and meta- analysis, including three studies with 569 women (209 cases and 360 controls), investigated whether uterine fibroid is associated with adverse pregnancy outcomes. Overall, women with uterine fibroids were found to have an increased likelihood of PPH, vaginal bleeding, C/S, abdominal pain, placenta previa/abruption, and low APGAR score as compared with women without uterine fibroids. However, there was no evidence for the association of UF with fetal malpresentation, miscarriage/abortion, preterm, IUGR, PROM, stillbirth and low birth weight.

5.5.1 Postpartum haemorrhage

In our review two studies assessed the relationship between fibroids and PPH (Egbe et al., 2018 and Mutua, 2014). When meta-analysed the result showed a strong association between fibroids and PPH. Our finding is consistent with previous systematic review by Klasky et al (2008), who explained that PPH is likely to result from decreased uterine contractility in women with fibroid. He again supported this hypothesis that two studies assessed during his review reported increased requirement for emergency hysterectomy in women with fibroids which presupposes that altered contractility of a uterus with fibroids renders it more prone to hemorrhage (Klatsky et al., 2008). However, none of the included studies has controlled for factors such as maternal age and parity

which are confounders (Ohkuchi et al., 2003). Furthermore, the sample size of the studies included was very small. And in addition, these are observational studies with little evidence compared to RCT. We were also unable to perform sensitivity test, and publication bias as a result of few studies included.

Vaginal bleeding

Studies reporting vaginal bleeding have attributed it to the presence of submucous fibroids or insertion of the placenta near a fibroid (Baird & Dunson, 2003; Benson et al., 2001). In our review we have also found that vaginal bleeding is associated with uterine fibroids and was statistically significant (table 6). However, the studies included were not able to perform subgroup analysis to investigate the effect of fibroid types and insertion of placenta near fibroids. This also calls for further and well-designed studies.

Caesarean section

Overall, two studies were identified to have reported on caesarean section (outcome) between pregnant women with fibroids and without fibroids. The result in table 6 has shown that the risk of having caesarean section is 2.82 times more among pregnant women with fibroids compared to those without fibroids and is statistically significant. The included studies have not adjusted for confounders. The indications for caesarean sections are many and Stout et al in their study have adjusted for placenta previa and malpresentation but still found an increased risk among pregnant women with fibroids (33.1% vs 24.2 1%, Adj OR. 1.2 (1.1–1.3))(Stout et al., 2010) Several other studies have also reported an increased risk of caesarean section among pregnant women with fibroids even after adjusting for age , number of fibroids, BMI and size of fibroids (Ciavattini et al., 2015b; Klatsky et al., 2008). Increased Caesarean section rate was attributed to malpresentation caused by fibroids in pregnancy, reported by Klatsky et al (2008). However, a large retrospective cohort study has found no significant difference in caesarean delivery rates

between pregnant women with fibroids and without fibroids (Exacoustòs & Rosati, 1993). Although the sample sizes of the included studies were small coupled with no adjustment for confounders the result of this review shows that physicians and all those who matters in the management of pregnancy with co-existing fibroids should anticipate increased caesarean section rate among such groups.

Abdominal pain

Large fibroids (> 5 cm) seen in pregnant women are noted for pain in the second and third trimesters and this was attributed to red degeneration (Burton et al., 1989; Katz et al., 1989; Lev-Toaff et al., 1987). A large prospective study has also found a significant association between fibroids and pelvic pain and in a further analysis has also found that pelvic pain was related to myoma volume greater than 200 cm3 (Exacoustòs & Rosati, 1993).

The findings above corroborate with the findings of this current review which has found a statistically significant association between UF and abdominal pain (table 6). However, the studies included in this review did analyse the effect of fibroid size.

Placenta previa and abruptio

Similarly, a large prospective study has found that placenta previa and abruptio were significantly associated with fibroid in cyesis. The study again found that Abruptio placentae were particularly evident in women with myoma volumes greater than 200 cm 3, submucosally located, or superimposed by the placenta (Rosati et al., 1992). The findings in this study were similar to the study above as there was statistically significant association between fibroid and antepartum haemorhage. In this study further analysis were not done to compare the effect of fibroid types.

Low APGAR score

In our review we have found a statistically significant association between fibroid and low APGAR score. This result was from a single study which compared average APGAR score instead. Our result is in contrast with several studies which reported no association between fibroids and low APGAR score (Ciavattini et al., 2015b; Vergani et al., 2007). We also call for further studies to be conducted on this outcome.

Malpresentation.

The result of a systematic review has shown that pregnant women with co-existing fibroids are about 3 times more likely to experience malpresentation compared to women without fibroids (Klatsky et al., 2008). Fibroid size (large), location (lower uterine segment located fibroids) and number (multiple) of fibroids were seen to have correlated strongly with foetal malpresentation among pregnant women with fibroids. In this systematic review two studies have assessed the effect of fibroids on malpresentation (Eze et al., 2013 and Mutua, 2014). Although, Eze et al has found that women with fibroids coexisting with pregnancy were more than (5% vs 3%) women without fibroids the statistical significance was not reached. The risk of malpresentation has increased by two folds among women with fibroids compared to women without fibroids p = 0.232 (0.64 – 6.46) (table 6). In the second study conducted by Mutua ,2014 there was an increased risk of 2.02 (95% CI 0.64 – 6.46, p= 0.232) among women with fibroids compared to those without. However, this result was also not statistically significant. Both studies are of small sample size and conclusion cannot be drawn on this outcome but enough studies with robust sample size will answer this relationship in our setting. Furthermore, the studies have not adjusted for confounders such as age and parity.

Miscarriage.

The hypotheses explaining the mechanism by which fibroids causes miscarriage are many. The hypothesis of large submucosal fibroids causing miscarriage was explained that large submucosal fibroids are likely to interfere with placentation by compressing on the decidua at the placenta

site leading to reduced blood supply and subsequent atrophy and miscarriage (Wallach & Vu 1995). it is further explained that rapid fibroid growth may increase uterine contractility or interfere with placental function resulting in miscarriage (Wallach & Vu 1995 and Blum .1978). Several studies have found an increased risk of miscarriage associated with fibroids(Ciavattini et al., 2015b; Klatsky et al., 2008; Pritts et al., 2009; Stout et al., 2010). Additionally, it was found that number of fibroids has correlated with the increased miscarriage rate and not the size of fibroids (Benson et al., 2001). However, this systematic review has accessed only two studies (Egbe et al., 2018 and Eze et al., 2013) that assessed the relationship between fibroids and miscarriage. Eze et al., has reported an increased rate of miscarriage among cases compared to controls (3.0% vs 33%). The study however has not performed sub-group analysis to ascertain fibroid size and number effect. The second study has reported that the odds of miscarriage is 1.2 times more in the cases compared to the controls. However, this has not reached statistical significance (p = 0.70; CI: 1.6 – 16.3). Overall, the above studies seem to suggest increased risk but there was no adjustment for confounders and coupled with minimal sample size we cannot conclude that presence of fibroids is a risk factor for miscarriage or not in SSA. Further studies are needed to evaluate this variable.

We have found no association between fibroids and preterm, IUGR, PROM, stillbirth and low birthweight. Our result is consistent with several studies which have also not found such significance (Klatsky et al., 2008; Rice et al., 1989)

CHAPTER SIX

6.1 CONCLUSION

The findings of this systematic review indicate that increasing age is associated with fibroid development, however, the prevalence of fibroid is reduced as one nears menopausal age. We have also found that fibroid is more common among women aged 30 -39 years in the sub-Saharan African region. Our study has also found that multiparous women were more likely to develop fibroids compared to primiparous and this was attributed to high early marriage in some part of Nigeria where the studies were conducted.

This systematic review has also found that intramural fibroids were the commonest among SSA women. However, estimation of fibroid size was generally underestimated. Fibroids were more located in the body of the uterus, implying the likelihood of PPH as such fibroids may not allow for effective uterine contraction post-delivery.

In this review we have found a statistically significant association between fibroid and PPH, vaginal bleeding, C/S, abdominal pain, placenta previa/abruptio, and low APGAR score. However, there was no evidence for the association of UF with fetal malpresentation, miscarriage/abortion, preterm, IUGR, PROM, stillbirth and low birth weight.

Although diagnoses were either ultrasound or histopathology the studies were not enough to draw a meaningful conclusion on outcome of pregnancy.

Overall, pregnant women with fibroids are not at a significant increased risk of adverse maternal, fetal and early neonatal outcomes compared to women without fibroids.

6.2 RECOMMENDATIONS

6.2.1 For Public Health

Continuous education on uterine fibroids and obstetric outcomes.

We also recommend that practitioners including Midwives, Physician Assistants, Obstetrician Gynaecologists and all others who matter in the care of pregnant women should anticipate adverse effects of fibroids co-existing with pregnancy and institute appropriate management measures for each client.

6.2.2 For Policy

Training of more radiologist to increase access to fibroid screening, and effective estimate of fibroid size, location and number.

Screening for uterine fibroids should be part of preconception care for women aged 30 -39 years in SSA.

6.2.3 For Research

Further researches on the fibroid's characteristics such location, size and number are very important

6.3.4 Contribution to knowledge

This review has brought to bare the adverse obstetric outcomes of pregnancy co-existing with uterine fibroids in SSA.

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APPENDIX 1

Search strategy (PubMed; adapted to all other databases and engines searched)

Search	Query
#1	Search: ((((Prevalence[Title/Abstract]) OR (incidence[Title/Abstract])) OR ("incidence rate"[Title/Abstract])) OR ("new case*"[Title/Abstract])) OR (epidemiology[Title/Abstract])) OR (burden[Title/Abstract])
#2	Search: (((((((("uterine fibroid*"[Title/Abstract]) OR ("uterine leiomyoma*"[Title/Abstract])) OR ("leiomyoma of the uterus"[Title/Abstract])) OR ("myoma of the uterus"[Title/Abstract])) OR (Fibromyoma[Title/Abstract])) OR (Leiofibromyoma[Title/Abstract])) OR (Fibroleiomyomata[Title/Abstract])) OR (Fibroma[Title/Abstract])) OR ("Uterine Myoma"[Title/Abstract])
#3	Search: (#1) AND (#2)
#4	Search: ((("sub-Saharan Africa") OR (SSA)) OR (Angola)) OR (Benin)) OR (Botswana)) OR ("Burkina Faso")) OR (Burundi)) OR (Cameroon)) OR ("Cape Verde")) OR ("Central African Republic")) OR (Chad)) OR (Comoros)) OR (Congo)) OR ("Cote d'Ivoire")) OR (Djibouti)) OR ("Equatorial Guinea")) OR (Ethiopia)) OR (Gabon)) OR ("The Gambia")) OR (Ghana)) OR (Guinea)) OR ("GuineaBissau")) OR (Kenya)) OR (Lesotho)) OR (Liberia)) OR (Madagascar)) OR (Malawi)) OR (Mali)) OR (Mauritania)) OR (Mauritius)) OR

Search	Query
	(Mozambique)) OR (Namibia)) OR (Niger)) OR (Nigeria)) OR (Rwanda)) OR ("Sao Tome and Principe")) OR (Senegal)) OR (Seychelles)) OR ("Sierra Leone")) OR (Somalia)) OR ("South Africa")) OR (Sudan)) OR (Swaziland)) OR (Tanzania)) OR (Togo)) OR (Uganda)) OR (Zaire)) OR (Zambia)) OR (Zimbabwe)
#5	**Search: (#3) AND (#4)**

APPPENDIX: 2 Quality assessment tool

Name of author(s): Year of publication: Study title:		
Risk of bias items	**Risk of bias levels**	**Points scored**
1.Was the study's target population a close representation of the national population in relation to relevant variables, e.g. age, sex, occupation?	**Yes (LOW RISK)**: The study's target population was a close representation of the national population.	0
	No (HIGH RISK): The study's target population was clearly NOT representative of the national population.	1
2. Was the sampling frame a true or close representation of the target population?	**Yes (LOW RISK)**: The sampling frame was a true or close representation of the target population.	0
	No (HIGH RISK): The sampling frame was NOT a true or close representation of the target population.	1
3.Was some form of random selection used to select the sample, OR, was a census undertaken?	**Yes (LOW RISK)**: A census was undertaken, OR, some form of random selection was used to select the sample (e.g. simple random sampling, stratified random sampling, cluster sampling, systematic sampling).	0
	No (HIGH RISK): A census was NOT undertaken, AND some form of random selection was NOT used to select the sample.	1
4. Was the likelihood of non-response bias minimal?	**Yes (LOW RISK)**: The response rate for the study was ≥75%, OR, an analysis was performed that showed no significant difference in relevant demographic characteristics between responders and non- responders	0
	No (HIGH RISK): The response rate was <75%, and if any analysis comparing responders and non-responders was done, it showed a significant difference in relevant demographic characteristics between responders and non-responders	1
5. Were data collected directly from the subjects (as opposed to a proxy)?	**Yes (LOW RISK)**: All data were collected directly from the subjects.	0
	No (HIGH RISK): In some instances, data were collected from a proxy.	1
6.Was an acceptable case definition used in the study?	**Yes (LOW RISK)**: An acceptable case definition was used. **No (HIGH RISK)**: An acceptable case definition was NOT used	0 1
7. Was the study instrument that measured the parameter of interest (e.g. prevalence of low back pain) shown to have reliability and validity (if necessary)?	**Yes (LOW RISK)**: The study instrument had been shown to have reliability and validity (if this was necessary), e.g. test-re- test, piloting, validation in a previous study, etc.	0
	No (HIGH RISK): The study instrument had NOT been shown to have reliability or validity (if this was necessary).	1
8. Was the same mode of data collection used for all subjects?	**Yes (LOW RISK)**: The same mode of data collection was used for all subjects.	0
	No (HIGH RISK): The same mode of data collection was NOT used for all subjects.	1
9.Were the numerator(s) and denominator(s) for the parameter of interest appropriate	**Yes (LOW RISK)**: The paper presented appropriate numerator(s) AND denominator(s) for the parameter of interest (e.g. the prevalence of low back pain).	0
	No (HIGH RISK): The paper did present numerator(s) AND denominator(s) for the parameter of interest but one or more of these were inappropriate.	1
10. Summary on the overall risk of study bias	**LOW RISK**	0-3
	MODERATE RISK	4-6
	HIGH RISK	7-9

APPENDIX 3; QUALITY ASSESSMENT

CHAMA ET AL., 2009

Risk of Bias	Level of risk	Author's reason
1.Was the study's target population a close representation of the national population in relation to relevant variables, e.g., age, sex, occupation?	High risk	Study's target population was not close to national population of women in their reproductive years and above
2.Was the sampling frame a true or close representation of the target population?	High risk	Sampling frame was too small as it used only histopathology report list.
3.Was some form of random selection used to select the sample, OR, was a census undertaken?	Low risk	Census was undertaken
4.Was the likelihood of non-response bias minimal?	Low risk	All case notes were available for review
5.Were data collected directly from the subjects (as opposed to a proxy)?	Low risk	Stored data (collected directly from subjects) were retrieved.
6.Was an acceptable case definition used in the study?	Low risk	Women with histologically confirmed fibroids were included
7.Was the study instrument that measured the parameter of interest (e.g., prevalence of low back pain) shown to have reliability and validity (if necessary)?	Low risk	Histology is of high reliability and validity
8.Was the same mode of data collection used for all subjects?	Low risk	Medical history collected during consultation and histopathology reports was collected from all subjects
9.Were the numerator(s) and denominator(s) for the parameter of interest appropriate?	High risk	Percentages were well calculated except for the grouping of parity which was not done accordingly
10.Summary on the overall risk of study bias;	Low risk	Overall score was 2 and therefore we awarded low risk

Ingala et al., 2017.

Risk of Bias	Level of risk	Author's reason
1.Was the study's target population a close representation of the national population in relation to relevant variables, e.g., age, sex, occupation?	High risk	Target population was far less than national population of women in their reproductive age and menopause
2.Was the sampling frame a true or close representation of the target population?	High risk	List of women (with ultrasound confirmed fibroids) receiving gynaecological care in three hospitals was used, however the target population is less than national population.
3.Was some form of random selection used to select the sample, OR, was a census undertaken?	Low risk	Simple random sampling was employed
4.Was the likelihood of non-response bias minimal?	Low risk	The response rate was 100%
5.Were data collected directly from the subjects (as opposed to a proxy)?	Low risk	Data was collected directly from subjects (medical records collected directly from patients)
6.Was an acceptable case definition used in the study?	Low risk	Women in their reproductive age with ultrasound confirmed Uterine fibroids were included
7.Was the study instrument that measured the parameter of interest (e.g., prevalence of low back pain) shown to have reliability and validity (if necessary)?	Low risk	Ultrasound has an accuracy of 93.8%
8.Was the same mode of data collection used for all subjects?	Low risk	Interviews during medical consultations and ultrasound reports was used for all subjects
9.Were the numerator(s) and denominator(s) for the parameter of interest appropriate?	High risk	Percentages were missed up
10.Summary on the overall risk of study bias;	Low risk	Had a score of 3

Owolabi et al., 2010.

Risk of Bias	Level of risk	Author's reason
1.Was the study's target population a close representation of the national population in relation to relevant variables, e.g., age, sex, occupation?	High risk	Study's target population was not close to national population of women in their reproductive years and above
2.Was the sampling frame a true or close representation of the target population?	High risk	List of women (with histologically confirmed fibroids) receiving gynaecological care in three hospitals was used, however the target population is less than national population.
3.Was some form of random selection used to select the sample, OR, was a census undertaken?	Low risk	It was a census
4.Was the likelihood of non-response bias minimal?e	Low risk	Response rate was 98%
5.Were data collected directly from the subjects (as opposed to a proxy)?	Low risk	Data was collected directly from subjects and stored as medical records which were used
6.Was an acceptable case definition used in the study?	Low risk	Women in the reproductive age and menopause who have had histologically confirmed uterine fibroids.
7.Was the study instrument that measured the parameter of interest (e.g., prevalence of low back pain) shown to have reliability and validity (if necessary)?	Low risk	Histopathology is the gold standard for diagnosing uterine fibroids
8.Was the same mode of data collection used for all subjects?	Low risk	Medical records taken during consultation and ultrasound documentations were used for all subjects
9.Were the numerator(s) and denominator(s) for the parameter of interest appropriate?	Low risk	Parameters of outcome were calculated properly
10.Summary on the overall risk of study bias	Low risk	Overall score is 2

Obuna et al., 2008.

Risk of Bias	Level of risk	Author's reason
1.Was the study's target population a close representation of the national population in relation to relevant variables, e.g., age, sex, occupation?	High risk	Study target was only taken from one referral hospital which is far less than national population of women in their reproductive years and also in their menopause.
2.Was the sampling frame a true or close representation of the target population?	High risk	The sampling frame was not a true representation of the target population since opd diagnosed uterine fibroids were not captured but only admitted subjects were included
3.Was some form of random selection used to select the sample, OR, was a census undertaken?	Low risk	Census was undertaken
4.Was the likelihood of non-response bias minimal?	Low risk	The response rate was 94%
5.Were data collected directly from the subjects (as opposed to a proxy)?	Low risk	Medical records which were given by the subjects (directly) was reviewed
6.Was an acceptable case definition used in the study?	Low risk	Women diagnosed of fibroids and whos' diagnosis were supported by ultrasound were included
7.Was the study instrument that measured the parameter of interest (e.g., prevalence of low back pain) shown to have reliability and validity (if necessary)?	Low risk	Ultrasound scan has good sensitivity and specificity
8.Was the same mode of data collection used for all subjects?	Low risk	Medical records of subjects and ultrasound findings were used for all subjects
9.Were the numerator(s) and denominator(s) for the parameter of interest appropriate?	High risk	Parity was not grouped appropriately (study has combined primiparous and multiparous)
10.Summary on the overall risk of study bias; LOW RISK 0-3 MODERATE RISK 4-6 HIGH RISK 7-9	Low risk	Scored 3 which was in the range of low risk (0-3)

Ezeama et al., 2012.

Risk of Bias	Level of risk	Author's reason
1.Was the study's target population a close representation of the national population in relation to relevant variables, e.g., age, sex, occupation?	High risk	The study was a hospital-based study and the target population is far less than the national population of women.
2.Was the sampling frame a true or close representation of the target population?	Low risk	Sampling frame was a true representation of all cases of histologically confirmed fibroids
3.Was some form of random selection used to select the sample, OR, was a census undertaken?	Low risk	Census was used. Thus, all cases of histologically confirmed fibroids
4.Was the likelihood of non-response bias minimal?	Low risk	The response rate was 88% (records with accurate)
5.Were data collected directly from the subjects (as opposed to a proxy)?	Low risk	Medical records of patients were retrieved and used
6.Was an acceptable case definition used in the study?	Low risk	Acceptable case definition of women with fibroids confirmed by histopathology were included
7.Was the study instrument that measured the parameter of interest (e.g., prevalence of low back pain) shown to have reliability and validity (if necessary)?	Low risk	Histopathology, the gold standard for fibroid diagnosis was used
8.Was the same mode of data collection used for all subjects?	Low risk	Medical records of all patients were used
9.Were the numerator(s) and denominator(s) for the parameter of interest appropriate?	High risk	Parity was wrongly classified as multiparity was stated as para 1 – 4
10.Summary on the overall risk of study bias; LOW RISK 0-3 MODERATE RISK 4-6 HIGH RISK 7-9	Low risk	Total score was 2 and therefore adjudged low risk

Muhammad et al., 2013.

Risk of Bias	Level of risk	Author's reason
1.Was the study's target population a close representation of the national population in relation to relevant variables, e.g., age, sex, occupation?	High risk	The study was a hospital-based study with minimal target population which is far less than national population
2.Was the sampling frame a true or close representation of the target population?	High risk	Sampling frame was not a true representation of target population since opd diagnosed fibroids may be missed.
3.Was some form of random selection used to select the sample, OR, was a census undertaken?	Low risk	Census was used. Thus, all cases of fibroids admitted to the gynaecological ward
4.Was the likelihood of non-response bias minimal?	Low risk	Response rate was 99%
5.Were data collected directly from the subjects (as opposed to a proxy)?	Low risk	Medical records of subjects were used
6.Was an acceptable case definition used in the study?	Low risk	A case was defined as women admitted to gynaecological ward with confirmed ultrasound diagnosis of fibroids
7.Was the study instrument that measured the parameter of interest (e.g., prevalence of low back pain) shown to have reliability and validity (if necessary)?	Low risk	Ultrasound scan was the instrument used and of high validity and reliability
8.Was the same mode of data collection used for all subjects?	Low risk	Medical records of all subjects were collected
9.Were the numerator(s) and denominator(s) for the parameter of interest appropriate?	Low risk	Percentage and mean were calculated
10.Summary on the overall risk of study bias; LOW RISK 0-3 MODERATE RISK 4-6 HIGH RISK 7-9	Low risk	Overall score was 2 and therefore the study was adjudged low risk

Osaikhuwuomwan et al., 2015

Risk of Bias	Level of risk	Author's reason
1.Was the study's target population a close representation of the national population in relation to relevant variables, e.g., age, sex, occupation?	High risk	The target population of all women who underwent surgical management was far less than the national population of women with fibroids
2.Was the sampling frame a true or close representation of the target population?	Low risk	The sampling frame was not a close representation of the target population because other women who were asymptomatic might have been opd patients
3.Was some form of random selection used to select the sample, OR, was a census undertaken?	Low risk	Census was undertaken
4.Was the likelihood of non-response bias minimal?	Low risk	The response rate was higher than 75% (i.e. 100%)
5.Were data collected directly from the subjects (as opposed to a proxy)?	Low risk	Medical records given by patients were retrieved and used
6.Was an acceptable case definition used in the study?	Low risk	Acceptable case definition was used
7.Was the study instrument that measured the parameter of interest (e.g., prevalence of low back pain) shown to have reliability and validity (if necessary)?	Low risk	Ultrasound scan is of high reliability and validity
8.Was the same mode of data collection used for all subjects?	Low risk	Medical records of all subjects were collected
9.Were the numerator(s) and denominator(s) for the parameter of interest appropriate?	Low risk	Mean and percentages were calculated with their 95% confidence intervals
10.Summary on the overall risk of study bias; LOW RISK 0-3 MODERATE RISK 4-6 HIGH RISK 7-9	Low risk	The scale of low-risk ranges between 0-3 and the overall score was 1

Fasubaa et al., 2019.

Risk of Bias	Level of risk	Author's reason
1.Was the study's target population a close representation of the national population in relation to relevant variables, e.g., age, sex, occupation?	High risk	The target population was not a close representation of the national population as subjects were only recruited from one gynaecological clinic
2.Was the sampling frame a true or close representation of the target population?	Low risk	The sample frame is a true representation of subjects as it listed the records of women attending the gynaecological clinic for fibroid consultation
3.Was some form of random selection used to select the sample, OR, was a census undertaken?	Low risk	All subjects were included (census was undertaken)
4.Was the likelihood of non-response bias minimal?	Low risk	Response rate was 100%
5.Were data collected directly from the subjects (as opposed to a proxy)?	Low risk	Medical records of all participants were used
6.Was an acceptable case definition used in the study?	Low risk	Cases were confirmed cases of fibroids
7.Was the study instrument that measured the parameter of interest (e.g., prevalence of low back pain) shown to have reliability and validity (if necessary)?	Low risk	The sensitivity and specificity of ultrasound is reliable and valid
8.Was the same mode of data collection used for all subjects?	Low risk	Medical records of patients were used
9.Were the numerator(s) and denominator(s) for the parameter of interest appropriate?	Low risk	Parameters of interest were well classified and calculated
10.Summary on the overall risk of study bias; LOW RISK 0-3 MODERATE RISK 4-6 HIGH RISK 7-9	Low risk	Overall score was 1

Okon et al., 2020.

Risk of Bias	Level of risk	Author's reason
1.Was the study's target population a close representation of the national population in relation to relevant variables, e.g., age, sex, occupation?	High risk	Target population was far less than national population of women in the reproductive age and menopause
2.Was the sampling frame a true or close representation of the target population?	High risk	The sampling frame covered only women managed surgically for fibroids whilst it could have included those managed medically
3.Was some form of random selection used to select the sample, OR, was a census undertaken?	Low risk	Census was undertaken
4.Was the likelihood of non-response bias minimal?	Low risk	Response rate was more than 75% (i.e., 86% response rate)
5.Were data collected directly from the subjects (as opposed to a proxy)?	Low risk	Medical records given by the patients were used.
6.Was an acceptable case definition used in the study?	Low risk	Acceptable case definition was used, thus women
7.Was the study instrument that measured the parameter of interest (e.g., prevalence of low back pain) shown to have reliability and validity (if necessary)?	Low risk	Ultrasound scans are reliable and valid for fibroid diagnosis
8.Was the same mode of data collection used for all subjects?	Low risk	Medical records were used for all the subjects
9.Were the numerator(s) and denominator(s) for the parameter of interest appropriate?	Low risk	The denominator and numerators were all appropriate
10.Summary on the overall risk of study bias; LOW RISK 0-3 MODERATE RISK 4-6 HIGH RISK 7-9	Low risk	We scored low risk on account of total score less than 4

Ijeruh et al., 2021.

Risk of Bias	Level of risk	Author's reason
1.Was the study's target population a close representation of the national population in relation to relevant variables, e.g., age, sex, occupation?	High risk	Target population was far less than national population of women in the reproductive age and menopause.
2.Was the sampling frame a true or close representation of the target population?	High risk	Sampling frame was not a close representation of women in child bearing age
3.Was some form of random selection used to select the sample, OR, was a census undertaken?	Low risk	Survey was done
4.Was the likelihood of non-response bias minimal?	High risk	Likelihood of non-response bias could not be not minimized
5.Were data collected directly from the subjects (as opposed to a proxy)?	Low risk	Data was collected directly from subjects
6.Was an acceptable case definition used in the study?	Low risk	Women in the reproductive age were considered
7.Was the study instrument that measured the parameter of interest (e.g., prevalence of low back pain) shown to have reliability and validity (if necessary)?	Low risk	Ultrasound scan was used.
8.Was the same mode of data collection used for all subjects?	Low risk	Ultrasound scan findings and data provided directly from the subjects were used
9.Were the numerator(s) and denominator(s) for the parameter of interest appropriate?	Low risk	The numerators and denominators were appropriate in the analysis
10.Summary on the overall risk of study bias; LOW RISK 0-3 MODERATE RISK 4-6 HIGH RISK 7-9	Low risk	This was awarded on account of study scoring less than 4 points.

Okunade & Gbadegesin, 2014.

Risk of Bias	Level of risk	Author's reason

1.Was the study's target population a close representation of the national population in relation to relevant variables, e.g., age, sex, occupation?	High risk	Target population was far less than national population of women.
2.Was the sampling frame a true or close representation of the target population?	Low risk	Sampling frame was true representation of the target population
3.Was some form of random selection used to select the sample, OR, was a census undertaken?	High risk	Consecutive sampling method was employed
4.Was the likelihood of non-response bias minimal?	Low risk	Sample size was calculated and furthermore 100% response rate was achieved
5.Were data collected directly from the subjects (as opposed to a proxy)?	Low risk	Subjects provided data directly
6.Was an acceptable case definition used in the study?	Low risk	Acceptable case definition was used, women in the reproductive age
7.Was the study instrument that measured the parameter of interest (e.g., prevalence of low back pain) shown to have reliability and validity (if necessary)?	Low risk	Ultrasound is of high sensitivity and specificity
8.Was the same mode of data collection used for all subjects?	Low risk	Interviews and ultrasound findings were used for all the subjects
9.Were the numerator(s) and denominator(s) for the parameter of interest appropriate?	Low risk	Calculations were properly
10.Summary on the overall risk of study bias; LOW RISK 0-3 MODERATE RISK 4-6 HIGH RISK 7-9	Low risk	Sored as low risk because total score is less than 4

Mohammed et al., 2005.

Risk of Bias	**Level of risk**	**Author's reason**
1.Was the study's target population a close representation of the national population in relation to	High risk	Target population was far less than national population of women in the reproductive age and menopause

relevant variables, e.g., age, sex, occupation?		
2.Was the sampling frame a true or close representation of the target population?	Low risk	Sampling frame was a true representation of the target population as the samples were retrieved from the histology department register
3.Was some form of random selection used to select the sample, OR, was a census undertaken?	Low risk	Census was undertaken
4.Was the likelihood of non-response bias minimal?	Low risk	There was 100% response
5.Were data collected directly from the subjects (as opposed to a proxy)?	Low risk	Data were collected directly from subjects' medical records
6.Was an acceptable case definition used in the study?	Low risk	A case was defined as fibroid confirmed by histology
7.Was the study instrument that measured the parameter of interest (e.g., prevalence of low back pain) shown to have reliability and validity (if necessary)?	Low risk	Histology is the gold standard for diagnosing uterine fibroids
8.Was the same mode of data collection used for all subjects?	Low risk	Same mode of data collection was adopted for all the subjects
9.Were the numerator(s) and denominator(s) for the parameter of interest appropriate?	Low risk	The parameters of interest were properly calculated
10.Summary on the overall risk of study bias; LOW RISK 0-3 MODERATE RISK 4-6 HIGH RISK 7-9	Low risk	Scored low risk because the total score was less than 4

Okezie & Ezegwui, 2006.

Risk of Bias	Level of risk	Author's reason
1.Was the study's target population a close representation of the national population in relation to relevant variables, e.g., age, sex, occupation?	High risk	Target population was far less than national population of women in the reproductive age and menopause

2.Was the sampling frame a true or close representation of the target population?	Low risk	Sampling frame was close representation of the target population
3.Was some form of random selection used to select the sample, OR, was a census undertaken?	Low risk	Census was undertaken
4.Was the likelihood of non-response bias minimal?	Low risk	94% response rate was achieved
5.Were data collected directly from the subjects (as opposed to a proxy)?	Low risk	Medical records given by clients were retrieved and used
6.Was an acceptable case definition used in the study?	Low risk	A case was defined as clinically diagnosed but with histological confirmation of fibroids.
7.Was the study instrument that measured the parameter of interest (e.g., prevalence of low back pain) shown to have reliability and validity (if necessary)?	Low risk	Histopathology is the gold standard for fibroids diagnosis and that was used
8.Was the same mode of data collection used for all subjects?	Low risk	The same mode of data collection was applied to all subjects
9.Were the numerator(s) and denominator(s) for the parameter of interest appropriate?	Low risk	The numerators and denominators of the parameters of interest were well calculated
10.Summary on the overall risk of study bias; LOW RISK 0-3 MODERATE RISK 4-6 HIGH RISK 7-9	Low risk	Overall score was less than 4, hence the award of low risk

Coulibaly et al., 2021.

Risk of Bias	**Level of risk**	**Author's reason**
1.Was the study's target population a close representation of the national population in relation to relevant variables, e.g., age, sex, occupation?	High risk	Target population was far less than national population of women in the reproductive age and menopause.
2.Was the sampling frame a true or close representation of the target population?	Low risk	Sample frame was not a true representation of target population since this was a hospital-based study.

3.Was some form of random selection used to select the sample, OR, was a census undertaken?	Low risk	Census was undertaken
4.Was the likelihood of non-response bias minimal?	Low risk	The response rate was 100%
5.Were data collected directly from the subjects (as opposed to a proxy)?	Low risk	Data collected were medical records of patients
6.Was an acceptable case definition used in the study?	Low risk	Acceptable case definition was used, thus women with uterine fibroids confirmed by ultrasound scan
7.Was the study instrument that measured the parameter of interest (e.g., prevalence of low back pain) shown to have reliability and validity (if necessary)?	Low risk	Ultrasound scans are of high reliability and validity
8.Was the same mode of data collection used for all subjects?	Low risk	Data from medical records of all clients were used.
9.Were the numerator(s) and denominator(s) for the parameter of interest appropriate?	Low risk	Mean and standard deviations and frequencies were appropriately calculated
10.Summary on the overall risk of study bias; LOW RISK 0-3 MODERATE RISK 4-6 HIGH RISK 7-9	Low risk	Total score was 2 and we therefore scored low risk

Egbe et al., 2018.

Risk of Bias	Level of risk	Author's reason
1.Was the study's target population a close representation of the national population in relation to relevant variables, e.g., age, sex, occupation?	High risk	Target population was far less than national population of pregnant women.
2.Was the sampling frame a true or close representation of the target population?	Low risk	sampling frame was a true or close representation of the target population
3.Was some form of random selection used to select the sample, OR, was a census undertaken?	High risk	Convenient and consecutive sampling was done

4.Was the likelihood of non-response bias minimal?	Low risk	The response rate was 100%
5.Were data collected directly from the subjects (as opposed to a proxy)?	Low risk	Subjects responded to questionnaires themselves and the findings of their ultrasound scan were also documented
6.Was an acceptable case definition used in the study?	Low risk	An acceptable case definition was used (thus pregnant women with uterine fibroid confirmed by ultrasound scan
7.Was the study instrument that measured the parameter of interest (e.g., prevalence of low back pain) shown to have reliability and validity (if necessary)?	Low risk	Ultrasound scan is of high sensitivity and specificity in fibroid diagnosis
8.Was the same mode of data collection used for all subjects?	Low risk	Questionnaires and ultrasound scan findings were used for all the subjects
9.Were the numerator(s) and denominator(s) for the parameter of interest appropriate?	Low risk	Numerators and denominators were appropriate
10.Summary on the overall risk of study bias; LOW RISK 0-3 MODERATE RISK 4-6 HIGH RISK 7-9	Low risk	The overall score was less than 4 and therefore we scored low risk

Eze et al., 2013.

Risk of Bias	**Level of risk**	**Author's reason**
1.Was the study's target population a close representation of the national population in relation to relevant variables, e.g., age, sex, occupation?	High risk	Target population was far less than national population of pregnant women.
2.Was the sampling frame a true or close representation of the target population?	Low risk	Sampling frame was true representation of pregnant women attending ANC
3.Was some form of random selection used to select the sample, OR, was a census undertaken?	High risk	Convenient sampling was done
4.Was the likelihood of non-response bias minimal?	Low risk	All the participants included in the study remained in the study to the end, thus 100% response

5.Were data collected directly from the subjects (as opposed to a proxy)?	Low risk	Medica records including sonographic findings were included
6.Was an acceptable case definition used in the study?	Low risk	A case definition was well spelt out (pregnant with ultrasound confirmation)
7.Was the study instrument that measured the parameter of interest (e.g., prevalence of low back pain) shown to have reliability and validity (if necessary)?	Low risk	Ultrasound scan is of good validity and reliability.
8.Was the same mode of data collection used for all subjects?	Low risk	Same mode of data collection was used for all participants
9.Were the numerator(s) and denominator(s) for the parameter of interest appropriate?	Low risk	Numerators and denominators for parameters of interest were well calculated
10.Summary on the overall risk of study bias; LOW RISK 0-3 MODERATE RISK 4-6 HIGH RISK 7-9	Low risk	Overall score was less than 4 and we therefore score low risk

Ago, 2017

Risk of Bias	Level of risk	Author's reason
1.Was the study's target population a close representation of the national population in relation to relevant variables, e.g., age, sex, occupation?	High risk	Target population was far less than national population of pregnant women.
2.Was the sampling frame a true or close representation of the target population?	Low risk	Sampling frame was close representation of the target population
3.Was some form of random selection used to select the sample, OR, was a census undertaken?	Low risk	Census was undertaken
4.Was the likelihood of non-response bias minimal?	Low risk	The response rate was 100%
5.Were data collected directly from the subjects (as opposed to a proxy)?	Low risk	Data was collected directly from the subjects using questionnaires
6.Was an acceptable case definition used in the study?	Low risk	A case is defined as ultrasound confirmed fibroid in pregnancy

7.Was the study instrument that measured the parameter of interest (e.g., prevalence of low back pain) shown to have reliability and validity (if necessary)?	Low risk	Ultrasound scan is of high sensitivity and specificity
8.Was the same mode of data collection used for all subjects?	Low risk	Questionnaires was used in collecting data from all subjects as well as ultrasound findings
9.Were the numerator(s) and denominator(s) for the parameter of interest appropriate?	High risk	Parity was not properly categorized
10.Summary on the overall risk of study bias; LOW RISK 0-3 MODERATE RISK 4-6 HIGH RISK 7-9	Low risk	Overall score was less than 4 and therefore we awarded low risk

Mutua, 2014

Risk of Bias	Level of risk	Author's reason
1.Was the study's target population a close representation of the national population in relation to relevant variables, e.g., age, sex, occupation?	High risk	Target population was far less than national population of pregnant women.
2.Was the sampling frame a true or close representation of the target population?	Low risk	Sampling frame was a true representation of the target's population
3.Was some form of random selection used to select the sample, OR, was a census undertaken?	High risk	Consecutive sampling was done
4.Was the likelihood of non-response bias minimal?	low risk	Calculated sample size was used
5.Were data collected directly from the subjects (as opposed to a proxy)?	Low risk	Data was directly collected from patients
6.Was an acceptable case definition used in the study?	Low risk	A case was defined as ultrasound confirmed fibroid
7.Was the study instrument that measured the parameter of interest (e.g., prevalence of low back pain) shown to have	Low risk	Ultrasound scan is of high sensitivity and specificity in diagnosing fibroids.

reliability and validity (if necessary)?		
8.Was the same mode of data collection used for all subjects?	Low risk	The same mode of data collection was used for all subjects. (Questionnaires)
9.Were the numerator(s) and denominator(s) for the parameter of interest appropriate?	Low risk	The mean with their standard deviations were calculated for continuous variables
10.Summary on the overall risk of study bias; LOW RISK 0-3 MODERATE RISK 4-6 HIGH RISK 7-9	Low risk	Awarded low risk on account of scoring less than 4 points

APPENDIX:4 META-ANALYSIS

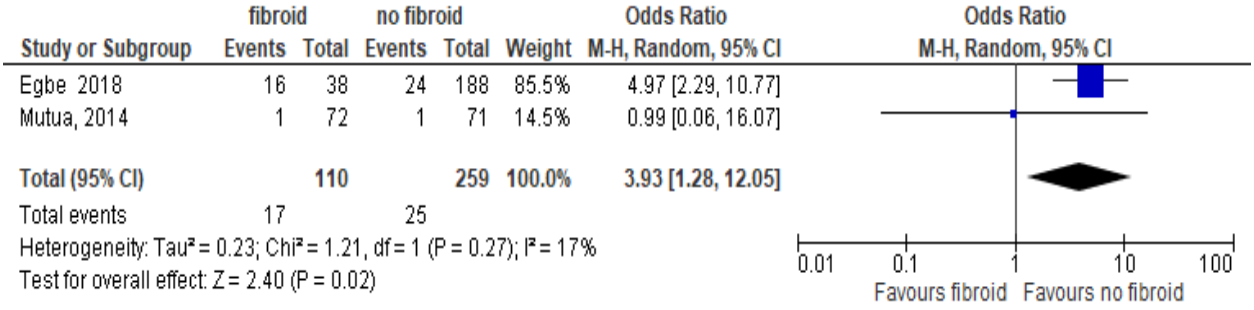
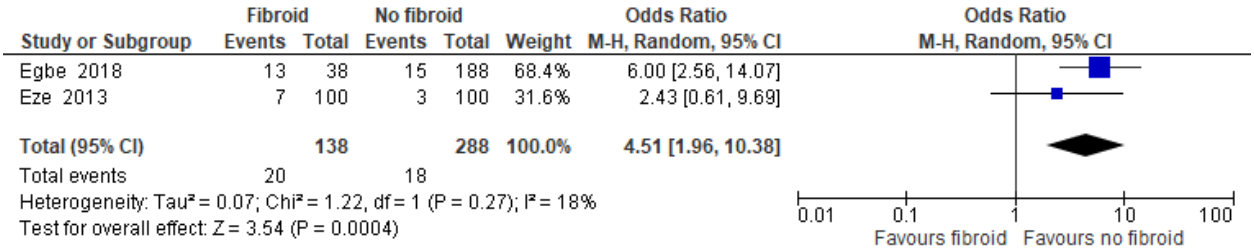


FIGURE 9 Forest plot showing individual and combined effect size estimates and 95% confidence intervals (CIs) in studies that evaluated the likelihood of postpartum haemorrhage among pregnant women with uterine fibroids.



wFIGURE 10 Forest plot showing individual and combined effect size estimates and 95% confidence intervals (CIs) in studies that evaluated the likelihood of bleeding per vaginum among pregnant women with uterine fibroids.

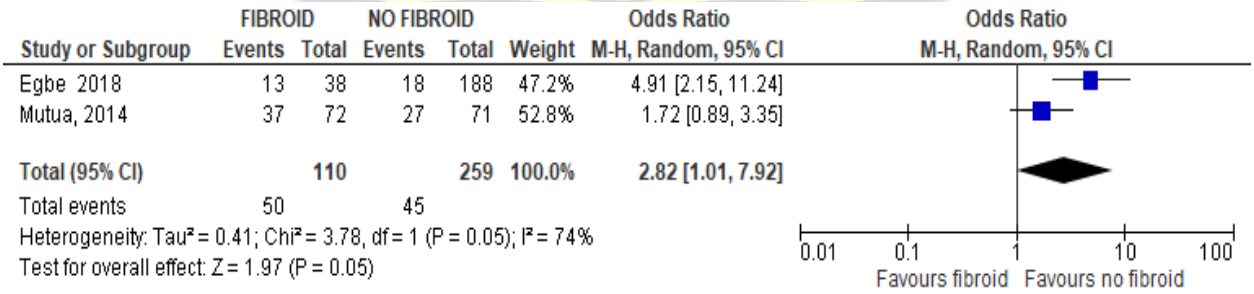


FIGURE 11 Forest plot showing individual and combined effect size estimates and 95% confidence intervals (CIs) in studies that evaluated the likelihood of caesarean section among pregnant women with uterine fibroids and without fibroids

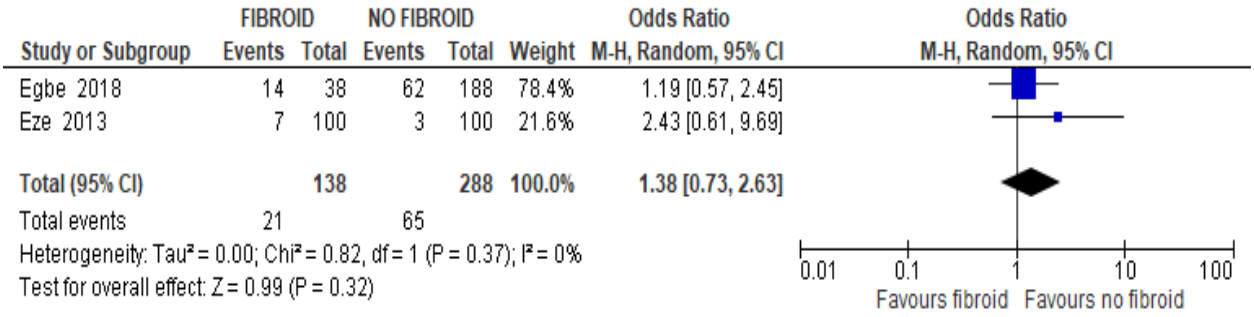


FIGURE 12 Forest plot showing individual and combined effect size estimates and 95% confidence intervals (CIs) in studies that evaluated the likelihood of miscarriage among pregnant women with uterine fibroids and without fibroids

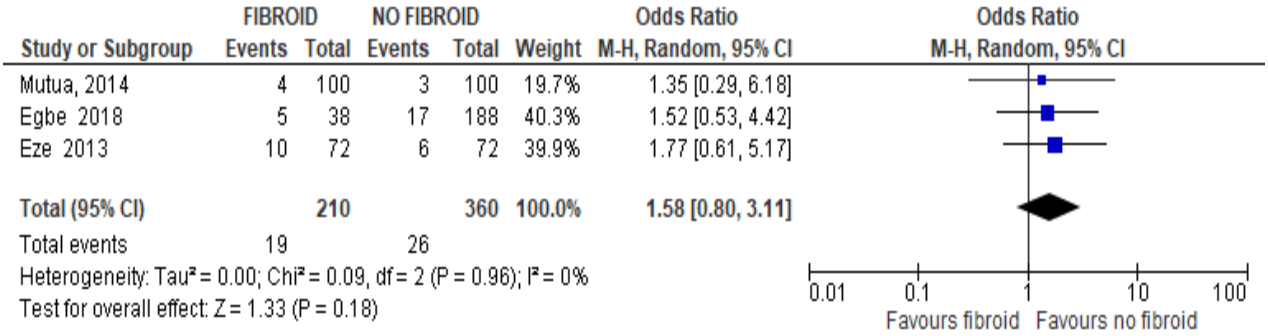


FIGURE 13 Forest plot showing individual and combined effect size estimates and 95% confidence intervals (CIs) in studies that evaluated the likelihood of preterm among pregnant women with uterine fibroids and without fibroids.

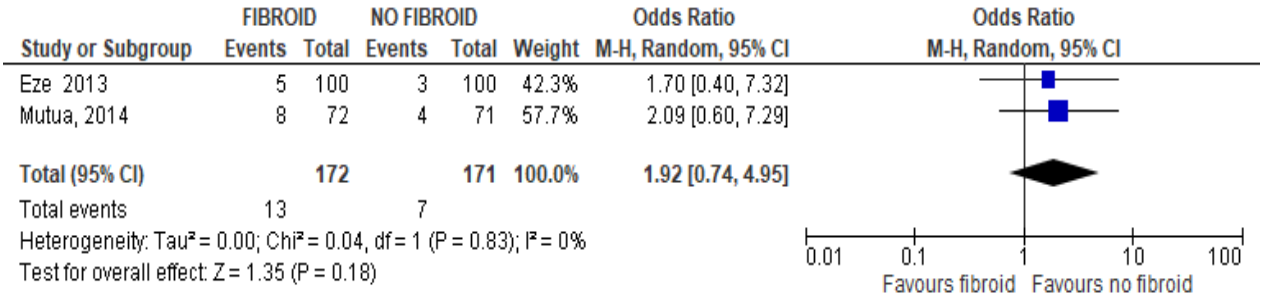


FIGURE 14 Forest plot showing individual and combined effect size estimates and 95% confidence intervals (CIs) in studies that evaluated the likelihood of malpresentation among pregnant women with uterine fibroids and without fibroids.

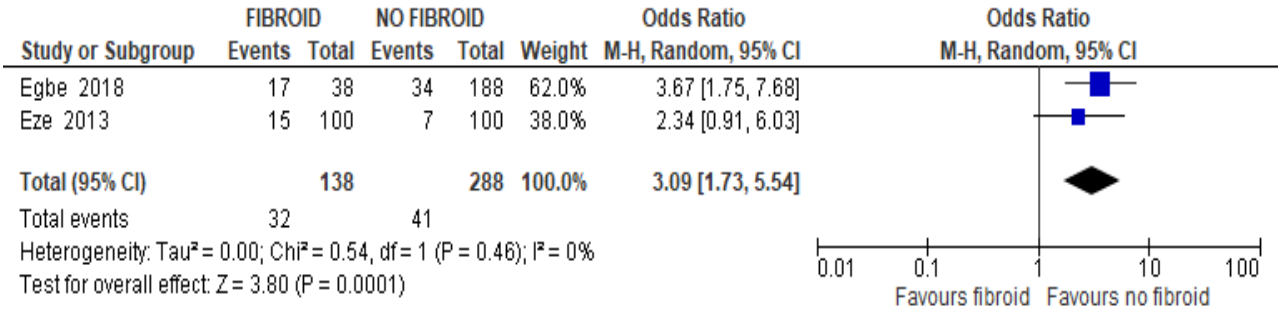


FIGURE 15 Forest plot showing individual and combined effect size estimates and 95% confidence intervals (CIs) in studies that evaluated the likelihood of abdominal pain among pregnant women with uterine fibroids and without fibroids.

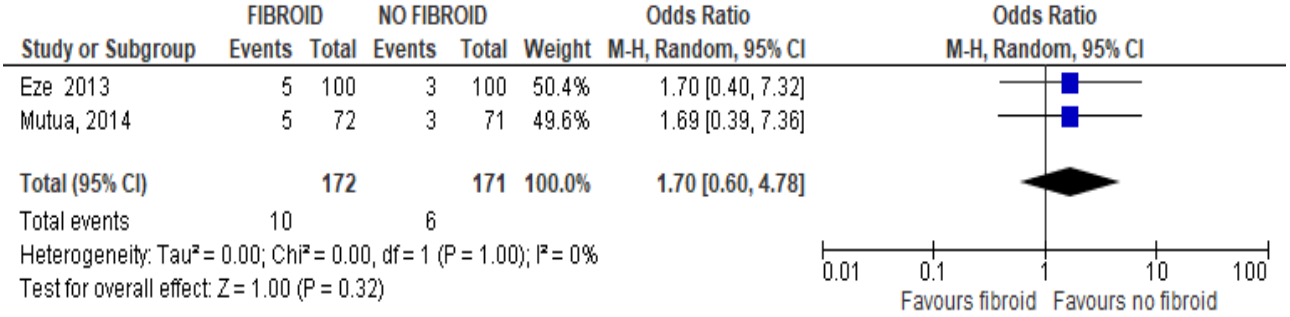


FIGURE 16 Forest plot showing individual and combined effect size estimates and 95% confidence intervals (CIs) in studies that evaluated the likelihood of IUGR among pregnant women with uterine fibroids and without fibroids.

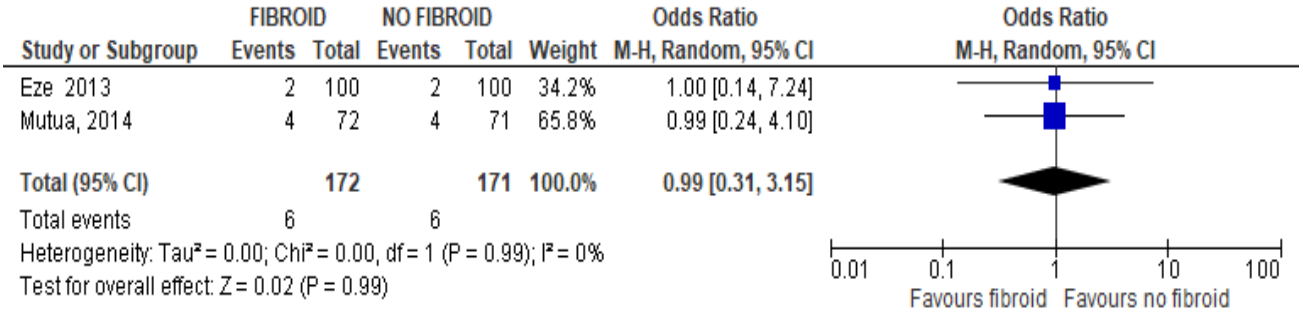


FIGURE 17 Forest plot showing individual and combined effect size estimates and 95% confidence intervals (CIs) in studies that evaluated the likelihood of PROM among pregnant women with uterine fibroids and without fibroids.