Preterm labour in Malawi. Prevention, treatment, complications.

A literature study.

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1.0 Abstract

1.0.1 English

Background: Malawi has the highest estimated preterm birth rate in the world, estimated at 18.1%. Preterm birth represent a major, largely unrecognized, public health problem contributing to the high rates of neonatal mortality in Malawi.

Objectives: This thesis gives an overview of the causes, prevention, treatment and complications of preterm birth. Special emphasis is on Malawi, and a presentation of the most relevant studies on preterm labour, conducted in Malawi, is included. With the articles from Malawi as a basis, I will discuss what they can do in this low-income country to reduce the rate of preterm birth.

Method: This is a literature study. The articles used for the chapters regarding causes, prevention, treatment and complications of preterm birth, are chosen through non-systematic searches on Pub Med, and articles were picked out from the criteria of being of recent date, updated and of good quality. The literature from Malawi is chosen through a systematic search on Pub Med using the search-words “preterm” AND “Malawi”, and 25 articles were picked out.

Discussion: Studies investigating risk factors associated with preterm birth in Malawi have identified several factors that can be modified. Focus on maternal health and nutrition in the preconception- and antenatal period can reduce the incidence of preterm birth. Increasing the coverage of prevention in adolescence, promoting family planning, and changing Malawi’s guidelines for prevention of malaria in pregnancy can contribute to reduction of the preterm birth rate.

Conclusion: Attacking risk factors found to be associated with preterm birth in Malawi, in studies where ultrasound were used to determine gestational age, will be important if Malawi’s preterm birth rate shall improve. Focus on pre-pregnancy- and antenatal care will be essential.

1.0.2 Resymè på norsk

Bakgrunn: Malawi har den høyest estimerte premature fødselsraten i verden, estimert til 18,1%. Prematur fødsel er et stort, hovedsakelig uidentifisert, offentlig helseproblem som bidrar til den høye neonatale dødsraten i Malawi.

Formål: Denne oppgaven gir en oversikt over årsaker, forebygging, behandling og komplikasjoner til prematur fødsel. Spesielt fokus er lagt på Malawi, og en presentasjon av de mest relevante studier utført i Malawi er inkludert. Med artiklene fra Malawi som utgangspunkt vil jeg diskutere hva de kan gjøre i dette lavinntektslandet, for å redusere den premature fødselsraten.

Metode: Dette er en litteraturstudie. Artiklene brukt til kapitlene om årsaker, forebygging, behandling og komplikasjoner, er funnet gjennom usystematiske søk på Pub Med, og artiklene er valgt ut fra kriteriene at de er nye, oppdaterte og av god kvalitet. Litteraturen fra Malawi er funnet gjennom et systematisk søk på Pub Med der søkeordene “premature” AND “Malawi” ble brukt, og 25 artikler ble valgt ut.

Diskusjon: Studier som har funnet risikofaktorer for prematur fødsel i Malawi har identifisert flere faktorer som kan påvirkes. Fokus på mors helse og ernæring i tiden før graviditet og under svangerskapet kan redusere insidensen av prematur fødsel. Å øke dekningsgraden av prevensjon til tenåringer, promotere familieplanlegging, og å endre Malawis retningslinjer for forebygging av malaria under svangerskapet, kan bidra til å redusere den premature fødselsraten.

Konklusjon: Å angripe risikofaktorer som er påvist å være assosiert med prematur fødsel i Malawi, i studier der ultralyd er brukt for å fastslå alderen på fosteret, vil bli viktig hvis den premature fødselsraten i Malawi skal forbedres. Fokus på mors helse før og under svangerskapet vil bli essensielt.

2.0 Introduction

2.0.1 Preterm labour. A definition

There is no internationally recognised definition of preterm labour. Preterm deliveries are those that occur at less than 37 weeks’ gestational age, however, the low-gestational age, or

that used to distinguish preterm birth from spontaneous abortion, varies by location. According to BMJ best practise, this cut-off is at 24 weeks, so that preterm birth occurs between 24 and 37 weeks of gestation. WHO defines preterm births as babies born alive before 37 weeks of pregnancy are completed.

The obstetric precursors leading to preterm birth are: (1) delivery for maternal or foetal indication, also called iatrogenic, in which labour is either induced or the infant is delivered by pre-labour caesarean section; (2) spontaneous preterm labour with intact membranes; and (3) preterm premature rupture of membranes (PPROM), irrespective of whether delivery is vaginal or by caesarean section. About 30-35 % of preterm births are indicated, most commonly because of preeclampsia or intra uterine growth restriction. 40-45 % of preterm births follow spontaneous preterm labour, and 20-30 % follow PPROM [1]. Births that follow spontaneous preterm labour and PPROM are together designated spontaneous preterm births, and account for two-thirds of preterm births.

Preterm births can also be subdivided according to gestational age. About 5 % of preterm births occur at less than 28 weeks' (extreme prematurity), about 15 % at 28-31 weeks' (severe prematurity), about 20 % at 32-33 weeks' (moderate prematurity), and 60-70 % at 34-36 weeks' (near term) [1].

2.0.2 Preterm labour on a global scale

An estimated 15 million babies are born too early every year [2]. Complications of preterm birth are the single largest direct cause of neonatal deaths, responsible for 35% of the world's 3.1 million deaths a year , and are now the second most common cause of death after pneumonia in children under 5 years old [3,4]. This means that altogether more than one million babies die each year due to complications of preterm birth.

Of all livebirths worldwide in 2010, 11.1% were born preterm [3]. In the USA, the preterm delivery rate is 12-13 %. In Europe and other developed countries, reported rates are generally 5-9 % [1]. In low-income countries, on average, 12 % of babies are born prematurely. The differences in rates are not so striking, but the differences in outcome is dramatic. More than 90% of extremely preterm babies (<28 weeks) born in low-income countries die within the first few days of life, yet less than 10% of babies of this gestation die in high-income settings [2].

Preterm birth accounts for 75 % of perinatal mortality and more than half of the long-term morbidity. Although most preterm babies in developed countries survive, they are at increased risk of neurodevelopmental impairments and respiratory and gastrointestinal complications [1]. Morbidity is inversely related to gestational age [5].

The rate of preterm birth has risen in most industrial countries, with the rate in USA increasing from 9.5 % in 1981 to 12.7 % in 2005 [1]. Of 65 countries with reliable trend data, all but 3 have an increase in preterm birth rate over the last 20 years [2]. Much of the increase in singleton preterm birth rate is explained by the rising number of indicated preterm births. A high number of preterm multiple gestations associated with the use of assisted reproductive technologies is also an important contributor to the overall increase in preterm birth [1].

2.0.3 Preterm labour in Malawi

Malawi is considered one of the poorest countries in the world with a gross national income (GNI) per capita of US$270 per year in 2013 [6]. 84% of the population live in rural areas and livelihoods are earned mainly through subsistence farming [7,8]. Malawi also has some of the poorest health indicators in the developing world. The perinatal mortality rate is estimated at 40 deaths per 1,000 births and the neonatal mortality rate is 31 per 1,000 live births, with 71% skilled attendance for deliveries. Skilled attendance is higher in urban areas at 84% compared to 69% in the rural areas [9]. The under-five mortality rate is 68 per 1,000 live births and the maternal mortality rate is 510 per 100,000 live births [10]. In 2014, 96.1% of women giving birth attended antenatal care at least once during pregnancy, but statistics from 2010 shows that only 45.5% vent to at least 4 antenatal care visits, as recommended by the World Health Organisation (WHO) [11,12].

Malawi has the highest incidence of preterm birth in the world, estimated at 18.1% [4]. The country has very limited neonatal care, with few units providing special care for preterm infants. Following is a description, from 2012, of the obstetric and neonatal care available in Lilongwe, the capital of Malawi, to emphasize how scarce these resources are: In Lilongwe there are two public hospitals, the tertiary level Kamuzu Central Hospital (KCH) and Bwaila Hospital (BH), a district hospital. The hospitals are situated 4 km apart. Sick infants are referred to these nurseries from health facilities in the entire central region with a population of 4 million people. KCH receives the sickest high-risk obstetric patients from the

same area, including BH. Annually, KCH conducts approximately 3,000 and BH 14,000 deliveries and their nurseries admit approximately 1,000 and 4,800 babies, respectively. BH is mainly run by midwives/nurses, clinical officers and non-specialized doctors. In KCH, there are in addition a small number of specialist-trained doctors in the obstetric and pediatric departments. Neither of the hospitals routinely uses tocolytics to prevent preterm delivery and the availability of antenatal corticosteroids and antibiotics is erratic. The nurseries have oxygen, heaters, intravenous fluids, aminophylline and antibiotics. Kangaroo Mother Care (KMC) with skin-to-skin contact, exclusive, early breast feeding, early discharge and close follow-up are the standard care for stabilized infants in the nurseries. However, KMC is seldom started in the labour wards and as most babies are kept in cot beds for the first few days, the establishment of the skin-to-skin contact is often delayed. One very simple continuous positive airway pressure (CPAP) machine is available in KCH. Mechanical ventilation and surfactant are not available [13].

2.3 Objectives

My objective with this assignment is to give an overview of the prevention, treatment and complications of preterm labour. As both prevention and treatment are closely linked to the causes of preterm labour, I will start with an introduction of the factors identified to be associated with preterm labour. I also want to give a presentation of the most relevant studies on preterm labour conducted in Malawi, and discuss what they can do in this low-income country to reduce the rate of preterm labour.

2.3.1 Causes of preterm labour

The pathogenesis of preterm birth is not well understood. Preterm labour is thought to be a syndrome initiated by multiple mechanisms, including infection or inflammation, uteroplacental ischemia or haemorrhage, uterine overdistension, stress, and other immunologically mediated processes. A precise mechanism cannot be established in most cases, therefore factors associated with preterm birth, but not obviously in the causal pathway, have been sought to explain preterm labour [1]. Following are the factors associated with preterm birth.

Pregnancy history: The recurrence risk in women with a previous preterm delivery ranges from 15 % to more than 50 %, depending on the number and gestational age of previous deliveries. The risk of another preterm birth is inversely related to the gestational age of the previous preterm birth [1]. One study reported that women with previous preterm deliveries had a 2.5-fold increased risk in their next pregnancy. Prior spontaneous preterm delivery was even more closely associated with subsequent early spontaneous preterm delivery at <28 weeks' gestation (relative risk, 10.6). An early prior spontaneous preterm delivery at 23-27 weeks' gestation was highly associated with early spontaneous preterm delivery (<28 weeks' gestation) in the current gestation (relative risk, 22.1) [14]. The mechanism for the recurrence is not always clear, but persistent or recurrent intrauterine infection probably explain many repetitive spontaneous preterm births. Also, the underlying disorder causing indicated preterm birth, such as diabetes, hypertension, or obesity, frequently persist between pregnancies.

Multiple gestations: Multiple gestations accounts for only 2-3 % of infants, but results in 15-20 % of all preterm births. Nearly 60 % of twins are born preterm. Nearly all higher multiple gestations will result in preterm delivery [1]. Uterine overdistension, resulting in contractions and PPROM, is believed to be the causative mechanism for the increased rate of spontaneous preterm births, while others have an indicated preterm birth because of pre-eclampsia, or other maternal or foetal disorders.

Assisted reproductive technology (ART): Singleton pregnancies achieved by assisted reproduction are at higher risk than spontaneous pregnancies for adverse outcomes, including preterm delivery. In addition, a significant risk of ART is multiple pregnancies. The number of multiple births has risen dramatically, and the majority of this increase is due to the growing use of ART and transfer of multiple embryos [15]. As stated in the previous paragraph, multiple gestations is a risk factor for preterm birth.

Time between pregnancies: Interpregnancy intervals (IPI) shorter than 18 months and longer than 59 months are significantly associated with increased risk of adverse perinatal outcomes, including preterm birth. A meta-analysis form 2006 showed that a dose-response association between IPI and the natural logarithm of the OR of 5 adverse perinatal outcomes in cohort and cross-sectional studies was J-shaped [figure 1]. For each month that IPI was shortened from 18 months, the risk increase for preterm birth, low birth weight (LBW), and

small for gestational age (SGA) was 1.9%, 3.3%, and 1.5%, respectively. Also, the risk for the 3 adverse perinatal outcomes increased by 0.6%, 0.9%, and 0.8%, respectively, for each month that IPI was lengthened from 59 months [table 1] [16].

The causal effects of IPI on birth outcomes has been vigorously debated. In support of IPI having a causal role, the "maternal depletion hypothesis" proposes that mothers with short IPI insufficiently recover from the physiological stresses of a previous pregnancy and subsequent lactation. A mechanism proposed for the effects of long IPI is that the benefits of a previous birth in terms of physiological adaptation are gradually lost, as though the mother returns toward an equivalent state to primigravidae; this is known as the "physiological regression hypothesis." Together, these hypotheses imply the existence of an optimal interval that affords enough time for recovery from a previous birth but is not so long that the benefits of adaptation are lost. The alternative view is that IPI is not causal, and that the relation between IPI and birth outcomes is entirely due to maternal factors that correlate with IPI and the birth outcome in question. Such confounders could include various aspects of socioeconomic status, ethnicity, demographics, and lifestyle. A recent study supports this view [17].

Vaginal bleeding: Vaginal bleeding caused by placental abruption or placenta praevia is associated with a very high risk of preterm delivery, but bleeding in the first and second trimesters that is not associated with either placental abruption or placenta praevia is also associated with subsequent preterm birth [1].

Cervical surgery: History of cervical cone biopsy or loop electrocautery excision procedures secondary to premalignant cervical disorders have been associated with an increase in spontaneous preterm delivery. A study from 2012 showed significantly higher rate of premature delivery (17% vs. 3.8%) in the group of patients with history of conisation, compared with the control group [18]. The significance of this association has also been confirmed by another study [19].

Maternal demographic characteristics: In the USA and in the UK, women classified as black, African-American, and Afro-Caribbean are consistently reported to be at higher risk of preterm delivery. Preterm birth rates are in the range of 16-18 % in black women compared

with 5-9 % for white women. Over time, the disparity in preterm birth rates between black and white women remains largely unchanged and unexplained [1].

Observational studies of the type of work and physical activity related to preterm birth have produced conflicting results. Investigation of work-related risk is made difficult by confounding factors, however, even after accounting for population differences, working long hours and undertaking hard physical labour under stressful conditions are probably associated with an increase in preterm birth [1]. One study that confirms this found that the risk of preterm birth was not related to employment, but was increased in women who worked more than 42 h per week (OR 1.33, 95% CI 1.1-1.6) and who were required to stand for more than 6 h per day (1.26, 1.1-1.5) [20].

Low socioeconomic and educational status, low and high maternal ages, and single marital status is also associated with preterm birth [1, 21-23]. The mechanisms by which the maternal demographic characteristics are related to preterm birth are unknown. The association between young maternal age and preterm labour is somewhat controversial, because many confounding factors are common among adolescents [24]. Anyhow, adolescents are a high-risk group because of factors that are more common among them, for example biologic immaturity, inadequate prenatal care, poverty, minority status, low pre-pregnancy weight, and sexually transmitted infections [25].

Stress: Mothers experiencing high levels of psychological or social stress are at increased risk of preterm birth (generally <2-fold) even after adjustment for the effects of sociodemographic, medical, and behavioural risk factors. Exposure to objectively stressful conditions, such as housing instability and severe maternal hardship, has also been associated with preterm birth [1].

Substance use: Alcohol consumption is associated with preterm birth. Moderate intake defined as three or more drinks a day increased the risk of preterm birth in an Italian study (OR 2.0, 1.8 and 1.9, respectively, for each trimester of pregnancy). There appeared to be a dose–response effect in a large Danish study with the highest risk for very preterm delivery among women consuming seven or more drinks per week (RR 3.26, 95% CI 0.80–13.24) [24]. The use of tobacco increase the risk of preterm birth (<2-fold) after adjusting for other

factors. Cocaine and heroin use have been associated with preterm birth in several studies [1].

Nutritional status: A low pregnancy BMI is associated with a high risk of spontaneous preterm birth, whereas obesity can be protective [1]. A study in 2005 showed that women with a body mass index of <19 kg/m2 had 16.6% spontaneous preterm birth (SPB), whereas women with a body mass index of 19 to 24.9 kg/m2 had only 11.3% SPB. In the same study the odds ratio (OR; 95% CI) of an obese patient (BMI >30) to have a SPB was approximately one-half that for a non-obese patient. The total rate of preterm deliveries, which included both spontaneous and indicated deliveries, was also lower in obese women (11.1% vs 15.3%; P =0.009), but indicated preterm birth accounted for a higher percentage of preterm birth in the obese than the non-obese patient (44% vs 24%; P = 0.003) [figure 2] [26].

Women with low serum concentrations of iron, folate or zinc, have more preterm births than those with measurements within the normal range [1]

There are many potential mechanisms by which maternal nutritional status might affect preterm birth. For example, spontaneous preterm birth can be caused by maternal thinness associated with decreased blood volume and reduced uterine blood flow. Thin women might also consume fewer vitamins and minerals, low concentrations of which are associated with decreased blood flow and increased maternal infections. Obese women are more likely to have infants with congenital anomalies, such as neural-tube defects, and these infants are more likely to be delivered preterm. Obese women are also more likely to develop pre-eclampsia and diabetes, and have indicated preterm births associated with these disorders [1].

Maternal medical disorders: Thyroid disease, asthma, diabetes, and hypertension, are associated with increased rates of preterm deliveries, many of which are indicated because of maternal complications [1].

In one study, maternal first-time diagnosis of thyroid dysfunction before, during or after pregnancy was registered in 32,809 (2.0%) of 1,638,338 singleton live births. Maternal diagnosis of hyperthyroidism (adjusted OR 1.22, 95% CI 1.15-1.30) and hypothyroidism (adjusted OR 1.17, 95% CI 1.08-1.27) were associated with increased risk of preterm birth [27].

In a meta-analysis form 2011, maternal asthma was associated with an increased risk of preterm delivery (RR 1.41, 95% CI 1.22–1.61), but the risk were reduced to non-significant levels by active asthma management (RR 1.07, 95% CI 0.91–1.26) [28].

In a study investigating the rate of preterm delivery in mothers with pre-gestational diabetes or pre-existing chronic hypertension, the overall rates of preterm delivery were significantly higher among women with diabetes mellitus (38%) and hypertension (33.1%) than among control women (13.9%). Women with diabetes mellitus, even though treated with insulin, had significantly higher rates of both indicated preterm delivery (21.9% vs 3.4%; odds ratio, 8.1; 95% confidence interval, 6.0-10.9) and spontaneous preterm delivery (16.1% vs 10.5%; odds ratio, 1.6; 95% confidence interval, 1.2-2.2) than did women in the control group. Compared with control women those with chronic hypertension, even though receiving proper treatment, had higher rates of indicated preterm delivery (21.9% vs 3.4%; odds ratio, 8.1; 95% confidence interval, 6.2-10.6), but there were no significant differences in rates of spontaneous preterm delivery [29].

In a retrospective cohort study of 70,895 Korean women, moderate-to-severe anaemia (Hb <10) before pregnancy was associated with preterm birth (OR, 1.53; 95% CI, 1.05–2.23; P=0.027) in adjusted analysis, when compared with pre-pregnancy haemoglobin of 120–149 g/l. Mild anaemia (Hb of 10–11,9) was not associated with preterm birth, but with low birth weight (OR, 1.21; 95% CI, 1.06–1.39; P=0.005) and small for gestational age (OR, 1.15; 95% CI, 1.06–1.25; P=0.001) [30].

Clinical depression during pregnancy has been reported in up to 16% of women, with up to 35% having some depressive symptoms. Although the results are inconsistent, several reports suggest a relation (risks generally rose <2–fold) between depression and preterm birth. Depression is associated with an increase in smoking, and drug and alcohol use, therefore, the relation between depression and preterm birth might be mediated by these behaviours. Nevertheless, in some studies that adjusted for smoking and drug and alcohol use, the association between depression and preterm birth persisted, suggesting that this relationship might be caused by more than confounding. Although, the mechanism(s) underlying the association of depression and preterm birth is unknown, there is an association between depressed mood and a reduction in natural killer cell activity, and higher plasma concentrations of proinflammatory cytokines and their receptors.

Inflammation, therefore, might also partly mediate the relation between depression and preterm birth [1].

Infection: Infection plays an important role in preterm birth. Bacterial vaginosis is associated with a 1.5 to 3-fold increase in the rate of preterm birth. The mechanism by which bacterial vaginosis is associated with preterm birth is unknown, but microorganisms that cause the infection probably ascend into the uterus before or early during pregnancy [1]. Urinary tract infections, HIV and syphilis are also all associated with increased risk of preterm birth [4]. Several non-genital tract infections, such as pyelonephritis and asymptomatic bacteriuria, pneumonia, appendicitis and malaria, are associated with, and probably predispose to, preterm birth [1,31].

Intrauterine infection is a frequent and important mechanism leading to preterm birth. The mechanisms by which intrauterine infections leads to preterm labour are related to activation of the innate immune system. Microorganisms are recognised by pattern-recognition receptors, for example toll-like receptors, which in turn elicit the release of inflammatory chemokines and cytokines, such as interleukin 8, interleukin 1β, and tumour necrosis factor (TNF) α. Microbial endotoxins and proinflammatory cytokines stimulate the production of prostaglandins, other inflammatory mediators, and matrix-degrading enzymes. Prostaglandins stimulate uterine contractility, whereas degradation of extracellular matrix in the foetal membranes leads to PPROM [32].

Microbiological studies suggests that intrauterine infection might account for 25-40 % of preterm births. 25–40% might be a minimum estimate because intrauterine infection is difficult to detect with conventional culture techniques. Accumulating evidence suggests that intra-amniotic infection is a chronic process. Women with positive Ureaplasma urealyticum amniotic fluid cultures, or who are PCR-positive for U. urealyticum at the time of midtrimester genetic amniocentesis, often have spontaneous preterm labour or PPROM weeks after the procedure. Importantly, the earlier the gestational age at which women present with preterm labour, the higher the frequency of intrauterine infection. The genital mycoplasmas and other organisms detected in the uterus before membrane rupture are typically of low virulence, probably accounting for both the chronicity of intrauterine infections and the frequent absence of overt clinical signs of infection [1].

Intrauterine infection can be confined to the decidua, extend to the space between the amnion and chorion, and reach the amniotic cavity and the foetus. The amniotic cavity is usually sterile for bacteria, but the significance of microorganisms in the membranes is less clear. Researchers suggest that the presence of bacteria in the chorioamnion alone cannot be sufficient to cause an inflammatory response, preterm labour, and preterm birth. The hypothesis is that only when the amnion and chorion become tightly applied to the decidua at about 20 weeks' gestation, do colonized women become symptomatic and progress to early preterm birth [1,32,33]

The role of oral pathogens in the aetiology of preterm labour is a relatively recent area of research. The hypothesis is that chronic periodontal infection serves as a reservoir for bacterial products and/or inflammatory mediators that play a role in the development of preterm labour and preterm low birth weight. The Oral Conditions and Pregnancy (OCAP) study investigated 1,020 women with antepartum and postpartum periodontal examination. Antepartum moderate–severe periodontal disease was associated with an increased incidence of spontaneous preterm births (adjusted RR 2.0, 95% CI 1.2–3.2). There was also a higher rate of very preterm delivery among women with periodontal disease progression (RR 2.4, 95% CI 1.1–5.2) [24].

Cervical shortening: As labour approaches, the cervix shortens, softens, rotates anteriorly, and dilates. Ultrasound examinations of the cervix have shown that cervical shortening is a risk factor for preterm delivery. The shorter the cervix, the greater the risk. Cervical length can discriminate between woman not in labour and those who carry a pronounced risk of early delivery. With a cervical length greater than 30 mm, the likelihood of delivering in the next week is about 1 %, and most women can be safely discharged without treatment [1].

Foetal fibronectin: Foetal fibronectin is a glycoprotein that is present in cervicovaginal fluid after choridodecidual disruption. Typically, foetal fibronectin is absent from cervicovaginal secretions from 24 weeks' until near term, however, 3-4 % of women undergoing routine screening at 24-26 weeks' are positive, and are at substantially increased risk of preterm delivery. For clinical care, an important characteristic of the foetal fibronectin is its negative predictive value. In questionable cases, only about 1 % of women with a negative test delivers in the next week [1].

2.3.2 Interventions to reduce the rate of premature labour.

There are many causes and many risk factors for premature labour and consequently there is no single preventative strategy. When considering the different factors associated with preterm birth, one should believe that eliminating these factors would decrease the rate of preterm birth. There is little evidence of this, but I still want to mention some of the factors that can be modified in this chapter.

2.3.2.1 Preconception care services for prevention of preterm birth for all women

Preconception care offers the earliest opportunity to reduce the risk of preterm birth, allowing women to enter pregnancy in the best possible health and to have the greatest chance of giving birth to a healthy baby.

Prevent pregnancy in adolescence: In some regions, cultural norms promote early marriage, which is a factor in high rates of adolescent pregnancy. Regulations to increase the legal age at marriage and educating communities to change cultural norms that support early marriage may be ways to prevent adolescent pregnancy in those countries. Particular emphasis must also be placed on ensuring universal access to primary and secondary education for girls, because girls who complete their education are less likely to become pregnant in adolescence.

Prevent unintended pregnancies, and promote birth spacing and planned pregnancies: One way to ensure that mothers and babies have good outcomes is to encourage pregnancy planning. Women who have very closely spaced pregnancies (within 6 months of a previous live birth or pregnancy) are more likely to have preterm or low-birth weight babies. The correct, consistent use of family planning methods leads to more women spacing their pregnancies 18 to 24 months apart, which is ideal. Encouraging family planning and the use of contraceptive methods (hormonal and barrier methods) has other advantages including reductions in maternal and infant mortality, lower rates of unintended pregnancies and prevention of STIs, including HIV.

Optimize pre-pregnancy weight: Optimizing weight before pregnancy is recommended since weight gain or loss during pregnancy increases the risk of adverse pregnancy outcomes. Women who are underweight before pregnancy (body mass index less than 18.5 kg/m2) are

at significantly greater risk of having premature, low birth weight newborns. Given that maternal undernourishment is a risk factor for being underweight, improving food security could reduce the rates of preterm birth, especially in impoverished nations.

Promote healthy nutrition including supplementation: Studies of the biological mechanisms leading to preterm birth indicate that more severe congenital disorders, including neural tube defects, might result in preterm delivery. Consuming a multivitamin containing 400 μg of folic acid in the pre-conceptional period is the best way to ensure adequate micronutrient intake to help prevent neural tube and other birth defects. Multivitamin supplementation reduces the risk of congenital malformations (e.g., neural tube, congenital heart, urinary tract and limb defects) by 42-62% and the risk of preeclampsia by 27%. Folic acid supplementation or fortification reduces the risk of neural tube defects by 53%. Although folic acid is known to protect against neural tube defects, there is little evidence to show that folic acid supplementation alone reduces the risk for preterm birth.

Promote vaccination of children and adolescents: Infections transmitted around the time of conception or during pregnancy may result in preterm birth. Not only does infection, especially with rubella virus, increase the risk for prematurity, it may lead to other devastating consequences such as congenital rubella syndrome or miscarriage. Many of these infections could be prevented through routine childhood vaccinations. However, the rubella vaccine can also be given at least 3 months prior to pregnancy to women who are not already immune. Vaccination campaigns against rubella have been able to increase coverage for adolescent girls and women [34].

Public educational interventions: An inaccurate perception held by the public is that improved neonatal care has resolved the problems of preterm infants. Increased awareness of preterm birth as the leading cause of infant mortality might offer an opportunity to inform the public about potentially avoidable risk factors. For example, greater public and professional awareness of evidence that repeated uterine instrumentation, for example, uterine curettage or endometrial biopsy, is associated with an increased risk of subsequent preterm birth might, over time, influence decisionmaking about these procedures. Similarly, choices made in fertility care might be affected by broader public knowledge of the increased risk of preterm birth in singleton gestations conceived with assisted reproductive

technology. Such educational efforts are not in place at the moment, but could be modelled on successful efforts to reduce the prevalence of smoking [20].

Public and professional policies: Policies adopted by government or medical bodies can exert an immediate effect on the rate of preterm labour. For example, policies specifically intended to reduce the risk of higher-order multiple gestation have been successful in Europe, Australia, and the USA. Rates of triplet and higher-order multiple pregnancies had been rising rapidly in the USA until 1998, when the increase was arrested by voluntary adoption of limitations on the number of embryos transferred. The rate of higher-order multiple pregnancies fell by 50% between 1996 and 2003.

A societal approach to improve pregnancy outcomes has been adopted in most European countries. Examples of policies to protect pregnant women are minimum paid-pregnancy leave of 14 weeks, time off for prenatal visits, exemption from night shifts, and protection from workplace hazards (even complete work leave, if necessary) [20].

2.3.2.2 Preconception care services for women with risk factors that increase the risk for preterm birth.

Screen for, diagnose and manage mental health disorders and prevent intimate partner violence: Maternal stressors such as depression, socioeconomic hardship and intimate partner violence have been linked to preterm birth. It has been hypothesized that physical and psychological stress acts through inflammatory pathways involving maternal cortisol to cause premature birth. Importantly, when such risks are present before pregnancy they are likely to continue throughout pregnancy as well. Moreover, women with psychosocial stressors have a greater likelihood of engaging in risky behaviours such as smoking and alcohol use and are less likely to seek health care.

Prevent and treat STIs, including HIV/AIDS: Reducing the incidence of infectious diseases, particularly syphilis, is a high priority to lower the rates of stillbirths and preterm birth. Focusing interventions on high-risk groups, including women, adolescents and intravenous drug users, can effectively reduce the transmission of STIs to the population in general and subsequently reduce preterm births.

Promote cessation of tobacco use and restrict exposure to secondhand smoke: Cigarette smoking approximately doubles the threat of preterm birth. Despite the risk of foetal growth

restriction and preterm birth, a survey of women in low- and middle-income countries found that many pregnant women currently used tobacco or were exposed to secondhand smoke. A few studies have shown, however, that preconception counselling and the involvement of husbands or partners in smoking cessation programmes can increase the number of women who quit smoking before pregnancy.

Screen for, diagnose and manage chronic diseases: Thyroid disease, asthma, diabetes, and hypertension, are associated with increased rates of preterm delivery. Although testing and treatment for women diagnosed with such medical problems prior to pregnancy are cost-effective and prevent further complications for the mother and baby, they do not necessarily lower the incidence of preterm births. However, achieving optimal control of the condition before pregnancy may lead to better long-term outcomes for the mother and the newborn [20].

2.3.2.3 Prevention of preterm birth during pregnancy for all women

Antenatal care: Increasing access to care during pregnancy for all women is an essential step towards addressing the growing problem of preterm birth. Research has shown that women who receive antenatal care services are at lower risk for having a preterm birth than women who are not reached by the health system prior to delivery. Coverage of antenatal care (at least one visit) is approximately 80% worldwide, with coverage levels dropping to about 50% for four or more visits. Inequities in coverage are pervasive, with coverage levels of four or more antenatal care visits hovering around 40% for the least developed countries.

Many countries around the world report high coverage levels of antenatal care, making antenatal care visits an opportune time to deliver proven interventions to all pregnant women. Basic services that can be delivered during antenatal care with a potential impact on reducing preterm birth rates include identification of women at high risk of preterm birth, screening for and treatment of sexually transmitted diseases, including HIV and other infections (tuberculosis, malaria, bacterial vaginosis, bacteriuria), identification and correction of malnutrition and nutrition counselling on multiple micro-nutrient supplementation, counselling on birth preparedness and complication readiness for identification of early labour and other risk factors, and behavioural and social support interventions such as smoking cessation programmes and programmes aimed at the prevention of violence against women [35].

Screening of low-risk women: Screening for and treatment of asymptomatic bacteriuria prevent pyelonephritis, and has been reported to reduce the rate of preterm birth. Optimum screening and treatment protocols to prevent preterm birth are not well defined.

Routine screening for and treatment of bacterial vaginosis to reduce preterm birth has been extensively studied. Although bacterial vaginosis can be eradicated by antimicrobial therapy, meta-analyses and reviews have shown that treatment does not reduce the occurrence of preterm birth in low-risk women and it is not recommended [20].

2.3.2.4 Prevention of preterm birth during pregnancy for women at high risk.

Women at increased risk of preterm delivery can be identified during antenatal care based on obstetric history (for example, known uterine or cervical anomaly or previous preterm birth, pre-existing conditions such as chronic diseases) or presenting pregnancy characteristics (for example, hypertensive disorder of pregnancy, diabetes, multiple gestation, bleeding).

Nutritional supplements: Trials of supplemental omega-3 polyunsaturated fatty acids have been done on the basis of low rates of preterm birth in populations with a high dietary intake. The postulated mechanism is that omega-3 polyunsaturated fatty acids reduce concentrations of proinflammatory cytokines. Dietary supplementation with omega-3 polyunsaturated fatty acids has been associated with reduced production of inflammatory mediators, and a randomised trial of omega-3 supplements undertaken in women at risk of preterm birth showed a 50% reduction in preterm–birth rate. A subsequent randomised trial of supplemental fish oil noted a reduction in recurrent preterm birth (RR 0.54, 95% CI 0.30–0.98) [20].

Improved care for women at risk: Although perhaps helpful in adolescents, more intensive prenatal care, including social support, home visits, and education, has not reduced rates of preterm birth in other women.

Progesterone: Administration of progesterone to prolong pregnancy in high-risk women with a history of previous preterm birth has been shown effective in preventing a recurrence of preterm birth in these women and in decreasing the prevalence of low birthweight [35]. The risk of preterm birth was reduced by about a third in two trials of progesterone supplementation, given as intramuscular injections of 250 mg per week of 17α-

hydroxprogesterone caproate and as daily vaginal progesterone. Meta-analyses have shown that the risk of recurrent preterm birth was reduced by 40–55% (RR 0.58, 95% CI 0.48–0.70 and 0.45, 0.25–0.80) [20].

Progesterone has not been uniformly beneficial in all populations at risk. A placebo-controlled trial done in 250 women with short cervices reported a reduced rate of preterm birth in women who received vaginal progesterone, but a randomised, placebo-controlled trial reported that 17α-hydroxyprogesterone caproate had no effect on the rate of preterm birth in 600 women with twin pregnancies [28]. Recent guidelines and professional opinion recommend administering vaginal progesterone to women with singleton pregnancies and short cervical length to reduce preterm birth and perinatal morbidity and mortality [35].

Cervical cerclage: Cervical length is inversely related to risk of preterm birth. Studies using cervical sonography to observe the process of cervical effacement in normal and complicated pregnancies have shown that a short cervix in mid-pregnancy is associated with an increased risk of early delivery, and is linked especially to recurrent preterm birth. In a meta-analysis of data from four trials, the risk of birth before 35 weeks' gestation was reduced with cerclage in women with previous preterm birth and a short cervix (defined as <2·5 cm) in the present pregnancy (RR 0·63, 95% CI 0·48–0·85). Cerclage in women with short cervices who did not have previous preterm births showed no advantage (0.84, 0.60–1.17). In women with twin gestations, cerclage for short cervix was associated with an increased risk of preterm birth (2.15, 1.15–4.01) [20].

2.3.3 Interventions to improve outcome for preterm infants

Early diagnosis: Detection of conditions proximate to preterm birth offers an opportunity to improve outcome, but detection of early preterm labour is a challenge because the symptoms and signs of preterm labour arise commonly in normal pregnancies. The clinical manifestations of true labour, contractions and cervical change, are the same whether labour occurs preterm or at term. The following are early signs and symptoms of labour, however, they are non-specific and can be present for several hours in women who do not exhibit cervical change:

- Menstrual-like cramping
- Mild, irregular contractions

- Low back ache
- Pressure sensation in the vagina
- Vaginal discharge of mucus, which may be clear, pink, or slightly bloody

Uterine contractions are the key manifestation of labour, but mild irregular contractions are a normal finding at all stages of pregnancy, thereby adding to the challenge of distinguishing true labour (contractions that result in cervical change) from false labour (contractions that do not result in cervical change). Increasing frequency of contractions suggests true labour, however, the frequency of contractions may increase transiently and increases with gestational age, the number of foetuses, and at night. Although many investigators have tried, no one has been able to identify a threshold contraction frequency that effectively identifies women who will progress to true labour. True labour is more likely when an increased frequency of contractions is accompanied by increased intensity and duration of contractions.

Cervical changes on physical examination that precede or accompany true labour include dilation, effacement, softening, and movement to a more anterior position. A short or a dilated cervix may be the first clinical manifestation of a parturition process triggered by decidual activation or inflammation. The rate of cervical change distinguishes cervical ripening, which occurs over days to weeks, from true labour, which occurs over minutes to hours [36].

Diagnosis of preterm labour might be improved by use of transvaginal sonographic measurement of cervical length or testing for the presence of foetal fibronectin in cervicovaginal fluid. Both tests improve diagnostic accuracy primarily by reducing false-positive diagnosis [20].

Antenatal transfer: antenatal transfer of the mother and foetus (especially those expected to be born before 32 weeks' gestation) to a hospital equipped to care for preterm infants, is associated with improved outcomes for preterm infants [20].

Corticosteroids: Antenatal administration of corticosteroids to the mother reduces neonatal morbidity and mortality from respiratory distress, intraventricular haemorrhage, necrotising enterocolitis, and patent ductus arteriosus. Glucocorticoids act generally in the developing foetus to promote maturation over growth. In the lung, corticosteroids promote surfactant

synthesis, increase lung compliance, reduce vascular permeability, and generate a greater response to postnatal surfactant treatment. Randomised, placebo-controlled trials and meta-analyses confirm the beneficial effects of antenatal corticosteroids, including reduced occurrence of respiratory distress syndrome, intraventricular haemorrhage, neonatal death, necrotising enterocolitis, patent ductus arteriosus, and bronchopulmonary dysplasia. A single course consists either of two doses of 12 mg betamethasone given intramuscularly, 24 hours apart, or four doses of 6 mg dexamethasone given intramuscularly every 12th hour. The duration of foetal benefit after a course of glucocorticoids is uncertain. Data suggest that a repeat course might confer modest additional neonatal benefit, whereas multiple courses can reduce foetal growth. The present practice is to limit antenatal steroids to a single course given when risk of preterm birth is first recognised after 24 weeks of gestation [20].

Antibiotic treatment: Antibiotic treatment of all women with threatened preterm labour to prevent neonatal infection with group B streptococcus is recommended because preterm infants have an increased risk of this infection. Rates of neonatal group B streptococcus infection and corresponding mortality rates have declined since this strategy was adopted in the USA [20].

If the preterm birth is due to PPROM the mother should receive prophylactic antibiotic treatment. The benefit of antibiotic treatment was established mainly by two clinical trials in which prophylaxis with ampicillin plus erythromycin and erythromycin or amoxicillin/clavulanic acid was associated with prolongation of pregnancy, a reduced rate of maternal chorioamnionitis, and a reduced frequency of neonatal morbidity, measured as composite neonatal outcome. One study reported higher rates of necrotising enterocolitis in neonates whose mothers were given amoxicillin/clavulanic acid and thus they recommended use of erythromycin [20].

Tocolysis: Tocolytic agents that inhibit uterine contractions to suppress labour (for example oxytocin antagonists, betamimetics or calcium channel blockers) are used to prolong pregnancy in women with acute risk of preterm birth. The provision of tocolytics has been shown effective in slowing down labour, enabling the administration of antenatal corticosteroids and transfer of mother and baby to a higher-level facility where appropriate care may be available. Any use of strategies to prolong labour must be evaluated against the

potential risk of continued exposure of mother and foetus to sub-optimal conditions that may result in harmful effects.

The Cochrane collaboration regularly produces meta-analyses of obstetric interventions including tocolytic drugs. These meta-analyses suggest that calcium-channel blockers and an oxytocin antagonist (atosiban) can delay delivery by 2–7 days with an optimum risk-benefit ratio. The Cochrane analysts concluded that β2-agonist drugs, such as ritodrine and terbutaline, can delay delivery by 48 h, but carry greater side-effects than other agents [20,35].

Magnesium sulphate: Magnesium sulphate is recommended for pregnancies at 24 to 32 weeks of gestation, for women with PPROM or preterm labour who have a high likelihood of imminent delivery (i.e. within 24 hours), or before an indicated preterm delivery. In utero exposure to magnesium sulphate provides neuroprotection against cerebral palsy and other types of severe motor dysfunction in offspring born preterm [37]

2.3.4 Complications of preterm birth

There is little doubt that gestational age exerts the greatest influence on outcomes of preterm births. In a prematurely born infant, most organs are immature. The brain and lung are especially susceptible to the consequences of preterm birth. Compared with infants born at term, preterm infants have higher rates of temperature instability, respiratory distress, apnoea, hypoglycaemia, seizures, jaundice, kernicterus, feeding difficulties, periventricular leucomalacia, and rehospitalisations. About a quarter of survivors have substantial neurological morbidity, examples of such are cerebral palsy, mental retardation, and sensory impairments (visual and auditory deficits). The prevalence of cerebral palsy is inversely related to gestational age [5].

Following is a list of specific risks that preterm infants face:

• Feeding difficulties since the coordinated suck and swallow process only starts at 34 weeks gestation. Preterm babies need help to feed and are more likely to aspirate.

• Severe infections are more common, and premature babies are at higher risk of dying once they get an infection. The majority of babies who die from neonatal sepsis are preterm.

• Respiratory Distress Syndrome (RDS) due to lung immaturity and lack of surfactant in the alveoli, resulting in collapsing lungs that take extra pressure to inflate. Below 32 weeks gestation, the majority of babies develop RDS, although this risk can be reduced by antenatal corticosteroids injections to women at risk or preterm labour, or in preterm labour and administration of surfactant to preterm babies, to replace the missing natural surfactant.

• Jaundice is more common in premature babies since the immature liver cannot easily metabolize bilirubin, and once jaundiced, the preterm baby's brain is at higher risk since their blood-brain barrier is less well developed to protect the brain.

• Brain injury in preterm babies is most commonly intraventricular haemorrhage, occurring in the first few days after birth in about 1 in 5 babies under 2,000 g and is often linked to severity of RDS and hypotension. Less commonly, preterm babies may have hypoxic brain injury with white matter loss, which differs from that seen in the brain of term babies.

• Necrotizing enterocolitis is a rarer condition affecting the intestinal wall of very premature babies, with a typical X-ray image of gas in the bowel wall. Formula feeding increases the risk tenfold compared to babies who are fed breast milk alone.

• Retinopathy of prematurity due to abnormal proliferation of the blood vessels around the retina of the eye, which is more severe if the baby is given too high levels of oxygen.

• Anaemia of prematurity, which often becomes apparent at a few weeks of age due to delay in producing red blood cells as the bone marrow is immature. [38]

2.3.5 Presentation of literature from Malawi.

I did a literature search in the Pub Med database using the combination "preterm" AND "Malawi", and got 37 hits. Of those 25 were relevant for my study. Out of the 25 relevant articles, 20 were available in full length. From the remaining 5 articles I have only read the abstracts. The articles can be divided into 5 groups according to what they investigate; (1) ultrasound estimation of preterm birth, (2) risk factors of preterm birth, (3) perceptions and knowledge of preterm birth among health-care providers and non-health-care providers, (4) malaria and its effect on preterm birth, and (5) HIV and its effect om preterm birth.

2.3.5.1 Ultrasound estimation of preterm birth

Because of uncertainties about gestational age calculation in many low-income populations, low birthweight is often used as a proxy measure for prematurity, but low birthweight can reflect foetal growth restriction, preterm birth, or a combination of both. Gestational assessment based on the date of last menstrual period (LMP) was previously the most widespread method used and remains the only available method in many settings. It assumes that conception occurs on the same day as ovulation (14 days after the onset of the LMP). It has low accuracy due to considerable variation in length of menstrual cycle among women, conception occurring up to several days after ovulation and the recall of the date of LMP being subject to errors. The most accurate "gold standard" for assessment of gestational age is routine early ultrasound assessment together with foetal measurements, ideally in the first trimester [4,39].

One study called *Preterm birth in rural Malawi: high incidence in ultrasound-dated population* [39], used ultrasound foetal measurement before 24 weeks gestational age, to find the rate of preterm delivery among 512 unselected pregnant women in rural communities in Malawi. 33.5% of the women were primigravid and 17.4% gravida ≥5. Mean age was 22.8 years (SD 5.6). Just over half of women had skilled assistance at delivery (hospital or health centre 53.2%), 39.2% delivered at home and 7.5% at a traditional birth attendant (TBA) hut. A TBA assisted at 25.6% of all deliveries (at home or in a TBA hut), the grandmother, mother or sister assisted in 16.9% (at home), and in 4% the woman was unattended. Most women had a normal vaginal delivery (93.8%), 4.2% had a Caesarean section, three women had a ventouse delivery and, for six women the type of delivery was not recorded.

Information on gestational age at delivery was available for 453 (88.5%) women. Preterm delivery (>24 and <37 completed weeks) occurred in 92 (20.3%) of the 453 women. 72 (16.0%) of these women delivered between 33 and 37 completed weeks, and 20 (4.4%) between 24 and 32 completed weeks.

The authors suggests that the high incidence of prematurity in this population can be explained by the high level of infections. They also state that the population in the study probably is representative for much of rural Africa, which may have similar levels of infection related preterm birth.

In the introduction to this article, another study conducted by the authors is mentioned. This was a randomized controlled trial of vitamin A supplementation to pregnant, anaemic women in a rural area of south Malawi, Namitambo. As part of the study protocol, women with singleton pregnancies underwent ultrasound measurements of the foetal biparietal diameter before 24 weeks. Unexpectedly, they found a high overall incidence of preterm delivery: 24.7% in women with mild anaemia (Hb 8.0–10.9 g/dl) and 29.7% in women with severe anaemia (Hb <8.0 g/dl). Since these rates were observed in a selected population (women with anaemia), they wanted to repeat the study in an unselected population of pregnant women. This led to the article described previously, where a preterm birth rate of 20.3 % was found.

The APPLe study: a randomized, community-based, placebo-controlled trial of azithromycin for the prevention of preterm birth, with meta-analysis [40], recruited women from three rural and one peri-urban antenatal clinic in Southern Malawi. 2,297 women with gestational age less than 24 weeks, determined by ultrasound were included. Whether delivery was preterm or not was known for 95 % of the women. Recruited women were randomly allocated to either 1 g azithromycin or placebo given at both 16–24 and 28–32 weeks gestational windows. Azithromycin was chosen because of its broad spectrum of antibacterial activity including effectiveness against Ureaplasma urealyticum (implicated as an important cause of preterm labour), its efficacy against sexually transmitted infections including syphilis and chlamydia, its antimalarial effects, its safety profile in pregnancy, and the convenience of a single oral dose with few side-effects. The overall incidence of preterm birth was 17.1% and there was no statistical difference between the treatment groups.

The article also includes a meta-analysis of eight different trials where routine antibiotic prophylaxis, with preterm birth as an outcome, were investigated. The analysis shows no effect on the risk of preterm birth. The authors state that their study adds further weight to the conclusion that pregnant women should not be treated with antibiotics unless for specific infections and with good evidence of likely benefit.

2.3.5.2 Risk factors of preterm birth

A study investigating *Factors Associated with Preterm, Early Preterm and Late Preterm Birth in Malawi* [41] used data from *The APPLe study* [40] for secondary analysis. In *The APPLe study* the primary outcome was incidence of preterm delivery, defined as <37 weeks

gestation. Secondary outcomes were mean gestational age at delivery, perinatal mortality, birthweight, maternal malaria, and anaemia. Since prophylactic treatment with azithromycin had no statistically significant impact on any of the outcome measures, including preterm birth, the participants' data was pooled for secondary analysis regardless of allocated treatment group. All women received iron tablets daily (60 mg elemental iron as ferrous sulphate) with 0.25 mg folic acid, and antimalarial prophylaxis (two doses of Fansidar: 500 mg sulphadoxine with 25 mg pyrimethamine).

For the secondary analysis, three groups of women were defined: those whose pregnancy resulted in an early (24-33) or late preterm birth (gestation 24–36 weeks), and those who delivered at term (37–41 weeks). Women who delivered after 41 weeks (post-term) were not included in the analysis. All women who delivered preterm started labour spontaneously. Data on the general demographics of the mother (age, parity, BMI and gestational age at booking, weight gain between booking and 28–32 week visit), outcome of previous pregnancy and information about the index delivery, including type of delivery, place and supervision of delivery was analysed for each group. Women found to be anaemic (Hb <11.0) or severely anaemic (Hb <8.0) both at booking and during the second visit, were considered 'persistently anaemic' or 'persistently severely anaemic'. Blood tests for malaria (peripheral parasitaemia on thick blood film) were done both at the booking and second visit, with women positive at both visits considered to have 'persistent malaria'. HIV testing was performed retrospectively on stored blood samples.

Women who gave birth preterm were more likely to report a history of previous preterm birth (13.2% vs. 6.1%, p = 0.001) and previous neonatal death (8.1% vs. 4.1%, p = 0.02) compared to women who delivered at term. Compared to women who gave birth at term, a significantly greater proportion of women with preterm births were less than 20 years old (33.6% vs. 27.9%, p = 0.03) and had lower mean BMI (22.3 vs. 22.8, p = 0.006). During pregnancy women who had a preterm birth had lower mean weight gain (kg) between the first (booking <24 weeks gestation) and subsequent assessment (28–32 weeks gestation) (2.95 vs. 3.39, p = 0.008). More women who delivered preterm were anaemic (73.5% vs. 64.2%, p= 0.001) or had malaria (36.4% vs. 28.5%, p = 0.004) at least once during their pregnancy. A significantly greater proportion also had persistent malaria (7.5% vs.

4.7%, p = 0.04). No statistical differences were noted for the prevalence of syphilis or HIV positive status between those who delivered preterm versus term.

Increasing BMI (Adjusted OR 0.91 (0.85–0.97), p = 0.005) and weight gain (Adjusted OR 0.89 (0.82–0.97), p = 0.006) had an independent, protective effect. Persistent malaria (despite malaria prophylaxis) increased the risk of late preterm birth (Adjusted OR 1.99 (1.05–3.79); p = 0.04). Age <20 (Adjusted OR 1.73 (1.03–2.90); p = 0.04) and anaemia (Adjusted OR 1.95 (1.08–3.52); p = 0.03) were associated with early preterm birth (<34 weeks).

This is the first study from sub-Saharan Africa to report on the factors associated with preterm birth for a cohort of women in which gestational age has been reliably assessed with ultrasound. In this population, the prevalence of HIV was 26.2%. Despite claims that HIV infection is an important cause of preterm birth in Africa, this study found no evidence of an association in this population (unexposed to anti-retroviral treatment).

In the article *Adverse birth outcomes in a malarious area* [42] a cross-sectional study of pregnant women attending and delivering at two study hospitals in Southern Malawi was undertaken, to determine factors associated with foetal growth, preterm delivery and stillbirth in an area of high malaria transmission. I will here only mention the factors associated with preterm birth. Gestational age was assessed by trained nurses using a modified Ballard scale. The Ballard scale assigns a score to various physical and neurologic criteria in the newborn, and the sum of the score is used to determine the gestational age of the baby. Preterm birth was found to occur in 17.3 % of all births.

Factors associated with preterm birth were: adolescence (OR 1.9, 95% CI 1.3–2.6), <5 antenatal visits (OR 2.3, 95% CI 1.7–3.1), short stature (height <150 cm) (OR 1.6, 95% CI 1.1–2.5), Right mid-upper arm circumference <23 cm (OR 2.0, 95% CI 1.4–2.9), Hb <10 g/dl at recruitment (OR 1.5, 95% CI 1.1–2.2), or <9 g/dl at delivery (OR 1.4, 95% CI 1.0–1.9) and peripheral (OR 1.6, 95%CI 1.1–2.2), or placental and peripheral malaria (OR 1.5, 95% CI 1.1–2.0). Taking ferrous sulphate supplements <5 times (OR 1.9, 95% CI 1.2–2.8) and taking sulphadoxine–pyrimethamine once, instead of twice (OR 1.6, 95% CI 1.0–2.4) were both associated with preterm birth. There was an increasing prevalence of preterm deliveries with increasing placental parasite density (P=0.02). HIV was not associated with preterm birth.

2.3.5.3 Perceptions and knowledge of preterm birth among health-care providers and non-health care providers.

The study *Perceptions and experiences of community members on caring for preterm newborns in rural Mangochi, Malawi: a qualitative study* [43] explores the perceived causes of preterm birth, care practices for preterm newborn babies and challenges associated with preterm birth among community members in Mangochi District, in southern Malawi. The researchers introduced the aim of the study to the local leaders in the community and engaged them to help in identifying potential participants to be included in the study. Men who were not yet grandfathers and had at least one infant at home born in the previous year, and women who had given birth in the previous year, were recruited, along with grandmothers who were staying with their grandchildren in the same household. Traditional birth attendants (TBA) and traditional healers were also recruited. Focus group discussions (FGDs) and in-depth interviews (IDIs) were used for data collection.

The participants listed many maternal factors that is acknowledged to be associated with preterm birth, like history of preterm birth in the family, short IPIs and young and advanced maternal age. Although it is well known that early pregnancies have public health consequences for both the mother and the newborn, participants reported that early childbearing was becoming more common in their community.

General social factors believed to be the cause of preterm birth were the use of family planning (especially injections), the will of God, witchcraft and the use of local medicine during pregnancy. A number of traditional illnesses were also commonly perceived to cause preterm birth or miscarriage [table 2].

All participants perceived a preterm newborn as a baby who was born before the pregnancy had lasted for nine complete months, and reported that they counted the number of months from the last menstrual period. Participants also used physical features to recognize a preterm baby:

- Baby is too small, fails to breathe properly and have transparent lips, which are soft.
- Baby fails to breastfeed, sunken forehead and skin having many wrinkles.
- Baby born with few hairs, have few eye lashes and nails not fully developed.
- Body looks watery to show that it is not fully developed.

- Looks malnourished and anaemic.
- Baby looks sick, has a pale body with pale teats and soft body scaring people to hold.
- Baby fails to pass stool in the first day of life.

Care practices and challenges of caring for preterm newborns in the community are summarised in [table 3]. Notably, none of the participants reported using skin-to-skin kangaroo care for preterm newborns. When asked, some acknowledged to have heard of it from the radio but did not know how to do it. However, a mother of a preterm newborn said that she practiced it in the hospital, but at home, it was difficult because of several household chores. Some reported using plastic bottles with hot water inside for keeping babies warm. This could be dangerous to the newborn skin if not properly handled.

Almost all participants reported that the care of a preterm newborn was demanding, requiring the mother to be available all the time, thereby affecting business, farming and household chores. Men reported that they did not take part in carrying the baby, and the women agreed with this assessment stating that having a preterm newborn was a burden on women because men did not help much in caring for the newborn.

Participants reported challenges of poverty and lack of knowledge on caring for preterm newborns. Because of poverty, parents failed to buy warm materials, lived in cold houses with grass thatched leaking roofs and failed to rush the baby to the hospital because of lack of money for transport and to pay for the hospital bills. Grandmothers and TBAs said that they always provided traditional medicine to the preterm newborns before going to the hospital. All participants concurred that many preterm newborns had failed to survive because of lack of proper care in the homes.

Another study, called *Qualitative assessment of attitudes and knowledge on preterm birth in Malawi and within country framework of care* [44], used focus-group discussions among community health workers (CHWs), patient couples, midwives and clinical officers, to qualitatively assess baseline knowledge and perceptions regarding preterm birth (PTB) and oral health in an at-risk, low resource setting surrounding Lilongwe, Malawi.

Normal length of gestation was most commonly described by men and women from the community as 9–10 months, by CHWs as 36 weeks, and by clinicians as 40 weeks. Clinicians mentioned ultrasound as a way of estimating due date, but most CHWs were not

aware of the role of ultrasound for dating a pregnancy. Of interest, clinicians stated that 28 weeks was the best time to do a dating ultrasound (in the United States the more accurate dating of early pregnancy is preferred), but they explained that the advantage of a 28 week scan was that it also provided documentation of the foetal presentation (obstetricians might argue that presentation is best assessed within one month of due date).

In this study, none of the participants mentioned traditional illnesses and witchcraft to be causes of PTB. The authors suggests that this might be explained by the fact that Caucasian U.S. physicians facilitated the focus groups with patients, which might have discouraged discussion of traditional beliefs. In addition, the physicians were obstetricians/maternal-foetal medicine specialists who had significant experience as global health providers and had worked in the region intermittently for 1 year. Another potential limitation in this study included the fact that all the participants were recruited through their health centre, which may have preselected for a more educated group of subjects than the average Malawian.

All participants agreed that going to the health centre or district hospital was an appropriate action to take if preterm contractions occurred. The health centres and district hospitals are less likely to have a steady supply of antenatal steroids and does not have a steady presence of a qualified paediatrician or advanced care nursery. Although there had been a recent regional recommendation to send all women with preterm contractions to the central, tertiary care hospital, most participants including clinicians were unaware of the new policy. Common barriers to seek health care included transportation, fear of the hospital and disrespectful treatment by hospital staff, and belief that nothing could be done if preterm labour occurred. Members of couples did mention that perhaps traditional healers would have medication to stop contractions. Patient couples and CHWs generally had not heard of the advantage and the availability of antenatal steroids to accelerate lung maturity. One clinical officer was equally unaware of this option. The concept of intramuscular or intravaginal progesterone to prevent PTB in a woman with a history of prior PTB as well as the possible role of good dentition in preventing PTB were new to all participants. However, the most common response to hearing this and other new information was: “Explain to us why and how this works and we might believe you”.

All participants were aware of many women who had babies which were born too soon, and felt that this was a significant health concern which needed to be addressed. Following this study, the researchers have collaborated with the Ministry of Health and regional obstetrical and oral health experts, with the overarching goal to develop tailored educational materials and readily deliverable health care messages for community health workers and clinicians, to assist them in effectively educating pregnant women about PTB and oral health. This work includes defining terms, underlying aetiologies, causative models, and risk associations, conveying current knowledge about prevention of PTB and periodontal disease in a culturally appropriate fashion, and providing knowledge regarding anticipated management and outcomes specific to preterm delivery.

2.3.5.4 Malaria and its effect on preterm birth

Malaria in pregnancy is a major, preventable cause of maternal morbidity, mortality, and poor birth outcomes in sub-Saharan Africa. Plasmodium falciparum infections increase the risk for intrauterine growth retardation (IUGR) and preterm delivery (PTD), especially in primigravidae. National guidelines in Malawi recommend provision of sulphadoxine-pyrimethamine (SP) as intermittent preventive treatment (of malaria) during pregnancy (IPTp), to HIV-uninfected women at around 18 and 32 weeks of pregnancy [45]. The prevalence of resistance to SP is increasing, particularly in Eastern and Southern Africa. Malawi has some of the highest rates of SP resistance documented, with fixation of the quintuple mutant profile most highly associated with clinical failure of SP in clinical efficacy studies. In the study *Effectiveness of intermittent preventive treatment with sulfadoxine-pyrimethamine during pregnancy on maternal and birth outcomes in Machinga district, Malawi* [46], the investigators wanted to see whether IPTp-SP was still effective, despite rising resistance to the drug. 703 women, who were documented HIV negative and had singleton pregnancies, were enrolled in the study at the time of delivery. Data on the number of SP doses received during pregnancy was recorded.

The primary outcome was placental infection demonstrated by histologic analysis. One of the secondary outcomes was composite birth outcome (small for gestational age, preterm delivery, or low birth weight). Composite birth outcome was used because of the small number of events. Gestational age was assessed by Ballard examination within 24 hours of delivery, by trained study nurses. Receipt of ≥2 SP doses had no impact on

histologically confirmed placental infection, but IPTp-SP was associated with a dose-dependent protective effect on composite birth outcome in primigravidae, with an adjusted prevalence ratio of 0.50 (95% CI, 0.30–0.82), 0.30 (95% CI, 0.19–0.48), and 0.18 (95% CI, 0.05–0.61) for 1, 2, and ≥3 doses, respectively, compared with 0 doses. The study also showed a reduction in low birth weight among multigravidae mothers receiving ≥2 doses of SP. In this study, SP was not associated with protection from preterm birth, but the number of preterm infants identified was also very small. Approximately one-third of women reported sleeping under an insecticide-treated nett (ITN) the previous night, and doing so was associated with a significant decrease in the risk of composite birth outcome.

The authors conclude that despite concerns that IPTp-SP no longer provides benefit to mothers in areas of East Africa with high rates of SP resistance, they showed a continued benefit of providing IPTp-SP to both primigravidae and multigravidae Malawian women. In the study, the majority of women received 2 SP doses. Even if SP provided a prophylactic effect for 4–6 weeks after exposure, a woman would be at risk of malarial parasite infection during most of her 40-week pregnancy. Data from a meta-analysis mentioned in the study suggest that ≥3 doses of IPTp-SP confer an additional benefit, compared with 2 doses, even in areas where there is fixation of the quintuple mutant to SP.

Malawi's 2-dose IPTp-SP policy was implemented in 1993. However, in the 2010 Malawi Demographic and Health Survey (DHS), only 55% of women received 2 doses of IPTp-SP. Ninety-five percent of women in the 2010 DHS reported attending at least 2 antenatal care visits, and 46% of women reported attending antenatal care ≥4 times during their last pregnancy. This highlights the many missed opportunities when IPTp-SP could have been provided. The authors suggests that modifying the policy in Malawi to provide IPTp-SP at each antenatal visit, starting in the second trimester, as recommended by the World Health Organization [47], might improve coverage of 2 doses, and would be programmatically simpler than the current policy. They end the article by stating that as SP resistance increases, it is likely that the small benefit of IPTp-SP will continue to decrease, therefore, it is prudent to explore new drugs for prevention. However, until additional data on these new drugs and strategies are available, IPTp-SP should continue to be provided to pregnant Malawian women, and ideally, women should receive more than the currently recommended minimum of 2 doses.

In the study *Effect of repeated treatment of pregnant women with sulfadoxine-pyrimethamine and azithromycin on preterm delivery in Malawi: a randomized controlled trial* [48] the authors compared three different intervention groups, receiving either a standard two-dose SP regimen (control group), monthly SP treatment, and monthly SP combined with two doses of azithromycin. The study claims to be the first trial in sub-Saharan Africa to address the impact on preterm deliveries of IPTp with a combination of monthly antimalarial drugs and antibiotics against reproductive tract infections (RTIs). 1,320 pregnant women were enrolled, and gestational age was assessed by ultrasound. The overall rate of preterm delivery was 15.1%. The incidence of preterm delivery was 17.9% in controls, 15.4% in the monthly SP group (P = 0.32), and 11.8% in AZI-SP group (risk ratio = 0.66, P = 0.01). Compared with controls, those in AZI-SP group had a risk ratio of 0.61 (P = 0.02) for LBW. Incidence of serious adverse events was low in all groups. The incidence of preterm delivery and LBW were approximately 35% lower among participants who were treated with monthly SP and two azithromycin doses than among those who received standard antenatal care with two doses of SP.

I have previously mentioned the APPLe study [40], which reported no impact on the incidence of preterm delivery among pregnant women treated with two doses of azithromycin. The dose and timing of azithromycin was the same as in the APPLe trial and the study described in the previous paragraph, but the APPLe intervention combined azithromycin to preventive malaria treatment with two doses of SP, whereas in the trial described above, SP was administered monthly, either with or without azithromycin. The participants in the APPLe trial were more often primigravidae, and the prevalence of syphilis and peripheral malaria parasitemia were higher at enrolment in the APPLe trial. These differences in the burden and preventive treatment of malaria could modify the effect of azithromycin and explain the seemingly conflicting results from the two studies.

The authors end their article by stating that the results on the safety and efficacy of a gestational intervention with monthly SP and two doses of azithromycin suggest that such this intervention could yield major public health benefits in sub-Saharan Africa. However, because the impact of this intervention would heavily depend on the local epidemiology and antimicrobial resistance of malaria, RTIs, and other etiologic factors for preterm delivery, further trials in Malawi and other settings are warranted.

2.3.5.5 HIV and its effect on preterm birth

In the article, *Severity of maternal HIV-1 disease is associated with adverse birth outcomes in Malawian women: a cohort study* [49], secondary analysis of data from a previous study was used. Included participants (n=809) were HIV-positive, normotensive, antiretroviral treatment naïve women who delivered a live, singleton infant. Gestational age at delivery was self-reported. 21% of participants delivered a LBW infant and 16% delivered preterm. Indicators of severe maternal HIV-1 infection were defined as high placental or peripheral viral load or a low CD4+ T-cell count.

HIV-1 concentration in the placenta was inversely correlated with both birth weight and duration of gestation. The effect of HIV-1 disease severity on prevalence of LBW and PTD differed meaningfully by maternal malaria status. Among women with malaria, no significant association between any measure of HIV-1 disease severity and prevalence of LBW was observed, in unadjusted or adjusted analyses (adjusted for residence, education level, primigravidae status and anaemia). Among malaria-negative women, for all measures of HIV-1 disease severity, more severe HIV-1 disease was significantly associated with increased prevalence of LBW in both unadjusted and adjusted models. The adjusted prevalence ratio (PR) for a 1-log increase in placental HIV-1 viral load was 1.22 (95% CI: 1.00, 1.48), for a 1-log increase in peripheral HIV-1 viral load was 1.38 (95% CI: 1.08, 1.77); and for a 100-cell/ µl decrease in CD4+ T-cells was 1.12 (95% CI: 1.05, 1.21).

Among malaria-positive women, neither placental viral load nor CD4+ Tcell count were significantly associated with PTD in unadjusted or adjusted analyses, but a 1-log increase in peripheral viral load was significantly protective against PTD in adjusted analyses (PR: 0.56, 95% CI: 0.47, 0.85). This finding was unexpected and the basis for this association is unknown. In the article, they mention one study who suggests that HIV-1 infection can suppress the innate immune response to P. falciparum, which has the potential to modulate inflammation and onset of delivery, and be protective of PTD through this mechanism. Among women without malaria, higher placental viral load and lower CD4+ T-cell count were both significantly associated with increased prevalence of PTD (adjusted PR for a 1-log increase in placental viral load: 1.29, 95% CI: 1.02, 1.63; adjusted PR for 100-cell/µl decrease in CD4+ T-cells: 1.16, 95% CI: 1.05, 1.28).

To conclude, in malaria-negative women, maternal HIV-1 disease severity was significantly associated with increased prevalence of LBW and PTD. Administration of antiretroviral therapy (ART) that reduces viral load to an undetectable limit could lead to extremely significant relative reductions in LBW, and probably PTD, among malaria-negative Malawian women.

3.0 Methods

3.1 The work process

This thesis is a part of the fifth year professionals study in medicine, at the University of Tromsø. During four weeks in January 2014, I worked out the project description. I have an interest for global health, and wanted my thesis to be on a subject regarding a health challenge, in a low-income country, in Africa. I talked to Jon Øyvind Odland, who has been part of many projects involving maternal health in Malawi, and he agreed to be my supervisor. I read some of his previous articles and about Malawi on the web. When I found out that Malawi had the highest estimated preterm birth rate in the world, I decided that preterm labour were to be the topic of my thesis. I read about preterm labour at BMJ best practice and on Up to date. I also used some of the time reading the documents from the university describing the terms of the thesis, and looking through previous thesis written by other students, for inspiration. I searched for articles on preterm birth in low-income countries through Pub Med, and decided that my theses would be a literature study. I discussed the objectives of my assignment with my supervisor and made a plan for the following work.

In august 2014, we had two weeks set aside for working on the thesis. During this time, I searched for articles I could use for the background chapters of my thesis, regarding causes, prevention, treatment and complications of preterm birth. The search for articles was not systematic, but I picked out the latest articles on the subjects, and tried to make sure that the research was updated and of good quality. Finally, I started to do systematic searches for articles on preterm birth in Malawi. I decided to use the search-words “preterm” AND “Malawi” in Pub Med. By using the conjunction AND you find articles having both preterm and Malawi as keywords. This resulted in 37 hits. By looking through the

abstracts, I identified 25 of them as relevant for my thesis. Out of these, 20 were available in full length. Of the remaining five, I have only read the abstracts. I emailed the articles to my supervisor and he agreed that they were suitable for my thesis.

From March until the beginning of June 2015, I had 12 weeks to complete the thesis. In the beginning, I used a lot of time on reading articles for the background chapters. I have written the assignment chronologically, starting at the first chapter and finishing with the last. Along the way, I have been alternating between reading and writing. I used the first six weeks on the background chapters, and the next five weeks on the chapters regarding literature from Malawi, method, discussion, conclusion and finally the abstract. During the process, I have corresponded with my supervisor on email, since he has been in Malawi for most of the time. He has been helpful with reading through my chapters along the way and making comments. The last week was busy with editing and making the final touches.

4.0 Discussion

Malawi has the highest incidence of preterm birth in the world, estimated at 18.1% [4]. Studies conducted in Malawi, using the accurate method of ultrasound foetal measurements for dating of gestational age, show preterm birth rates in the range of 17-20 % in unselected women, and as high as 25-30 % in women with anaemia. The population in the studies are probably representative for much of rural Africa, which may have similar high levels of infection-related preterm birth [39,40]. Complications of preterm birth are the single largest direct cause of neonatal deaths globally, and are now the second most common cause of death after pneumonia in children under 5 years old [3,4]. The high rates of preterm birth represents a major, largely unrecognized, public health problem contributing to the high rates of neonatal mortality in Malawi. An estimate from Malawi suggests that prematurity makes at least as significant a contribution as maternal HIV infection to later infant mortality. These findings suggests that prevention of prematurity should be a priority in any attempts to tackle the problem of neonatal mortality in Malawi [39].

Studies investigation risk factors associated with preterm birth in Malawi have identified several factors that can be modified. Anaemia has been shown to increase the risk of preterm birth. Prevalence of anaemia among pregnant women in Malawi is very high. A

study using data from the APPLe trial found that over 60 % of pregnant women had anaemia (Hb <11.0) at first antenatal visit, and 7.6 % severe anaemia (Hb < 8.0). Of the women who had anaemia, only 21.4 % had anaemia at the second antenatal visit [41]. During the trial participants received tablets of ferrous sulphate daily. This shows that taking iron supplement is effective at reducing anaemia. Making effort to increase the coverage of iron supplements in the preconception and antenatal period could probably reduce the number of preterm births due to anaemia.

Adolescence and age less than 20 years at pregnancy, have been shown to increase the risk of preterm birth in Malawi [41,42]. One study investigating perceptions and experiences of preterm birth among people living in rural Malawi, reported that many participants said early childbearing was becoming more common in their community [43]. Particular emphasis must be placed on ensuring access to primary and secondary education for girls, because girls who complete their education are less likely to become pregnant in adolescence. In 2010 it was estimated that 25.2 % of Malawian girls aged 15-19 years old had unmet needs for family planning [8]. This estimate tells the proportion of women of reproductive age (15-19 years) who are married or in union and who does not want any more children, or want to wait at least two years before having a baby, and yet are not using contraception. Doctors and nurses should use every opportunity at antenatal care visits to give information about and offer prevention. The coverage of at least one antenatal visit among girls aged 15-19 years was 95.6 % in 2010. This means that using the opportunity to inform about the advantage of contraception at antenatal care visits could possibly increase the coverage in this age group, and hereby reduce the risk of preterm birth. One study reported that some community members in rural Malawi has the perception that family planning is a risk factor for preterm birth [43]. Traditional perceptions like this must be overcome through spreading of science-based information.

Both low BMI and right upper arm circumference <23 cm are risk factors of preterm birth in Malawi [41,42]. Optimizing pre-pregnancy weight would lower this risk. Malawi is an impoverished nation and 72 % of the population is living on less than $1 a day [8]. Improving food security for all inhabitants is important, so that all women in fertile age can achieve a healthy weight. A healthy diet during pregnancy is also important, as weight gain in pregnancy has been found to reduce the risk of preterm birth in Malawi [41].

Malaria is a considerable contributor to Malawi's high preterm birth rate. Several studies report rates of malaria around 30% when screening pregnant women at first antenatal visit [39,41,42]. Using insecticide-treated nets (ITN) at night is advised in malarious areas, to prevent infection. In a study on malaria prevention only one of three pregnant women reported sleeping under an ITN the previous night. Distributing ITNs and informing about its effectiveness at reducing malaria could probably increase the use.

Intermittent preventive treatment (of malaria) during pregnancy with sulphadoxine-pyrimethamine (IPTp-SP) is used in Malawi. Malawi's 2-dose IPTp-SP policy was implemented in 1993. Since then WHO has given new guidelines for IPTp-SP, recommending provision of SP at every antenatal visit, starting from the second trimester. However, in 2010 only 55% of women received 2 doses of IPTp-SP. Ninety-five percent of women reported attending at least 2 antenatal care visits, and 46% of women reported attending antenatal care ≥4 times during their last pregnancy. This highlights the many missed opportunities when IPTp-SP could have been provided [46]. Changing the policy in Malawi to providing IPTp-SP at each antenatal visit, might improve coverage of 2 doses or more. There are strong indications that this would reduce the preterm birth rate in Malawi. In one study, participants received two doses of azithromycin in addition to IPTp-SP at every antenatal visit. This reduced the preterm birth rate in the studied population with 35% [48]. Further investigation is needed on malaria-prevention, but this result was very promising.

From the study investigating perceptions and experiences of preterm birth among community members in rural Malawi, some important pointes stand out. When asked about care practices for preterm newborns, providing warmth was the main method of care. Preterm newborns loose warmth more quickly than term babies, and providing warmth is indeed very important. Usual ways to keep the newborn warm was to make fire inside the house, wrap the baby in blankets or placing bottles of warm water next to it. The use of skin-to-skin contact for providing warmth was not mentioned and the majority of participants when asked reported lack of knowledge about skin-to-skin kangaroo mother care. Kangaroo mother care is the method recommended by WHO for providing warmth to preterm babies in low-resource areas, and it should be started immediately after birth. Spreading information about this and training all mothers in kangaroo mother care could improve the survival of preterm newborns in Malawi.

Participants in another study, including community health workers (CHWs) and clinical officers, reported that delays in seeking help at the hospital for women presenting with symptoms of preterm labour was common [44]. Common barriers to leaving home included transportation, fear of the hospital and disrespectful treatment by hospital staff, and belief that nothing could be done if preterm labour occurred. Members of couples did mention that perhaps traditional healers would have medication to stop contractions. Lack of money was also often reported as a reason for not going to the hospital. Patient couples and CHWs generally had not heard of the advantage and the availability of antenatal steroids to accelerate lung maturity. One clinical officer was equally unaware of this option. The concept of intramuscular or intravaginal progesterone to prevent PTB in a woman with a history of prior PTB were new to all participants. However, the most common response to hearing this and other new information was: "Explain to us why and how this works and we might believe you". This shows that information campaigns addressing lack of knowledge among both health care workers and community members could be effective in closing these gaps and improving the care of preterm newborns.

Two studies conducted in Malawi investigating risk factors for preterm birth, surprisingly shows no association between HIV in the mother and preterm birth [41,42]. One study, specifically investigating association between adverse birth outcomes and severity of HIV infection among pregnant women naïve to anti retroviral treatment (ART), found that among women without malaria, higher placental viral load and lower CD4+ T-cell count were both significantly associated with increased prevalence of PTD [49]. The ART coverage among people in Malawi with advanced HIV infection was 63% in 2009. The estimated percentage of pregnant women living with HIV who receives ART for preventing mother-to-child transmission was 79% in 2013 [8]. This indicates that better ART coverage can be achieved, and this could in turn decrease the risk of preterm birth among pregnant women without malaria.

5.0 Conclusion

Studies conducted in Malawi, using the accurate method of ultrasound foetal measurements for dating of gestational age, show preterm birth rates in the range of 15-20 % in unselected women, and as high as 25-30 % in women with anaemia. The high rates of preterm birth represents a major, largely unrecognized, public health problem contributing to the high rates of neonatal mortality in Malawi. These findings suggests that prevention of prematurity should be a priority in any attempts to tackle the problem of neonatal mortality in Malawi.

Studies investigating risk factors associated with preterm birth in Malawi have identified several factors that can be modified. Attacking risk factors proven to be of importance in Malawi, in studies using ultrasound dated gestational age, will probably be the best way to reduce the preterm birth rate. Increasing the coverage of prevention in adolescence, promoting family planning, and changing Malawi's guidelines for prevention of malaria in pregnancy can contribute to reduction of the preterm birth rate. Focus on maternal health and nutrition in pre-pregnancy- and antenatal care is essential.

Further studies investigating factors associated with the occurrence of preterm labour is warranted. Identifying micronutrient deficiencies associated with preterm birth, and investigating the use of antibiotics for prevention of infections in pregnancy, will be especially important.

Figure 1: From figure in reference 16.

Scatterplot of Natural Logarithm Odds Ratio and Meta-regression Curves of Adverse Perinatal Outcomes According to Interpregnancy Interval in Cohort and Cross-sectional Studies.

The dose-response curve line represents estimates from a smoothed spline regression. The horizontal line at y = 0 represents no effect. Most studies provided ≥1 odds ratio estimate for several categories of interpregnancy intervals.

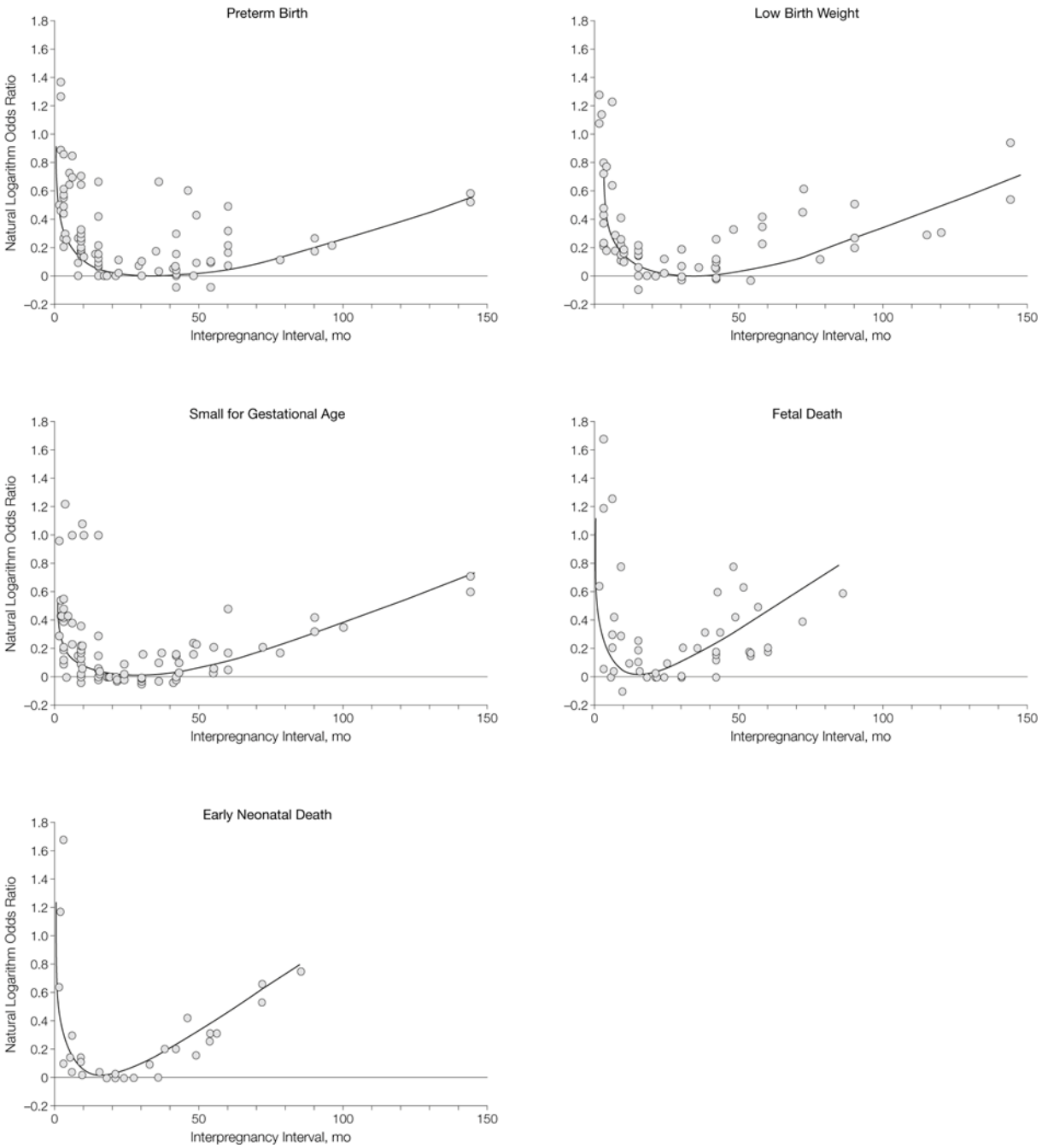

Figure 2: From figure 4 in reference [1]

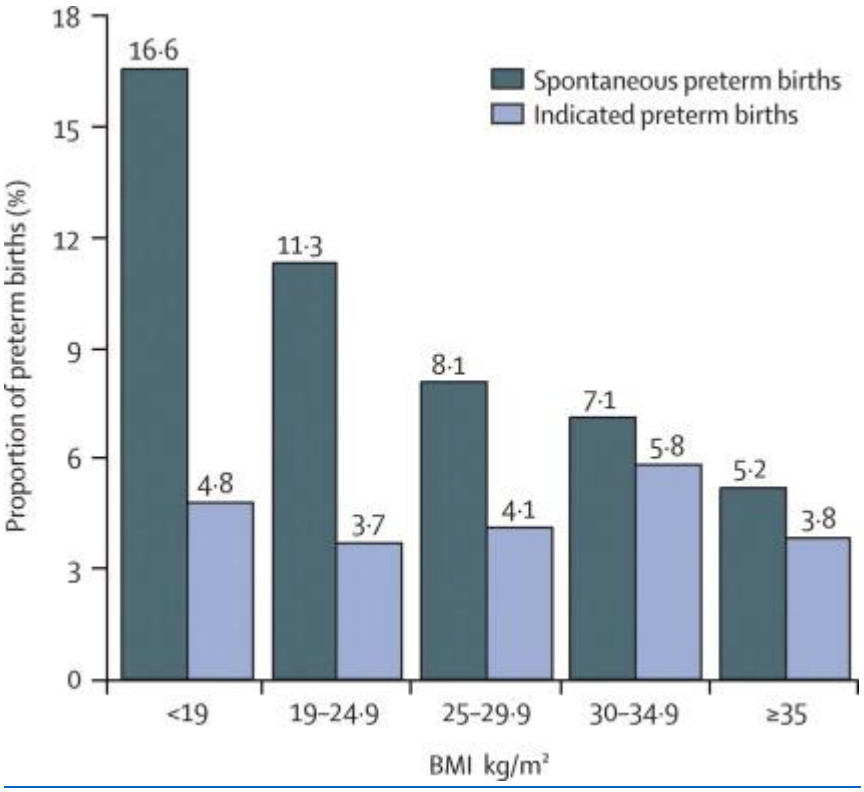

Figure 4.

Comparison of spontaneous and indicated preterm birth by maternal body-mass index (BMI)

Table 1: From table 5 in reference 16.

Table 5. Meta-analysis of Dose-Response Regression Slopes and Prediction of the Risk of Adverse Perinatal Outcomes for Interpregnancy Intervals <18 Months and >59 Months

Risk Increase	Increase, % (95% CI)		
	Preterm Birth (12 Studies)	LBW (7 Studies)	SGA (12 Studies)
Per month for intervals <18 mo*	1.92 (1.80-3.04)	3.25 (3.09-3.41)	1.52 (1.40-1.64)
Per month for intervals >59 mo†	0.55 (0.49-0.61)	0.91 (0.83-0.99)	0.76 (0.71-0.81)
Predicted by the model			
Interpregnancy interval, mo			
3	28.8 (27.0-30.6)	48.8 (46.4-51.2)	22.8 (21.0-24.6)
6	23.0 (21.6-24.5)	39.0 (37.1-40.9)	18.2 (16.8-19.7)
9	17.3 (16.2-18.4)	29.3 (27.8-30.7)	13.7 (12.6-14.8)
12	11.5 (10.8-12.2)	19.5 (18.5-20.5)	9.1 (8.4-9.8)
15	5.8 (5.4-6.1)	9.8 (9.3-10.2)	4.6 (4.2-4.9)
18-59‡	1.00	1.00	1.00
72	6.6 (5.9-7.3)	10.9 (10.0-11.9)	9.1 (8.5-9.7)
96	19.8 (17.6-22.0)	32.8 (29.9-35.6)	27.4 (25.6-29.2)
120	33.0 (29.4-36.6)	54.6 (49.8-59.4)	45.6 (42.6-48.6)
144	46.2 (41.2-51.2)	76.4 (69.7-83.2)	63.8 (59.6-68.0)

Abbreviations: CI, confidence interval; LBW, low birth weight; SGA, small for gestational age.
*Risk increase per each month that interpregnancy interval is shortened from 18 months.
†Risk increase per each month that interpregnancy interval is lengthened from 59 months.
‡Reference category.

Table 2: From table 3 in reference 43.

Most common words	Meaning
Mwanamphepo *(Chichewa/Chiyao*)	Traditional illness found in women believed to cause sores inside the womb and causes miscarriage or preterm birth
Likango (*Chichewa/Chiyao*)	Traditional illness found both in men and women. Causes preterm birth and also death to the newborn before the preterm newborn reaches one year. Can be cured by traditional medicine.
Ndaka/nsanjiko (*Chiyao*) or tsempho/moto (*Chichewa*)	Caused by sexual impurity if the husband of a pregnant woman is having sex outside marriage while the wife is pregnant.
	Sometimes caused by the pregnant woman herself if she is having sex with other men besides the husband
	Causes preterm birth if the pregnant woman carelessly eats or shares utensils with a woman who had miscarried before, had a preterm newborn or a woman who is engaging in sex
Kupyapyala (*Chichewa*)	A state of being weak and thin
Anamutembereza (*Chichewa*)	Expression of been cursed by someone

Table 3;

Definitions of vernacular terms related to perceived causes and care of preterm baby.

Table 3: From table 4 in reference 43.

Care practice for preterm newborns	The preterm newborn is not bathed until it reaches 9 months corrected gestational age
	Keeping the baby inside the house until it reaches 9 months corrected gestational age
	Windows and doors of the house are kept closed all the time
	Maintaining a clean environment (washing newborn clothes and sprinkling water around the house to control dust)
	Use of plastic bottles and bags with hot water inside to provide warmth
	Make fire inside the house to keep the house warm
	Wrap the baby with blankets
	Expressing breast milk (mothers squeezing the breast milk into a cup and using a spoon to feed the newborn)
	Couples with a preterm newborn refrain from sex until required time when couples take traditional medicine
Challenges faced in caring for preterm newborns	The preterm newborns fall sick often times
	Poverty- no money to buy paraffin, to pay hospital bills and transport, to buy warm materials and to improve the condition of the house if leaking
	Mother to preterm baby fails to do business and household chores i.e. farming and fetching firewood
	Men start having other sexual affairs outside marriage
	Lack of knowledge on how to properly care for preterm newborns

Table 4; Summary of care practices and challenges.

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