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Prevalence of hyperglycemia in pregnancy, risk factors and simplified method for identification of pregnant women at risk in Arusha, Tanzania

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NM-AIST

PREVALENCE OF HYPERGLYCEMIA IN PREGNANCY, RISK FACTORS AND SIMPLIFIED METHOD FOR IDENTIFICATION OF PREGNANT WOMEN AT RISK IN ARUSHA, TANZANIA

Safiness Simon Msollo

A dissertation submitted in partial fulfilment of the requirements for the Degree of Doctor of Philosophy in Life Sciences of the Nelson Mandela African Institution of Science and Technology

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ABSTRACT

Hyperglycemia in pregnancy is increasing in Tanzania; however, timely diagnosis is limited. This study therefore, aimed to establish the prevalence of hyperglycemia in pregnancy, risk factors and develop a simple method for identification of women with gestational diabetes mellitus in Tanzania. A cross-sectional study was conducted in Arusha City, between March and December, 2018 among 468 pregnant women at second and third trimesters. Blood glucose was tested using Gluco-Plus™ and the World Health Organization's criteria, while insulin resistance was calculated using the Homeostasis Model of Assessment formula. Anthropometrics were assessed using standard procedure and knowledge on hyperglycemia in pregnancy, demographics, and maternal characteristics were collected through face-to-face interviews using a questionnaire. The prevalence of hyperglycemia in pregnancy was 16.2% (n = 76) of which 13% had gestational diabetes mellitus and 3.2% diabetes in pregnancy. Additionally, the prevalence of insulin resistance was 21% (n=49). Knowledge about hyperglycemia in pregnancy was low on existence (10.7%, n=50), effects (23%, n=14), symptoms (26%, n=13) and risk factors (30%, n=15). Hyperglycemia in pregnancy was significantly associated with body fat percentage ≥ 38, delivery macrosomic babies, insulin resistance, mid-upper arm circumference ≥ 28 cm and family history of type 2 diabetes mellitus. These risk factors, except insulin resistance, were used to develop a risk score which was simplified into risk factors checklist to identify women with gestational diabetes mellitus. The score correctly identified 98% of hyperglycemic women, with an area under the receiver operating characteristic curve of 0.971 (95% CI 0.955-0.993, $p < 0.001$), sensitivity of 0.980 and specificity of 0.458. The high prevalence of hyperglycemia in pregnancy creates a need for regular screening and management. Hence, the developed screening method can be validated for use when resources are limited to give priority to high risk women while planning for universal screening.

DECLARATION

I, Safiness Simon Msollo, do hereby declare to the Senate of the Nelson Mandela African Institution of Science and Technology that this dissertation is my own work and that it has neither been submitted nor being concurrently submitted for degree award in any other institution.

13/08/2020

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Name and signature of the candidate

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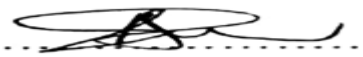

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CERTIFICATION

The undersigned certify that they have read and hereby recommend for acceptance for the dissertation entitled “Prevalence of hyperglycemia in pregnancy, risk factors and simplified method for identification of pregnant women at risk in Arusha city, Tanzania”. In partial fulfilment of the Award of Doctorate of Philosophy in Life Sciences at the Nelson Mandela African Institution of Science and Technology.

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DEDICATION

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LIST OF ACRONYMS, ABBREVIATIONS AND SYMBOLS

ACOG	American College of Obstetricians and Gynecologists
ADA	American Diabetes Association
ANC	Antenatal Care /Clinic
BMI	Body Mass Index
CI	Confidence Interval
CM	Centimeter
CREATES	Centre for Research, Agricultural, Advancement, Teaching Excellence and Sustainability in Food and Nutrition Security
DIP	Diabetes in Pregnancy
DM	Diabetes Mellitus
DHIS	District Health Information System
FANC	Focused Antenatal Care
GDM	Gestational Diabetes Mellitus
HIP	Hyperglycemia in Pregnancy
IADPSG	International Association of Diabetes and Pregnancy Study Group
IDF	International Diabetes Federation
IUFD	Intrauterine Fetal Death
IR	Insulin Resistance
Kg	Kilogram
Ml	Milliliter
MUAC	Mid-upper Arm Circumference
MoHCDGEC	Ministry of Health, Community Development, Gender, Elderly and Children
MoH	Ministry of Health
MoHSW	Ministry of Health and Social Welfare
NCDs	Non-Communicable Diseases
NIMR	National Institute for Medical Research
OGTT	Oral Glucose Tolerance Test
PIH	Pregnancy Induced Hypertension
T1DM	Type 1 Diabetes Mellitus
T2DM	Type 2 Diabetes Mellitus
WHO	World Health Organization

CHAPTER ONE

INTRODUCTION

1.1 Background of the study

Diabetes mellitus (DM) is a cluster of metabolic diseases characterized by hyperglycemia that results from defects in insulin secretion, insulin action, or both which is categorized as Type 1 diabetes mellitus (T1DM), Type 2 diabetes mellitus (T2DM), or gestational diabetes mellitus (GDM) (American Diabetes Association [ADA], 2010). Although it is difficult to distinguish the types of diabetes mellitus at onset, the real diagnosis becomes more evident over time (ADA, 2017). Type 1 diabetes mellitus or juvenile-onset diabetes, which is termed as insulin dependent, results from a cellular-mediated autoimmune damage of the beta cells of the pancreas caused by autoimmune response (ADA, 2010). In this case the defense system of the body attacks the insulin-producing beta cells resulting in failure of the body to produce the insulin it needs (International Diabetes Federation [IDF], 2013; ADA, 2010). Type 2 diabetes mellitus is the most common type of diabetes mellitus where the body produces insulin, but the production is either insufficient or uptake is ineffectual, leading to raised levels of glucose in the blood (IDF, 2013; ADA, 2010). At the molecular level, insulin resistance (IR) is usually a failure of insulin signaling, causing inadequate plasma membrane translocation of glucose transporter 4, which is the primary transporter for glucose into the cell to use as energy (Plows *et al.*, 2018). The third type of diabetes mellitus, GDM, aligns with physiological alterations during pregnancy (World Health Organization [WHO], 2013).

Hyperglycemia in pregnancy (HIP) is a common health problem resulting from either pre-existing diabetes or development of IR, which is accompanied by impaired glucose tolerance with first recognition during pregnancy (Negrato & Gomes, 2013; WHO, 2013). In other words HIP is defined as any glucose intolerance that is first detected at any time during pregnancy (WHO, 2013; Hod *et al*., 2015). This study used HIP to include both GDM and DIP, because GDM is not the only form of hyperglycemia which may first be detected during pregnancy, as diabetes in pregnancy (DIP) is a more severe form of HIP in which diagnostic criteria and glucose levels are the same as those for non-pregnant adults (WHO, 2013; Hod *et al*., 2015). Therefore, it is important to combine both GDM and DIP to include pregnant women with pre-existing diabetes in planning interventions. Moreover, DIP increases complications because of the high level of hyperglycemia and the uncertainty as to whether

the onset of hyperglycemia was prior to pregnancy or during pregnancy (Hod *et al.*, 2015). Furthermore, HIP should be considered because, in populations with high prevalence of T2DM but do not have access to screening before pregnancy, are at high risk for pre-existing diabetes mellitus (Kjos *et al.*, 1990).

During pregnancy, HIP in a form of GDM occurs due to pregnancy-induced changes in maternal glucose metabolism and insulin sensitivity, whereby demand for insulin production on the mother's pancreas increases as pregnancy continues to grow. In most instances, women meet the increased insulin demand, but failure to accommodate results in poor glycemic control (Palani *et al.*, 2014).

Although HIP disappears after delivery if it is due to pregnancy, misdiagnosis and/or mismanagement may lead to short and long-term health risks to the mother and her new born within five to ten years post-delivery (IDF, 2017; Kitzmiller *et al*., 2007). Up to 36% of women with GDM, may experience abnormal glucose tolerance postpartum, creating a need for both short- and long-term follow-up to prevent poor pregnancy outcomes as well as T2DM, and GDM in subsequent pregnancies (Russell *et al*., 2006; Tovar *et al*., 2011; ADA, 2013). Evidence shows that 2.6% to 38% of pregnant women with GDM developed T2DM within 12 weeks following delivery (Carson *et al*., 2013). Women with HIP experience; abortion/miscarriage (death before 20 weeks of gestation), and/or a pregnancy resulting into preterm birth (birth before 37 weeks of gestation), stillbirth (death after 20 weeks of gestation) and/or neonatal death (death within 28 days of life) (IDF, 2017; Wendland *et al.*, 2012).

Furthermore, these women can deliver a macrosomic baby (> 4 kg at birth) and increase birth trauma (Hartling *et al*., 2013). Macrosomic infants are at risk of hypoglycemia soon after birth because their bodies continue producing extra insulin in response to the mothers' excess glucose (Plows *et al.*, 2018). Newborns with excessive body fat stores as a result of high maternal sugar levels during pregnancy, often continue to be overweight in childhood and adulthood which may increase the risk of developing non-communicable diseases (NCDs) such as diabetes (Palani *et al*., 2014). It is also associated with caesarean section resulting from large for gestational babies (Wendland *et al*., 2012). Hyperglycemia in pregnancy can cause pregnant induced hypertension (PIH), a major risk factor for preeclampsia, which affects 25% of these women, in contrast to 5% of women without preexisting hypertension.

Also, the levels for hypertension may remain elevated beyond 12 weeks postpartum, leading into chronic hypertension (Carson *et al*., 2013).

Globally, it is estimated that 21.3 million or 16.2% of live births involved women with some form of HIP (IDF, 2017). These estimations show that 86.4% of those cases were due to GDM, 6.2% due to diabetes detected prior to pregnancy and 7.4% due to other types of diabetes (including TIDM and T2DM) first detected in pregnancy (IDF, 2017). The majority (88%) of the HIP cases were in low- and middle-income countries, where access to maternal care is limited. The pooled prevalence of GDM in Africa was 13.6% and 14.28% in the sub-Saharan African region (Muche *et al*., 2019). The reported high prevalence of HIP (GDM and DIP) globally, and in Africa, specifically, reveals a significant public health concern. The prevalence of different forms of HIP, especially GDM, often varies within a single nation depending on geo-local nuances in demographics, economics and ethnicities. For-example in Tanzania a higher prevalence was reported in urban areas with 18% in Dar es Salaam and about 20% in Kilimanjaro Region (Mwanri *et al*., 2014; Njete *et al.,* 2018).

The risk factors which predict the development of HIP in a form of GDM include: Family history of diabetes, GDM in previous pregnancy and obesity/overweight (Imoh *et al.*, 2016). Overweight/obesity ≥ 25 kg/m^2 have been reported to increase from 28% in 2015 to 31.5% in 2018 among women of reproductive age (15-49 years of age) in Tanzania (Ministry of Health, Community Development, Gender, Elderly and Children [MoHCDGEC] *et al.,* 2016; 2018). Hence, specific consideration is required as the majority of women start pregnancy while overweight/obese, which increases their chance of developing NCDs including HIP. On the other hand a woman with tendency of delivery macrosomic babies and/or stillbirth in previous pregnancies, previous intrauterine fetal death (IUFD), and preterm delivery might have HIP in the previous pregnancies which was undiagnosed (Imoh *et al*., 2016).

In addition, sedentary lifestyles, poor dietary intake, smoking habits, and extreme pregnancy weight gain accompanied by high body fat accumulation, places women at high risk for HIP. This is due to fact that, body fat percentage can alter body composition leading to HIP and other complications, such as pregnancy induced hypertension (PIH) and predisposition of the newborn to overweight or obese later in life (Jensen *et al.*, 2005; Ay *et al.,* 2009). It can also affect fetal growth; therefore, assessment of changes in body fat content is important to understand the effects of maternal health on neonate and future child health (Reilly *et al.*, 2005). The overt symptoms of GDM are rare, making it difficult to identify women who need

testing as it may be difficult to distinguish from normal pregnancy symptoms which need the inclusion of risk factors for easy identification of women who need additional tests. This creates a need for appropriate interventions to screen, prevent and/or manage HIP (IDF, 2017).

The Ministry of Health and Social Welfare (MoHSW) and Tanzania Diabetes Association through the Case Management Desk Guide, which is focusing on chronic NCDs such as cardiovascular disease, T2DM and cancer has included GDM. This guideline included GDM as a risk factor and criteria for screening DM although not well explored (MoHSW & Tanzania Diabetes Association, 2013). In addition, the Standard Treatment and Essential Medicines List guideline has included and reported that GDM screening has to be done using fasting plasma blood and 2 hours oral glucose tolerance test (OGTT) as well as management throughout pregnancy and post-delivery (MoHSW, 2013). Although GDM has been included in some guidelines in Tanzania, there is low emphasis on the antennal care (ANC) guidelines which may have contributed to low consideration of GDM in the regular ANC programs offered. This may be attributed by fragmentation of care caused by poor coordination of the health system and/ or emanating costs.

The current Focused Antenatal Care (FANC), has abandoned the traditional ANC (Kearns *et al.*, 2014), which involved numerous visits and accurate identification of high-risk individuals. This traditional ANC was found to present challenges in resource-constrained settings which encouraged the exploration of the FANC model, based on an individualized, targeted approach, to detect complications as they arise (Kearns *et al*., 2014). This practice fails to recognize that, prevention is better than waiting until when the problem develops and subsequently treating.

Furthermore, the FANC model suggests ANC visits to take place before 12 weeks, at 26 weeks, at 32 weeks, and between 36-38 weeks with a strict checklist of assessments and interventions to be included in each of the four visits (Kearns *et al*., 2014). This is challenging because, women who do not attend all visits, do not receive important interventions, which may risk the health of both women and newborns. Hence, due to late initiation of ANC or poor attendance (Ramaiya *et al.*, 2018), there is a need to include risk factor identification during the first visit or even before pregnancy for preventative purposes. These factors can help in self-identification before pregnancy and/or assessed during history taking and applied in the counselling session or during the regular ANC education programs.

Early diagnosis and identification of women at risk, is essential for proper management and treatment of GDM to prevent future complications (Mwanri *et al*., 2014).

The FANC model integrates ANC with care and counselling related to several other conditions and women are immunized against tetanus, tested and treated for anaemia, vitamin A, or iodine deficiencies. They also receive testing and, if necessary, treatment for Human Immunodeficiency Virus or acquired immunodeficiency syndrome (HIV/AIDS), sexually transmitted infections (STIs), malaria and tuberculosis (Kearns *et al*., 2014) however, HIP screening and management has not been prioritized among services offered. The Tanzania National Health Policy on the other hand, has put more efforts in expanding, improving and distribution of the reproductive, maternal, newborn, child and adolescent health services to the target population. The main services are related to family planning, pregnancy, sexually transmitted diseases, gender based violence, violence against children, female genital mutilation, harmful traditional practices, breast and cervical cancer screening, prevention and treatment of infertility (MoHCDGEC, 2017). However, HIP (GDM and DIP) is not mentioned as a priority health condition in the health policy while this policy is the source of many health related guidelines.

The implementation of maternal and child health programs in Tanzania may be affected by several drawbacks that have been reported in a study done to assess the capacity and capability of Tanzania health facilities to diagnose and manage GDM. These drawbacks include understaffing, late initiation of ANC and limited screening for GDM due to lack of equipment and supplies (Ramaiya *et al.,* 2018). Also, the facility staffs were under-trained and received fewer refresher courses in diabetes. These ranges from 0–5% for diabetes as compared to hypertension (4–6%), other NCDs (0–16%), Prevention of Mother to Child Transmission (39%), management of postpartum bleeding (31%) and HIV/AIDs (31%) (Ramaiya *et al.,* 2018). These drawbacks may have also affected the screening and management of diabetes including HIP which creates a need to address the existing gaps on screening, managements and knowledge, to better incorporate HIP in the ANC services. Evidence-based findings are thus urgently needed to provide best practice standards for testing, management and care of women with HIP (Hod *et al*., 2015).

The guidelines for screening HIP in a form of GDM varies from universal to selective methods. The universal screening and diagnosis recommendation include oral glucose tolerance test (OGTT) using one step provision of 75 g or two steps provision of 50 g

followed by 100 g of glucose solution, and fasting glucose plasma test (Sharma *et al*., 2013; International Association of Diabetes and Pregnancy Study Group [IADPSG], 2010; WHO, 2013; ADA, 2014). The common selective screening strategies include simple identifiable maternal and clinical risk factors (ADA, 2010). The fasting screening test needs a woman to stay without eating anything for 8-12 hours and OGTT needs a woman to remain in the ANC for more than 2 hours where multiple samples for analysis are needed increasing, the workload of the care providers and testing costs (Agarwal *et al*., 2011; Pastakia *et al*., 2017). The risk score can be a good option, but the identification of risk factors may be difficult and complex arithmetic's are involved. Considering the doubling rate of the population and concomitant resource constraints, it is important to determine early predictors of pregnancy complications to plan for early prevention strategies (Lekva *et al*., 2010). Hence, as HIP contributes to poor pregnancy outcomes, it is important to be given priority like other pregnancy conditions listed in the FANC model. However, due to limited resources there is need to develop a screening method which is sensitive and administrable by lesser trained health workers or self-administered (Agarwal *et al*., 2011; Utza *et al*., 2017). This can give priority to high risk women for thorough glucose control before conception for effective preparations before pregnancy, throughout pregnancy, and during post-delivery period.

Early identification of women at risk of HIP and performing additional testing in selected women, minimizes inconvenience for pregnant women, as well as saves time and healthcare costs (WHO, 2013). Hence, cost-effective models must be developed and individualized by country for optimal testing and managing of GDM given their specific burden of disease and resource gaps (Hod *et al*., 2015). This study therefore, aimed to determine the prevalence of HIP, IR and their determinants to develop a simplified method which can be incorporated in ANC for identification of women with/at risk of GDM to prevent poor pregnancy outcomes where universal screening is challenging. The study also aimed to understand knowledge gaps on HIP, for appropriate intervention to enhance self-care among pregnant women.

1.2 Statement of the problem

Globally, child and maternal mortality is decreasing significantly, although Sub-Saharan Africa continues to have the highest child mortality at about twice the global mortality rate (Morton *et al*., 2017). In Tanzania, the rate of under-5 mortality has decreased significantly from 81 in 2010 to 67 per 1000 death in 2015 while neonatal mortality has a slower decrease rate from 26 in 2010 to 25 deaths per 1000 in 2015. (National Burew of Statistics [NBS],

2011; MoHCDGEC *et al*., 2016). Furthermore, maternal mortality ratio has increased from 454 in 2010 to 556 deaths per 100 000 live births in 2015 (NBS, 2011; MoHCDGEC *et al*., 2016). Most of these neonatal and maternal deaths could be prevented by providing high-quality care during pregnancy and at birth, as children are most vulnerable in the first 28 days of life (neonatal period) (Morton *et al*., 2017). In addition, due to the doubling rate of overweight and obesity among Tanzanian women of reproductive age in urban areas (MoHCDGEC *et al*., 2016), many women may start pregnancy while overweight or obese which increases their chances of developng NCDs such such as diabetes, and cardiovascular diseases.

Therefore, inaction to maternal and child health agenda may lead to increasing mortality and morbidity burden in the future which can impact the social capital of the nation. In this case, pregnancy as a window of opportunity for maternal and child health, has been given specific consideration in the Sustainable Development Goal number three (SDG 3), to reduce global maternal death to less than 70 per 100 000 live births, end preventable neonatal deaths to atleast 12 per 1000 live births, and children under five years to 25 per 1000 live births (Morton *et al*., 2017). It also aims to reduce by one third premature mortality from NCDs through prevention and treatments (Morton *et al*., 2017). This created a need to conduct a study in Arusha District, which has a high prevalence of T2DM especially in urban (22.9%) compared to rural (9.9%) areas, which may, in part, be the aftermath of previously undiagnosed and unmanaged HIP (Masaki *et al*., 2015). This is because screening and management for HIP are not commonly practiced in ANC in Tanzania. As the progression of HIP to T2DM may augment the T2DM prevalence (Zhu & Zhang, 2016), HIP (GDM and DIP) and its determinants need attention to avert future health impacts.

1.3 Rationale of the study

Screening for HIP is an important step for management however, it has received little attention in Tanzanian ANC guideline as compared to HIV/AIDS, malaria and tuberculosis (Ramaiya *et al*., 2018) which may be attributed by limited resources. This creates a need for developing a simple selective method with less costs for screening and managements of HIP. It is therefore, important to recognize that, countries opt for their own diagnostic and management criteria due to resource constraints and applicability in their settings. Some guidelines recommend universal screening by oral glucosetolerance test (OGTT) and or fasting blood glucose test for all pregnant women (WHO, 2013) while others exempt low risk

women from testing (ADA, 2010). There is lack of evidence on how universal strategies improve maternal/child health compared to selective strategies, given the increase in associated costs, clinician workloads, and potential inconveniences (Farrar *et al.*, 2017). Hence, the design and implementation of programs to screen and manage HIP need to be determined by individual countries, considering their differences in glucose intolerance, competing priorities, resource availability and gaps.

Several selective screening strategies have been developed in different settings and population groups for detection of undiagnosed diabetes and identification of women at risk. However, most strategies have been developed in Caucasian and Asian populations (Naylor *et al*., 1997; Caliskan *et al*., 2004; van Leeuwen *et al*., 2010; Teede *et al*., 2011; Sweeting *et al*., 2017) with few based in African populations (Fawole *et al*., 2014; Adam & Rheeder, 2017; Nombo *et al*., 2018). The developed risk scores cannot be generalized due to differences in methods used to identify risk factors which vary across countries depending on the research design, selection of participants and diagnosis criteria used (Adam & Rheeder, 2017). In addition, risks for HIP varies within and across settings due to differences in body composition, lifestyle, health care systems and genetic predisposition among certain high-risk racial/ethnic groups (Kim *et al*., 2013; Tarquini *et al*., 2014).

Furthermore, most selective strategies do not consider body fat percentages which is simple to measure for assessing nutritional status during pregnancy compared to pre-pregnancy BMI and or weight gain which depends on an individual's ability to recall her pre-pregnancy weight and early starting of ANC. The previous risk score developed in Tanzania inluded mid upper circumference (MUAC) ≥ 28 cm, previous stillbirth, and family history of T2DM as significant risk factors for GDM, calling for further development of a tool that involves more risk factors such as maternal age, macrosomic delivery, pre-pregnancy BMI, hypertension and pregnancy weight gain (Nombo *et al*., 2018).

This study therefore, aimed to establish the prevalenc of HIP, IR and associated risk factors to develop a risk score which can be simplified into a cheklist for Tanzania's ANC setting. This can be applied during regular ANC education to enable high risk women understand their condition, to take responsibility of visiting their health practitioners on their own initiative and alter their lifestyles including; poor dietary intake and low physical activities (Koning *et al.*, 2016).

1.4 Objectives

1.4.1 General objective

To determine the prevalence of hyperglycemia in pregnancy, insulin resistance, their determinants and knowledge gaps, as well as develop a simplified method for identification of pregnant women at risk of gestational diabetes mellitus in Arusha Urban, Tanzania.

1.4.2 Specific objectives

(i) To determine the prevalence of hyperglycemia in pregnancy among pregnant women attending selected ANC sites in Arusha Urban.

(ii) To assess risk factors associated with hyperglycemia in pregnancy among pregnant women attending select ANC sites in Arusha Urban.

(iii) To determine the prevalence of insulin resistance among pregnant women attending selected ANC sites in Arusha Urban.

(iv) To assess the determinants of insulin resistance among pregnant women attending selected ANC sites in Arusha Urban.

(v) To assess knowledge regarding hyperglycemia in pregnancy among pregnant women attending selected ANC sites in Arusha Urban.

(vi) To develop a risk score for selective screening of pregnant women at risk of gestational diabetes mellitus in selected ANC sites in Arusha Urban.

1.5 Research questions

(i) What is the prevalence of hyperglycemia in pregnancy and its associated factors among women in Arusha Urban?

(ii) What is the prevalence of insulin resistance and its relationship with hyperglycemia in pregnancy among pregnant women in Arusha Urban?

(iii) What is the level of knowledge on hyperglycemia in pregnancy among pregnant women in Arusha Urban?

(iv) Which risk factors were included in the model and how many women with GDM were identified using risk scores in Arusha Urban?

(v) What is the performance of the risk score in identification women at risk of GDM compared to fasting, urine and OGTT methods in Arusha Urban?

1.6 Significance of the study

The study determined prevalence of HIP (that is GDM and DIP) among women attending ANC in Arusha, Tanzania and developed a risk score which was simplified into a checklist for rapid identification of women with or at risk of GDM. The developed checklist can help in selective screening to give priority to the high-risk women when resources are limited while improving evidence-based treatments and practices in Tanzania. The study also established the prevalence of IR and provided information on the level of HIP knowledge among pregnant women in Arusha. This helps to build knowledge of HIP in Tanzania to prevent poor pregnancy outcomes and mitigate associated long-term health effects. This approach provides evidence to the policy makers to potentiate future application in the country for appropriate and cost-effective interventions for testing HIP and provision of knowledge for enhancing self-care to improve management.

1.7 Delineation of the study

This cross sectional study was done to establish the prevalence of hyperglycemia in pregnancy (HIP) to include both gestational diabetes mellitus (GDM) and diabetes in pregnancy (DIP) as well as insulin resistance (IR) and their associated risk factors. These helped to develop a simplified selective screening strategy for early identification of pregnant women at risk of GDM to give priority to high risk women for proper use of limited resources.

Knowledge on HIP was also assessed to understand the gaps for evidence based intervention to be planned to enhance self-care among pregnant women. The study covered urban areas of Arusha City with high prevalence of type 2 diabetes mellitus which may be partly attributed by undiagnosed and unmanaged HIP. The study involved 468 randomly selected pregnant women at second and third trimesters, attending ANC at Kaloleni and Ngarenaro health centers in 2018.

CHAPTER TWO

LITERATURE REVIEW

2.1 An overview of the study

Hyperglycemia in pregnancy is a public health problem that affects a significant portion of the population. The incidence of HIP increases in the presence of identifiable predisposing factors and, concomitantly decreases in the absence of risk factors, suggesting selective screening to be a cost-effective option in population health determination (Ben-Haroush *et al.*, 2003). Higher prevalence of HIP in women with at least one risk factor compared to the general population implies that selective screening and/or counselling of high-risk groups could be a better option in sub-Saharan Africa due to limited resources. However, the use of selective screening needs to establish a simple, suitable and acceptable strategy for identifying women at risk in sub-Saharan Africa (Mwanri *et al.*, 2015). Hence, Tanzania, as a resource-constrained sub-Saharan country, needs a simple to apply with less cost method for early identification and management of GDM to prevent its short- and long -term effects to the mother and her newborn.

2.2 Etiology of hyperglycemia in pregnancy in forms of gestational diabetes mellitus

During a normal pregnancy, the mother's body undergoes a series of physiological changes to support the demand of the growing fetus including; adaptation of the cardiovascular, renal, hematologic, respiratory, and metabolic systems. An important metabolic adaptation is insulin sensitivity, which changes in accordance with varying needs over the course of pregnancy. During the early gestational stage, insulin sensitivity increases, promoting the uptake of glucose into the adipose stores to prepare for the future energy demands of the pregnancy however, as pregnancy proceeds, placental hormones promote a state of IR (Di-Cianni *et al.*, 2003; Catalano *et al.*, 1991).

Hence, pregnancy is associated with IR and hyperinsulinemia which may predispose women to develop GDM (Alfadhli, 2015). Insulin resistance during pregnancy is the inability of a defined concentration of insulin to affect an expected biological response of nutrient metabolism at the level of the target tissue, which result from increased maternal adiposity and insulin-desensitizing effects of placental hormones (Lain & Catalano, 2007; Buchanan & Xiang, 2005). This occurs when pancreatic β-cells are unable to produce sufficient insulin to

offset IR which starts near mid-pregnancy and persists in the third trimester to levels similar to T2DM individuals (WHO, 2013; Buchanan & Xiang, 2005). If IR becomes dominant, the women develop hyperglycemia with IR increasing progressively until delivery, when it often quickly disappears in most cases (Ben-Haroush *et al.*, 2003).

As pregnancy progresses, the production of placental hormones, such as estrogen, progesterone, cortisol, and lactogen also increases, hindering the functions of insulin and gradually reducing insulin sensitivity to 50% of the expected value (McLachlan *et al.*, 2006). These placental hormones cause enlargement of the islets of Langerhan cells and/or the hyperplasia of the pancreatic β-cells (Ramiya *et al.*, 2000) to increase the secretion of more insulin, resulting in compensated hyperinsulinaemia (Ryan *et al.*, 1985).

In addition to placental hormones, many metabolic changes during pregnancy increase adipose tissue which produces numerous adipocytokines which can act as hormones involved in regulation of maternal metabolism and gestational IR like adipokines (tumor necrosis factor [TNF]-alpha and leptin). These can impair insulin signaling which leads into to IR condition (Wiznitzer *et al.*, 2009; Retnakaran *et al.*, 2009; Palani *et al.*, 2014). Insufficient insulin secretion to offset the decreased insulin sensitivity may result in development of GDM (Palani *et al.*, 2014).

The fasting plasma glucose, leptin, progesterone and cortisol significantly increase, as evidenced by pregnant women who develop GDM as the rate of insulin-stimulated glucose uptake is reduced by up to 54% in GDM affected women (Ngala *et al.*, 2017; Catalano, 2014). As GDM and T2DM share a similar genetic background, and IR represents an important risk factor for T2DM (Kwak *et al.*, 2012), screening for IR can be a strategy for identifying high-risk women for appropriate actions to be taken to prevent GDM and T2DM. With this association, there is a need to establish the prevalence of HIP and IR, given the high prevalence of T2DM that is reported in urban areas of Arusha Region (Masaki *et al.*, 2015).

2.3 Risk factors for insulin resistance and hyperglycemia in pregnancy

Hyperglycemia in pregnancy is related to potential risk factors such as history of stillbirths, high parities, MUAC > 28 cm, family history of diabetes, advanced maternal age, and overweight/obesity (i.e., BMI > 25 kg/m^2) (Asare-anane *et al.*, 2014; Buhling *et al.*, 2004; Mwanri *et al.*, 2014). Most women with GDM are obese however, those who are not obese

by traditional weight criteria may have an increased percentage of body fat distributed predominantly in the abdominal region which increases the risk of GDM (ADA, 2010).

Pregnancy is associated with increased maternal adiposity and storage of carbohydrate and fat, possibly as an evolutionary adaptation to facilitate successful lactation. If body fat accumulation becomes excessive, it may cause diabetes mellitus, high blood pressure, or other complications during pregnancy (Ay *et al.*, 2009). Studies on people with T2DM have identified that, fat deposition within skeletal muscle and liver cells is a major contributory factor to IR but, it is not well explored on whether fat deposition during pregnancy explains the development of IR (Ravikumar *et al.*, 2005).

Pregnancy BMI reported as degrees of overweight or obesity is a commonly used indicator to determine nutrition status in pregnancy; though, it does not distinguish between fat and lean body mass (Kotnik & Golja, 2012). In addition to late staring of the ANC, most women start their pregnancy without knowing their weights, making it difficult to estimate their BMI and weight gain during pregnancy which is strongly correlated with fat mass change (Berggren *et al.*, 2016). Measuring body fat content is very important because, in addition to fat and lean body mass, the fetal mass and amniotic fluid represent unknown contributions to the total body mass, which are not distinguished by BMI calculation (Fakier, *et al*., 2017). However, more exploration of the appropriate stage in pregnancy at which body fat percentage can be estimated is needed.

Monitoring a total weight gain could be a good indicator and simple to determine but, it is based on the pre-pregnancy BMI which also relies on ability of the pregnant women to recall her pre-pregnancy weight. Weight during pregnancy can also be estimated before 16 weeks of gestation which depends on early initiation of the first ANC visit (Institute of Medicine [IOM], 2009; Siega-Riz *et al.,* 2009), but is often impractical in Tanzania's ANC context where most of the women cannot recall their pre-pregnancy weights and start the first ANC visit late (Mwanri *et al*., 2014). The delayed start of the first ANC visit is one of the challenges in FANC guideline implementation in Tanzania where only 20% of women attended their first ANC visit during the first trimester of pregnancy (Kearns *et al*., 2014).

Dietary intakes before and during pregnancy can influence glucose level of the woman (Macaulay *et al.*, 2014), which depends on the type of food and nutritional contents. High glycemic index (GI) foods, including rice, white bread, and potatoes, cause a sharp rise in

blood glucose levels which decline rapidly. On the other hand low GI foods; such as fruits or dairy products, introduce slowly digestible carbohydrates which result in a lower postprandial glucose response (Brouns *et al.*, 2005; Zhang *et al.*, 2006). There is a significant positive associations of maternal dietary heme iron intake with the risk of GDM potentially due to the predominant heme-iron contribution from animal sources, including red meat and poultry which are also increasing the effects of fat accumulation hence HIP (Qiu *et al.*, 2011).

Some vitamin deficiencies may increase the risk of HIP, such as Vitamin D which is a fat-soluble hormone known to play a role in maintaining calcium homeostasis and bone integrity including its role in glucose metabolism, angiogenesis, inflammation and immune function. It also regulates gene transcription and expression (Mousa *et al.*, 2015) however, micronutrients assessments need more resources for laboratory analysis. As they can simply be included in dietary counselling, there is no need of including them in screening strategies.

Advanced maternal age is an established risk factor for GDM, and may be a result of age-related changes, which are particularly characterized by an impaired response to glucose challenge, which is partly due to physical inactivity and a decrease in muscle mass. This may have a similar effect on IR in pregnant women, which needs more exploration (Kuo *et al.*, 2017). Studies done in Bangladesh and India have reported that, the odd of GDM is increasing with age > 25 years (Begum *et al.*, 2017; Seshiah *et al*., 2008).

Family history of T2DM has been reported as a potential determinant for GDM in several studies in Africa and outside Africa (Asare-anane *et al.*, 2014; Nombo *et al.*, 2018). The influence of T2DM on development of GDM may be due to genetic predisposition as a result of belonging from high-risk racial/ethnic groups (Tarquini *et al.*, 2014). This have been reported in Bangladesh that, 74.4% of the GDM patients had family history of DM compared to 39.1% among normal pregnant women (Monir *et al*., 2018). This shows how family history of diabetes contributes highly in the development of GDM. Hence, early identification of these women even before pregnancy could help to lower the risk of developing GDM and later on T2DM through controlling of their lifestyles (Monir *et al*., 2018).

The association between parity and diabetes is strongly linked to obesity and age. Women with higher parity normally are older and more obese (Dode & dos Santo, 2009). Obesity is an intermediate outcome in the causal pathway between parity and GDM, possibly a facilitating factor; however, age is a potential confounder in the relationship between parity

and GDM (Dode & dos Santo, 2009). Likewise, parity is not directly linked to insulin sensitivity deterioration, to fasting plasma glucose increase during pregnancy, or to the occurrence of GDM, though it is linked through the mediation of progressive ageing and weight gain either before or during pregnancy (Seghieri *et al*., 2005).

Preeclampsia is defined as a new onset of hypertension with blood pressure consistently > 140/90 mmHg in previously normotensive women and new onset proteinuria (defined as > 300 mg per 24 hours or > 2+ by dipstick) occurring after the 20th week of gestation accompanied by the presence of edema (American College of Obstetricians and Gynecologists [ACOG], 2003). Insulin sensitivity in late normal pregnancy is 45% to 70% lower than that of non-pregnant women; however, it plays a major role in T2DM development and in the pathogenesis of hypertension, dyslipidemias, and coronary artery diseases (Cunningham *et al.,* 2010; ACOG, 2003). Almost all obese women with hypertension have elevated insulin and the highest levels occur in obese women with excessive abdominal adipose tissues (Cunningham *et al*., 2010; ACOG, 2003).

Also, in pregnant women, obesity is a consistent risk factor for preeclampsia. Insulin resistance may lead to hypertension by changes in the levels of intracellular sympathetic nervous system over activity and renal sodium retention (Kaplan, 1994). Maternal mid-trimester IR increased significantly with increasing BMI and subsequent preeclampsia which is a combination of hypertension, proteinuria and edema (Hauth *et al*., 2011). Women who develop preeclampsia have higher insulin levels before clinical evidence of disease than women who remain normotensive during pregnancy (Malek-Khosravi & Kaboudi, 2004). This creates a need for early identification of women at risk of the conditions for appropriate interventions to prevent short- and long-term health effects to the mother and her newborn.

Increased maternal adiposity, as a result of high fat accumulation and placental hormones, is attributed to insulin-desensitizing effects which lead to gestational insulin resistance. Additionally, both increase pre-pregnancy BMI and weight gain during pregnancy are positively associated with gestational insulin resistance and obesity is a risk factor for GDM (Catalan *et al*., 1998; McIntyre *et al*., 2020).

2.4 Knowledge of hyperglycemia in pregnancy among pregnant women

Hyperglycemia in pregnancy is increasing in different parts of Sub-Saharan Africa including Tanzania. Despite the increasing prevalence of HIP and its effects, the majority of the

pregnant women, and other community members may be unaware of its existence, risk factors, and its associated consequences which may delay diagnosis, prevention and management. As knowledge is an important component of health literacy, insufficient knowledge about any disease leads to poor understanding of medical information limiting adherence to management strategies and, in the case of GDM, may contribute to adverse pregnancy and post-natal outcomes (Koning *et al.*, 2016; Baker, 2006). Adequate knowledge about HIP will potentiate opportunities to adopt healthier lifestyles and better healthcare-seeking patterns (Elamurugan & Arounassalame, 2016).

This needs attention from healthcare providers to raise awareness among pregnant women as undiagnosed and unmanaged GDM may subject the women and newborns to increased health effects (Staynova *et al.*, 2017; Lehnen *et al.*, 2013). A study done in Ghana showed a significant relationship between knowledge and risk factors which implies that the higher the level of knowledge on GDM and on its risk factors leads to proper management and lastly better outcomes (Azu & Essel, 2017). Another study done to assess the perceived risk of GDM using theoretical models of risk perception found that, women who had greater perceptions of risk, more often intended to improve their behavior in the future (Kim *et al*., 2007). Another study reported that, having a higher 2 hours OGTT value in pregnancy was associated with higher rates of return, since women are generally aware of the risk of developing T2DM after having a GDM diagnosis (Zera *et al*, 2013).

In Tanzania, there is limited evidence regarding knowledge about HIP, which leads to a research imperative to assess knowledge among pregnant women. It is important to understand that, knowledge on a disease and its consequences can lead to behavior change as it makes an individual to understand or become aware of the condition, its effects and prevention strategies. Therefore, a person can take actions accordingly to prevent the occurrence of the condition, leading to a new behavior development. This can be explained by behavior change model which demonstrates how knowledge may cause an individual to be aware on different aspects of the condition and decide to take actions to change behaviors accordingly (Fig. 1).

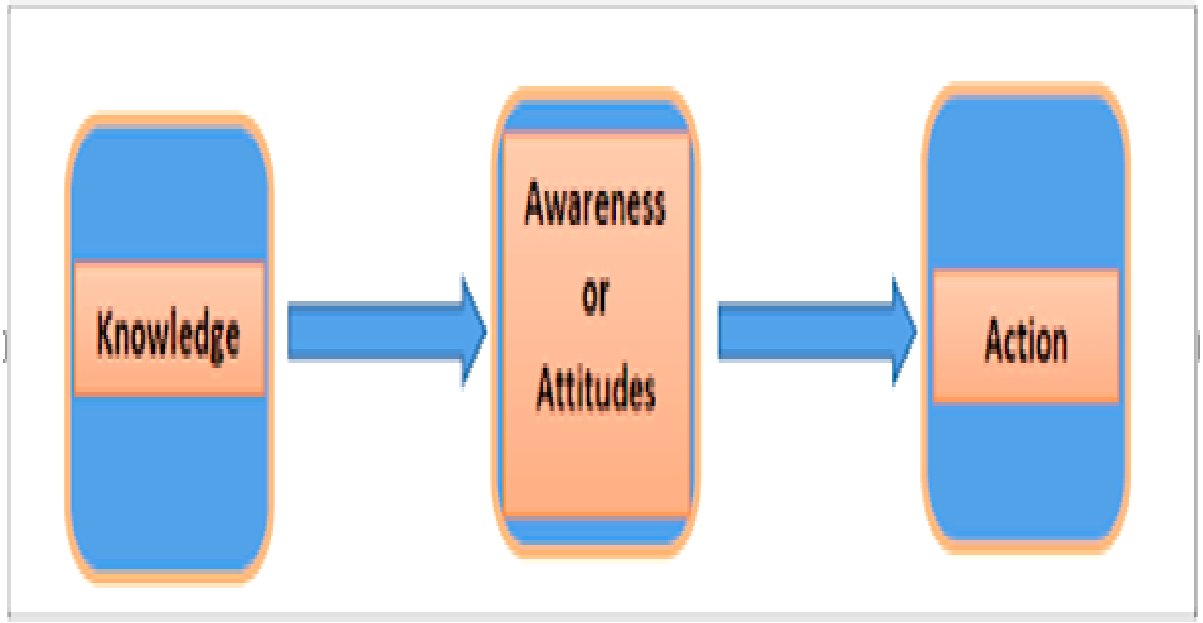


Figure 1: General behavior change model (Hungerford & Volk, 1990)

The interaction between knowledge and behavior change can be explained well by the Health Belief Model (HBM) (Irwin, 1974; Janz & Marshall, 1988). The HBM is a cognitive model suggesting that, behavior is determined by beliefs about threats to an individual's well-being, as well as the effectiveness and outcomes of particular actions or behaviors (Irwin, 1974; Janz & Marshall, 1988). This model was developed to understand the reasons for failure of people to adopt disease prevention strategies or screening tests for early detection of disease, which relates much with the current study.

The HBM explains that, after having knowledge of the condition, behavior change occurs when people feel to be personally vulnerable to the health threat or condition, and view the possible consequences of the condition as severe. People must see that, taking action may either prevent or reduce the risk at an acceptable cost with few barriers. In addition, a person must have self-efficacy to execute and maintain the new behaviors (Irwin, 1974; Janz & Marshall, 1988) (Fig. 2). At this point, internal and external factors are required to ensure that the acquired behavior is maintained. These factors may include different sources of information such as media, relatives, family and in the case of pregnant women, the regular ANC education program can be an external factor.

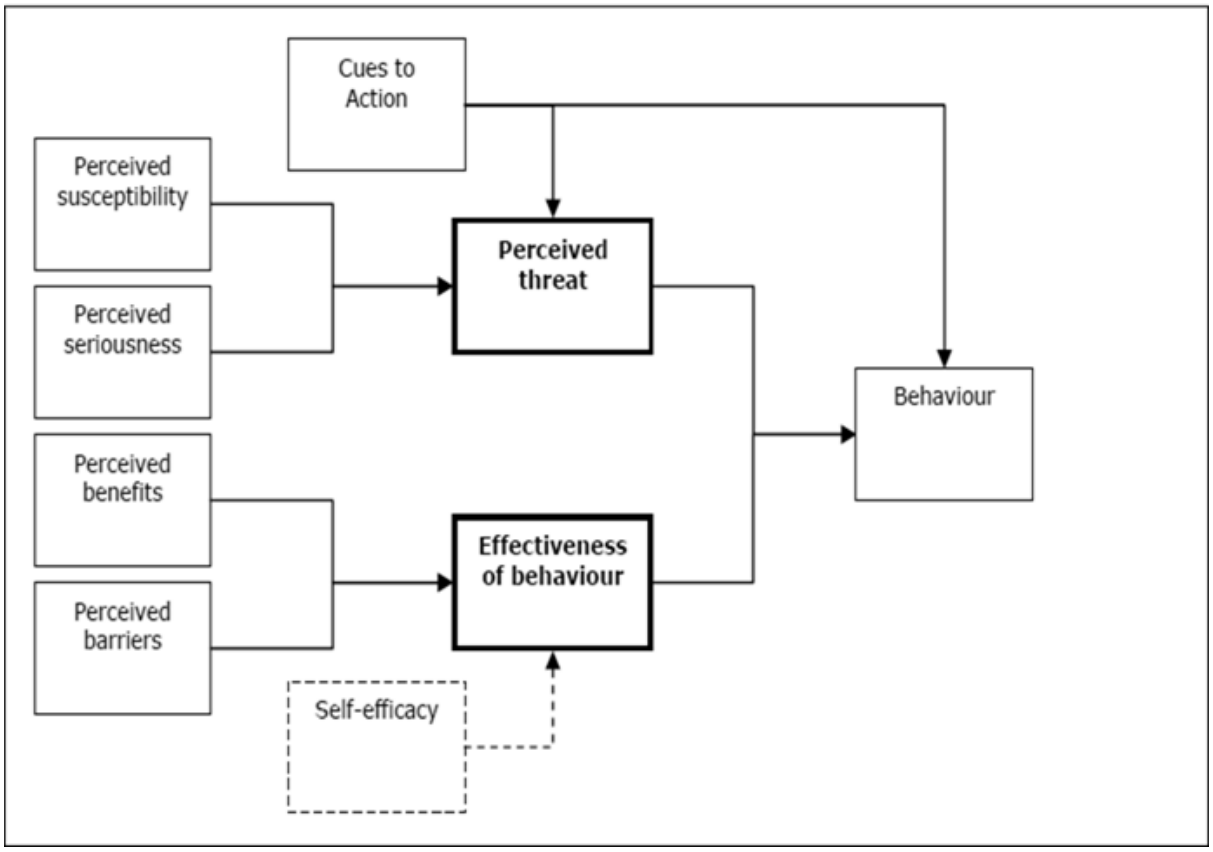


Figure 2: The health belief model (Irwin, 1974; Janz & Marshall, 1988)

2.5 Methods of screening for gestational diabetes mellitus

Timely diagnosis of GDM is the first step towards effective management and prevention of adverse outcomes however, the case detection of GDM in sub-Saharan Africa remains sub-standard (Macaulay *et al.*, 2014; Mwanri *et al.*, 2015). The WHO has adopted the criteria developed by the International Association of Diabetes and Pregnancy Study Group (IADPSG) for the diagnosis of GDM which recommends universal screening of all pregnant women using OGTT and/or fasting blood glucose test (Metzger *et al.*, 2010; Wendland *et al.*, 2012).

The use of OGTT and/or fasting blood glucose test may also be a good approach but has limited applicability for GDM screening in resource constrained sub-Saharan Africa where the testing requirements are prohibitive and/or inconvenient for the women who must travel long distances, for ANC in fasting state and incur additional transport costs (Ntui *et al.*, 2013; Mrisho *et al.*, 2009). Moreover, women who are not informed during an earlier visit or forget to come in fasting state, require a successive visit for the test. Several samples are required for glucose testing which becomes a burden to the woman and healthcare personnel (Agarwal *et al.*, 2011). The associated costs for IADPSG testing standards are unaffordable by the

majority of low-income clients and the method requires women to stay at the ANC for more than two hours without eating (Agarwal *et al.*, 2011; WHO, 2013).

On the other hand, universal screening by using fasting serum insulin can be a sensitive method because the main mechanism for HIP is dysfunction of pancreatic beta cells, manifesting in IR during pregnancy (Reece *et al.*, 2009). Hence, this indicator could be a helpful parameter in individualization of treatment and early prevention of complications, but it is very expensive compared to other methods and often not applicable to scarce resource settings.

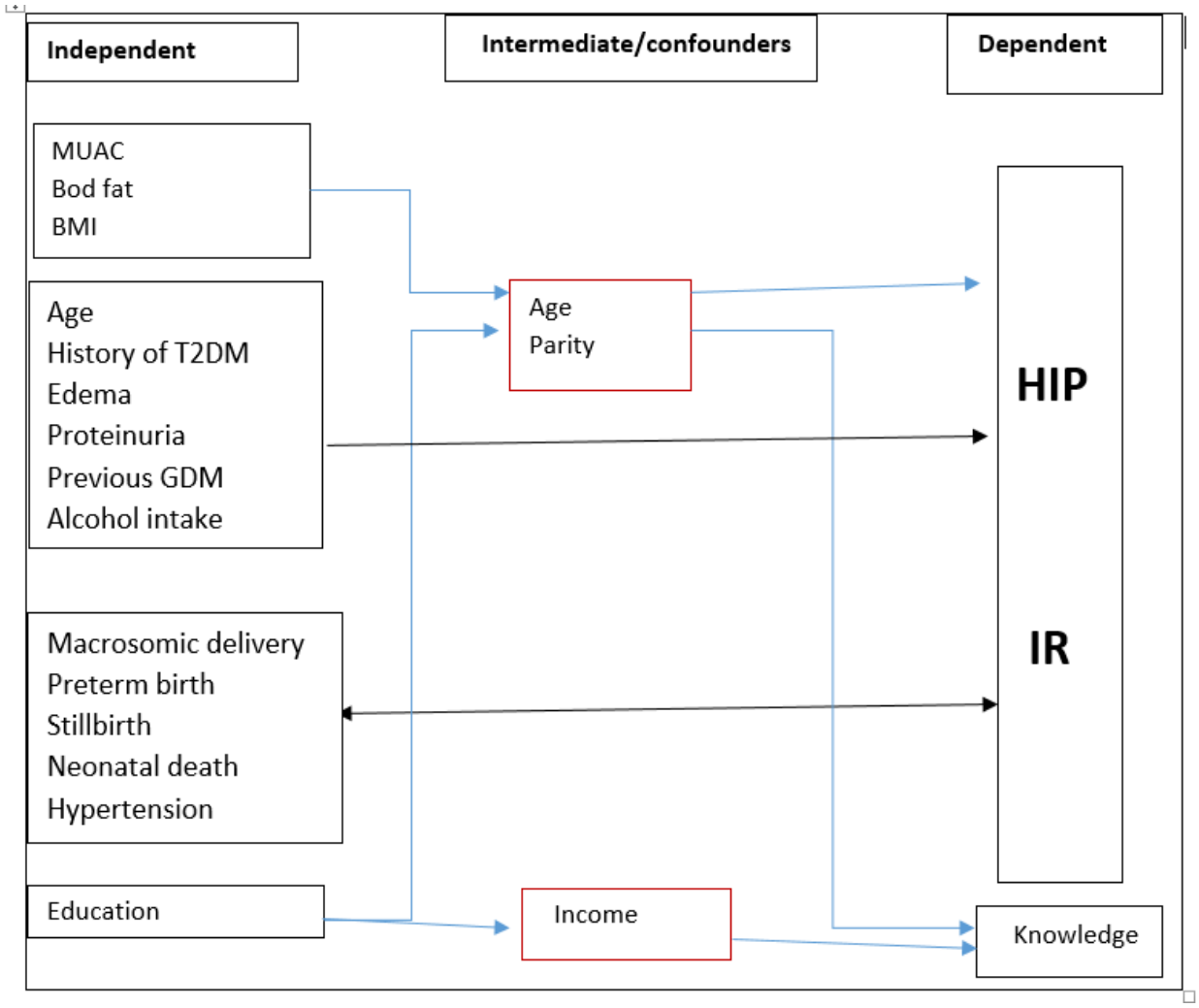
A formal risk assessment for GDM could be undertaken at the first prenatal visit and for the women with high risk of GDM with clinical characteristics, such as obesity, personal history of GDM, glycosuria, advanced maternal age, strong family history of IR and/or diabetes should undergo glucose testing as soon as feasible (Plows *et al.*, 2018; ADA, 2010). It may not be a proper use of limited resources to screen women at low risk, such as < 25 years of age, normal body weight, no family history of diabetes or abnormal glucose metabolism, and no history of poor obstetric outcome (ADA, 2010).

A risk score can be used in limited resources, but accurate identification of risk factors may be difficult. This made FANC to change from the traditional risk identification with more numbers of ANC visits, due to high or nearly similar costs to the existing model. However, the current FANC is still facing challenges in implementation of its guideline in Tanzania's ANC due to limited resources (Kearns *et al*., 2014). This may have contributed largely to poor consideration of GDM screening and management in the guideline as extra resources may be required following the costs associated with the recommended universal screening by OGTT and/or fasting glucose tests (WHO, 2013). In this case, the available resources can be used to high risk women while planning for universal testing. Hence, due to limited resources, risk score can be simplified into a factors checklist which can be easily understood by health care workers and women of reproductive age for self-identification and care. This approach could provide a simple and easily up taken intervention that will articulate with plans for universal screening.

Although many risk scores have been developed in different settings, the establishment of a scoring system should be country specific due to differences in the levels of fat adiposity, glucose intolerance, and ability to cover the associated costs (Kim *et al.*, 2013; Farrar *et al.*,

2017). To be more effective, the developed risk scores should be simplified for easy of interpretation and application by the health care providers and women themselves to promote self-care among pregnant women.

Figure 3: Conceptual frame work for dependents and independent variables



CHAPTER THREE

MATERIALS AND METHODS

3.1 Description of the study area

Arusha Region is one of Tanzania's 31 administrative regions with a total population of 1 694 310 (NBS, 2013). The capital city of Arusha has a total population of 416 442 plus 323 198 people living in Arusha District (NBS, 2012). The region is bordered by Kajiado and Narok County in Kenya to the North, Kilimanjaro Region to the East, Manyara and Singida regions to the South, Mara and Simiyu Regions to the West. Arusha Urban (City Council) is one of the seven districts of the Arusha Region which is bordered to the South, West and North by Arusha Rural District and to the East by Meru District (Fig. 4).

The city has 6 hospitals, 15 health centers, 64 dispensaries and 25 specialized facilities. Among these facilities 56 have ANC of which 24 has both ANC and delivery services. The city has a total number of 26 167 pregnant women who started first ANC visits in 2018 (District Health Information System [DHIS], 2018). The study was conducted in two health centers with a total number of 10 422 pregnant women who started first visits in 2018 (DHIS, 2018).

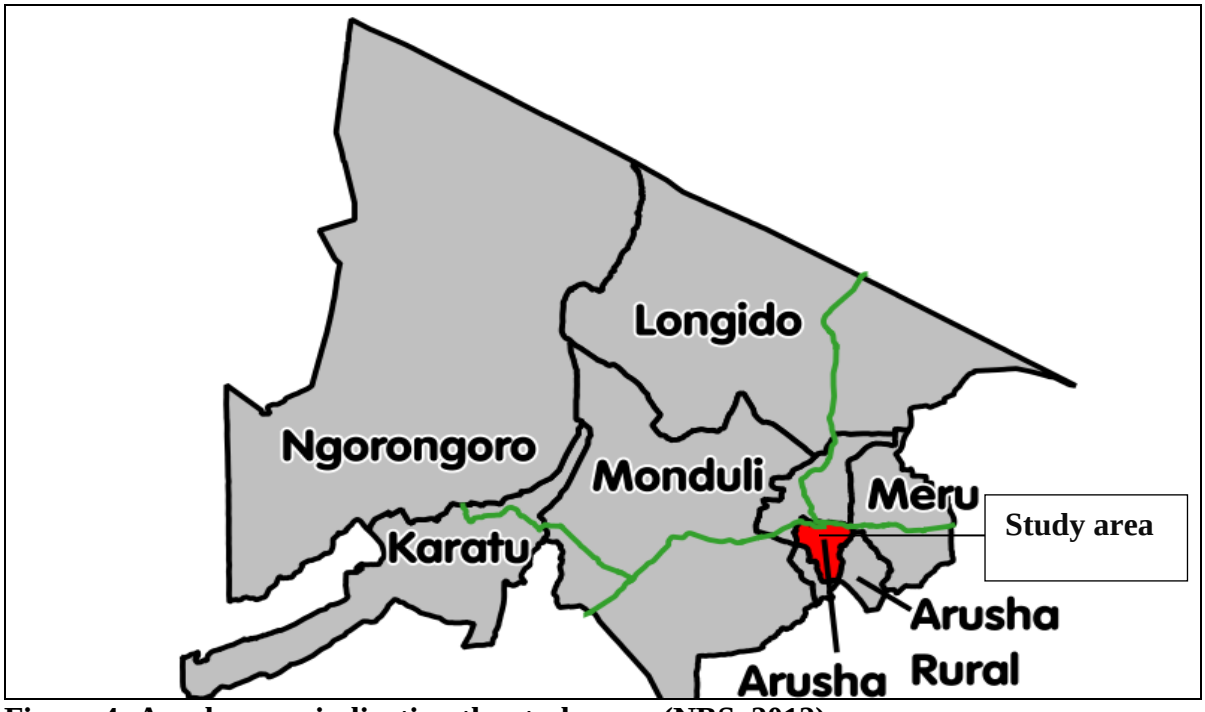


Figure 4: Arusha map indicating the study area (NBS, 2012)

3.2 Study design

This was a cross-sectional study that was conducted in urban areas of Arusha City between March and December 2018. This involved pregnant women attending ANC at Ngarenaro and Kaloleni Health Centers. These centers were selected among 24 health facilities which offer both, ANC and delivery services. The two centers have a total of 10 422 out of 26 167 pregnant women which is about 40% of all women who started their first ANC visit in Arusha City (DHIS, 2018). Two centers were purposive selected due to their central location in the district, and enabling services reach for the largest number of pregnant women.

3.3 The study population

3.3.1 Inclusion criteria

The study included pregnant women at the second and third trimesters between 24-36 weeks of gestation as HIP is defined as any glucose intolerance that is first detected at any time during pregnancy (ADA, 2018; WHO, 2013).

3.3.2 Exclusion criteria

The study excluded pregnant women with diabetes before pregnancy and are under- diabetes management or treatments. All women who were unwilling to participate or provide consent were excluded from the study.

3.4 Sample size determination

Eligible women were selected with assistance of the nurses' in-charge at each participating site until a total of 468 women were recruited to the study. This sample size was obtained using the formula for prevalence studies (Daniel, 1999):

$$n = [z^2 * p * q]/d^2$$

Where: n = desired sample size

Z = standard normal deviation set at 1.96 corresponding to 95% CI

q = 1.0 – p

d = degree of accuracy desired (0.05)

p= proportion of the target population with HIP

Due to limited national data for prevalence of HIP (GDM and DIP), and the assumption of a high risk of HIP for a transitioning urban population, p = 50 % was used as the prevalence to capture the maximum reality (MacFarlane, 1997). The response rate was assumed to be 78%; yielding a consideration of 20% non-respondent rate. The percentage for non-response was set due to the experience from a study done in Kilimanjaro where the rate of loss to follow up for the subsequent testing was > 20% (Njete *et al*., 2018).

3.5 Sampling techniques

Purposive sampling was employed to obtain one district located in urban area out of seven districts of Arusha Region. Two ANC centers (Ngarenaro and Kaloleni) were purposively selected from the 24 facilities with both ANC and delivery services due to the large number of pregnant women (40%) accessing ANC services from across the District in 2018. Proportionate sampling was used to select pregnant women from the two ANCs to ensure a total of 468 respondents where by 31% of the pregnant women were selected from Kaloleni and 69% from Ngarenaro. These women were stratified by age (< 25 years and ≥ 25 years of age) to avoid the selection of women from one age category which might be at low or high risk only. Random selection using a table of random numbers was done to obtain 468 pregnant women who met the inclusion criteria. Due to high number of women attending ANC per day, a maximum of 12 pregnant women were selected per day. Among the 468 pregnant women who were sampled, half of them were randomly selected for IR testing whereby 230 pregnant women were included while four women were excluded as their blood samples coagulated before laboratory tests were performed.

3.6 Data collection and laboratory analysis

3.6.1 Training of the research assistants and pretesting of research tools

Before the actual data collection processes, nurses and research assistants who were nutritionists with enough experience on human research, were trained on the study protocol and how to use the research tools. The training was done for five days using English and Kiswahili language and the questionnaire was translated to Kiswahili as well. After the training, all trainees were involved in pretesting the tools with 20 randomly selected women from Ngarenaro health facility who were not part of the study and the resultant data was not included in the actual study. The pre-test results were discussed, and appropriate changes were made to improve the research tools (Appendix 1).

3.6.2 Recruitment and overall data collection procedure

The study was introduced to pregnant women who met the selection criteria. A total of 500 pregnant women were recruited of which 94% (n=468) consented to participate in the study. The remained 6% (n=32) of the pregnant women could not consent after explanation of the whole data collection procedure including, harms and benefits of participating in the study. These women complained on the costs that may arise if several visits would be required for subsequent testing. They also complained on the long time that is required to complete all data collection procedure especially the OGTT which required women to stay in the facility for more than two hours.

After women have consented, those who come while fasting were tested for fasting plasma glucose and performed the OGTT procedure in the same day. During assessments half of the women in each day were randomly selected from the same group for venous blood samples collection to test for IR. Selected women were also interviewed in the same day to reduce transport costs. Women who consented but came while eaten food, were requested to come the next day while fasting for 8-12 hours where all the assessments would be done. These women were given a tag with the number of researchers for confirmation on the exactly day of retuning to avoid taking large number of women in a day. Majority of the women who were selected and agreed to come another day for assessments, were requested to go back home without performing their regular ANC assessments so that they can be served when they return to participate in the study. In this way loss for follow- up tests was minimized.

During the assessments, women started with fasting glucose test, followed by urine and venous blood samples collection. Thereafter, women were provided with 75 g of glucose powder dissolved in 300 ml of clean water to test for OGTT. Disposable cups were used for drinking glucose solution to avoid sharing of utensils. Women were requested to finish drinking their solution within five minutes. For time management after glucose consumption, each woman was given a tag which indicated the time at which glucose was consumed and the time for the second test. Their names and times after glucose consumption were recorded by the researchers for reminder.

During the two hours waiting for OGTT testing, interviews and other assessments, such as anthropometric measurements, and normal ANC services were conducted. This helped to minimize time for commitment and encourage compliance. All pregnant women with high

fasting glucose levels (≥ 5.1 mmol/L) were requested to come for another fasting test in the next day or within a week to confirm. After confirmation, all women with HIP were advised and refereed to the doctor for further actions to be taken. After referrals, all pregnant women with HIP were followed up through phones to know their progress and provide them with advices accordingly (Fig. 5).

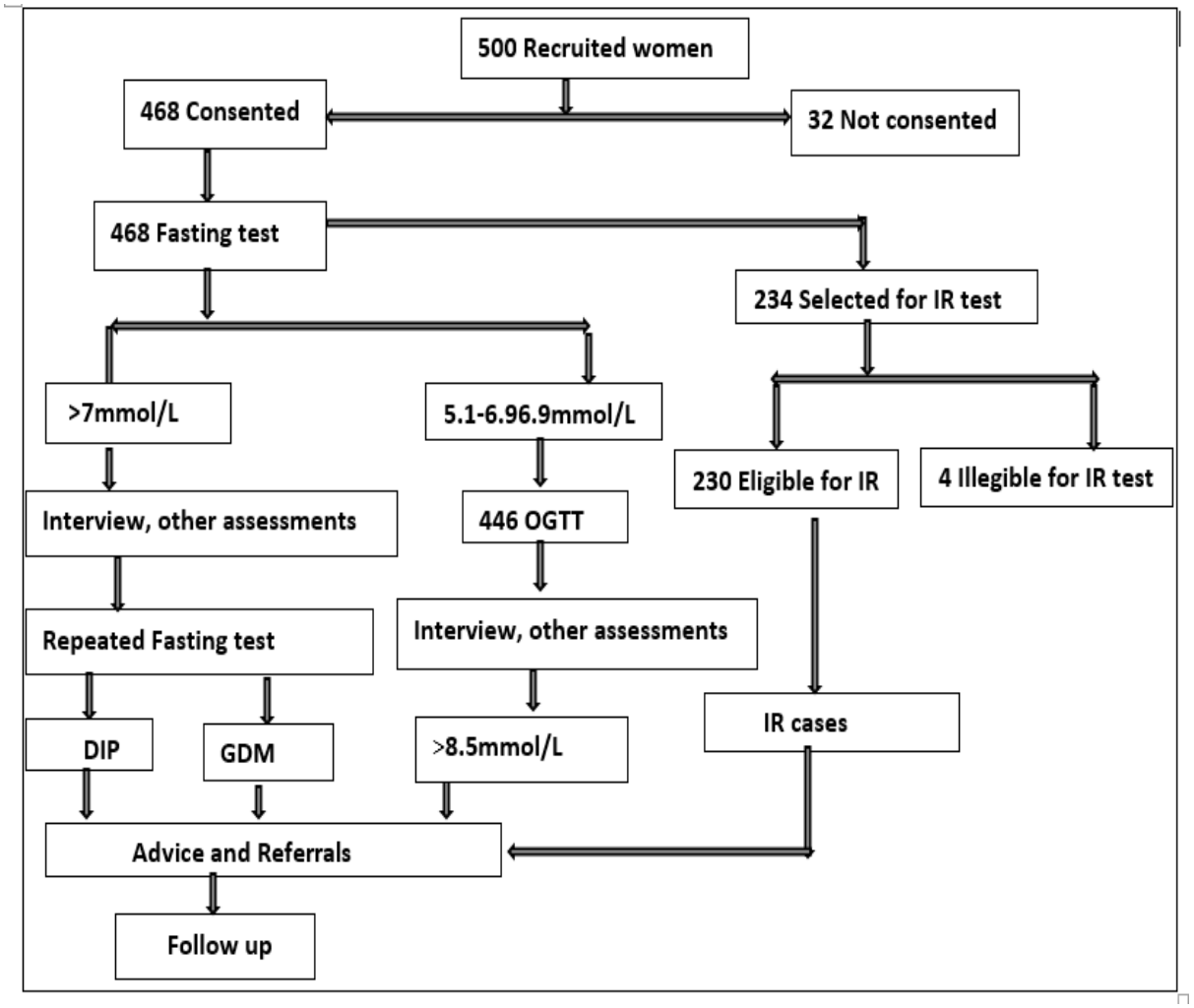


Figure 5: Flow chart for recruitment and data collection procedure

3.6.3 Assessment of demographic characteristics and selected risk factors for hyperglycemia in pregnancy

Recalled information with respect to weight before pregnancy, previous birth modalities (caesarian section or normal delivery), family history of T2DM, previous history of GDM, symptoms of T2DM, and previous delivery to babies with ≥ 4 kg at birth (macrosomic) were collected through face-to-face interviews using a questionnaire with structured questions (Appendix 1).

Other clinical and maternal characteristics, such as age, previous history of stillbirth, neonatal death, gravidity, education level, occupation, marital status, and weight during the first antenatal visit were obtained from the participants' ANC records and confirmed by the women through face to face interviews. Gestational age was estimated using the last menstrual period as reported by pregnant woman during her first ANC visit and for those who could not remember their last menstrual period, ultrasound assessment was conducted.

3.6.4 Laboratory assessments for hyperglycemia in pregnancy and insulin resistance among pregnant women

(i) Blood samples collection

The fasting capillary blood samples were taken using a finger prick with a sterile lancet after cleaning the site with an antiseptic alcohol swab. Additionally, 5 mls of fasting venous blood was taken from 50% of the randomly selected participants using a sterile syringe and drawn out of the syringe into vacutainer tubes containing no anticoagulant. Venous blood samples were stored in a cool box and transported to the Nelson Mandela African Institution of Science and Technology laboratory to analyze insulin concentrations for determining IR. Urine samples were also collected using disposable hospital urine sample containers (60 ml) in the morning and tested for glucose and protein The fasting capillary blood samples were tested for glucose within five minutes after drawn and 2 hours followed the consumption of glucose solution.

(ii) Test for hyperglycemia in pregnancy

Fasting blood glucose and OGTT were tested using Gluco-plus^{TM} (Glucoplus Inc. 2323 Halpern, Ville St. Laurent, Quebec, Canada). The capillary plasma glucose values obtained were converted to venous plasma glucose using the regression equation developed for diabetes screening in the low resource areas where venous blood test is challenging (Bhavadharini *et al.*, 2016). Women with fasting blood glucose levels ≥ 5.1mmol/L were requested to return the next day for another fasting glucose test. All women with < 7 1 mmol/L were requested to consume 75 g of glucose dissolved in 300 ml of water and stayed for 2 hours without eating, after which capillary blood was measured for levels of plasma glucose (WHO, 2013).

Women were classified as having HIP if they met the criteria for either DIP and/or GDM. Women with GDM were classified as having fasting plasma glucose (5.1-6.9 mmol/l (92 - 125 mg/dl), or a 2-hour plasma glucose (8.5-11.0 mmol/l (153 -199 mg/dl) following a 75-gram oral glucose load. In addition, women with DIP were classified by fasting plasma glucose ≥ 7.0 mmol/l (126 mg/ dl) and/or 2-hours plasma glucose ≥ 11.1 mmol/l (200 mg/dl) following a 75 g oral glucose load (WHO, 2013). Urine samples were tested within one hour using multi-sticks with color sensitive pads (Urine strips 388-25, Gomo-ro, Gimhae-si, Gyeongsangnam-do, 621-881, Korea). All women identified with HIP were referred to the doctor for further actions and follow-up were done through phone calls, messages and physically during their ANC visits.

(iii) Tests for insulin resistance

Serum was obtained by centrifuging (Eppendorf Centrifuge 3500R) the blood sample for 15 minutes, separated from clot by pipetting the supernatant into vials, and stored in the refrigerator at -80˚C before analysis (Tuck *et al.*, 2009). Serum insulin concentrations were measured using a Synergy/HTX**™** (BioTek instrument, Inc. Highland Park Winooski, VT 05404-0998, USA) machine with Human Serum Crystal Chem™ (Crystal Chem Inc. Elk Grove USA) high performance assays as explained in the procedure below.

(iv) Preparation of reagents according to the manufacturer's instructions

(a) The instruction manual from the ELISA kits manufacturer was read, discussed, and well understood by the researcher and the laboratory technician before the actual analysis (Fig. 6).

(b) The antibody-coated micro plate was provided as ready to use.

(c) The standards were provided by manufactures in lyophilized form and diluted by 1.0 ml of de-ionized water. This involved 1-6 standards in the concentrations of (0, 3, 10, 30, 110 and 220 mU/L) which sat for 5 minutes at room temperature and then were mixed gently to dissolve all solid particles.

(d) The controls provided were also diluted by 1.0 ml of de-ionized water, allowed to sit for 5 minutes at room temperature and then mixed gently to make all solids dissolve. These were provided in the concentration of 13:150 mU/L.

(e) The provided HPR binding labeled antibody was also diluted in the ratio of 1:12 using a provided ready to use diluent and mixed thoroughly.

(f) The wash buffer provided was 30x concentrate requiring dilution with distilled water in ratio of 1:30 (i.e., 50 ml were diluted by 1450 ml of distilled water).

(g) The substrate and stop solutions were provided as ready to use.

Figure 6: Internalizing the instruction manual for preparation of analytical reagents

(v) Assay procedure (aliquot)

(a) Before running the assay, all reagents and samples were brought to room temperature to sit for 5 minutes and then introduced in the Vortex^{TM} (mixer) for thorough mixing.

(b) The samples were run in duplicate.

(c) In each well of the antibody-coated micro plate, a 100 µl of HPR labeled antibody solution was added followed by 25 µl of the sample, standard, control and mixed well by repeated pipetting.

(d) The wells were covered with a plate sealer and incubated for 2 hours at $37\ ^{0}$ C.

(e) The contents were well aspirated and washed three times in an Accuwash™ machine using 300 µl of wash buffer per well.

(f) After washing, 100 µl of substrate solution was added in each well and incubated for 15 minutes at room temperature in a dark place.

(g) The reaction was stopped by adding 100 µl of the stop solution (Fig. 7).

(h) The plates were placed in a Biotech biosciences Synergy/HTX™ ELISA machine and absorbance were measured within 30 minutes using a plate reader (measured at A_{450} and A_{630} values) and mean difference was obtained (Fig. 8).

(i) A computer software was used to construct the insulin calibration curve by plotting the mean change in absorbance values for each calibrator on the Y-axis versus the corresponding insulin concentration on the X-axis. This formed a typical standard curve with equation for calculating insulin concentration in each plate (Fig. 9).

(j) From the above standard equation, that is Y=0.013x -0.0566, the concentrations for each sample in a plate (represented by X) was calculated given the values of Y (Absorbance).

(k) Then insulin concentration was interpolated using the calibration curve and the mean of each absorbance values for each sample and insulin concentration was expressed in mU/L.

Figure 7: Addition of stop solution to stop the reaction

Figure 8: A plate placed in an ELISA machine for reading

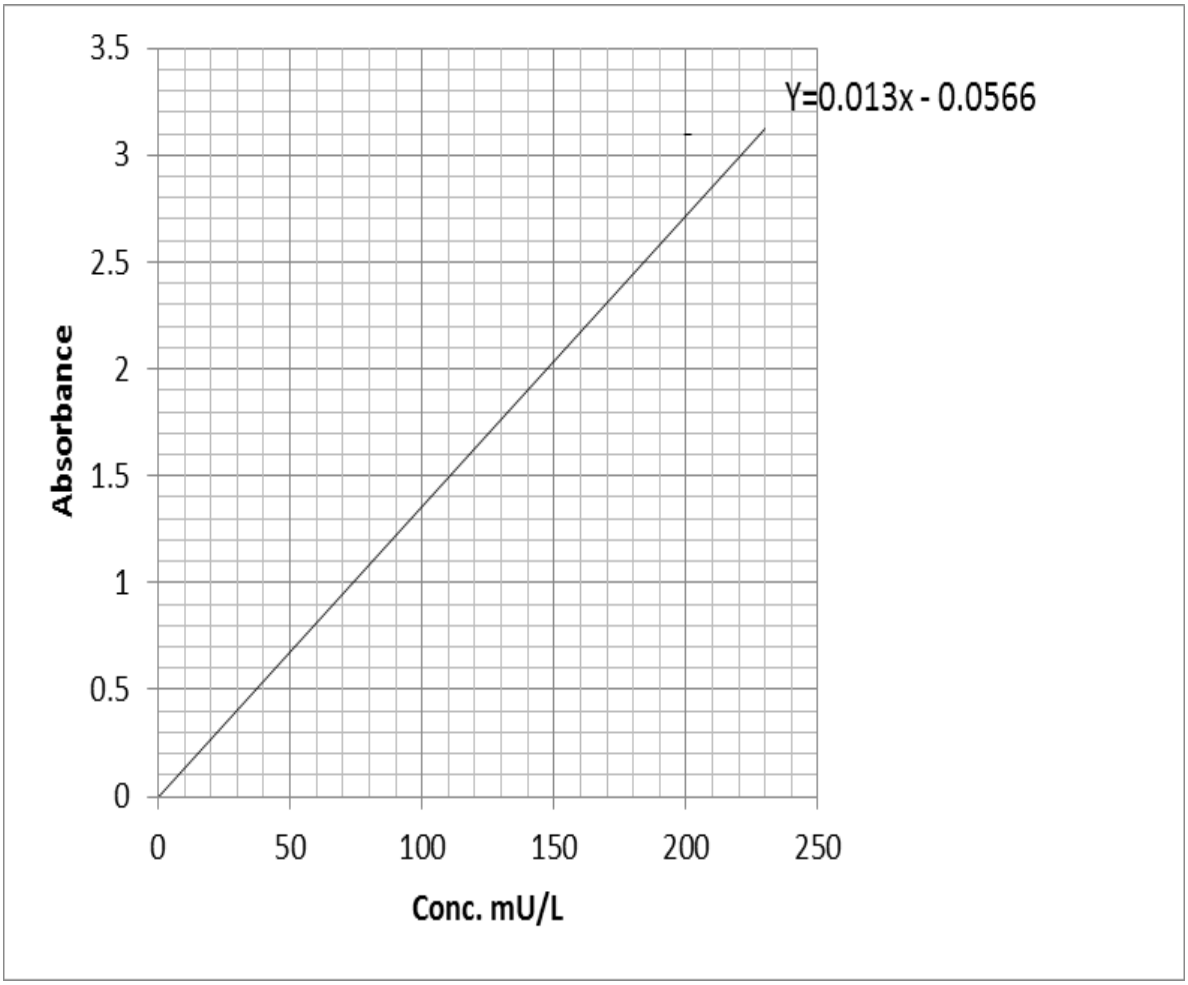


Figure 9: The graph for absorbance's against the standard concentrations

Lastly, IR was calculated using the Homeostasis Model Assessment (HOMA-IR) formula (Matthews *et al.*, 1985) and defined by a HOMA-IR score ≥ 2.5 (Longo-Mbenza *et al.*, 2011).

$$\text{HOMA} - \text{IR} = \frac{\text{fasting serum insulin (mU/L)} * \text{(fasting blood glucose (mmol/L)}}{22.5}$$

3.6.5 Anthropometric assessments

Mid-upper arm circumference (MUAC) was measured using a non-stretchable standard tape. The participant stood upright with the weight evenly distributed on both feet with shoulders relaxed, and the arms hanging loosely at the sides. Some studies reported that MUAC may be used instead of BMI due to its relative stability during the course of pregnancy and high correlation with pre-pregnancy BMI (Fakier, *et al.*, 2017; Gale *et al.*, 2007). Women were categorized as normal with a MUAC of < 28 cm and overweight with MUAC ≥ 28 cm.

Weight was measured with minimal clothing and without shoes using a digital bathroom weighing scale (SECA-Germany), placed on a flat surface. The participants were requested to stand on the center of the scale platform facing the recorder and looking straight ahead. Two measurements were taken and recorded to the nearest 0.1 kg.

Height was measured using a stadiometer (Shorr Productions, Maryland USA) where the participant was requested to stand up straight against the backboard with the body weight evenly distributed and both feet flat on the platform, with the heels placed together and toes apart. The back of the head, shoulder blades, buttocks and heels were made to contact with the backboard. The head was aligned in the Frankfort horizontal plane and the stadiometer head piece was lowered to rest firmly on top of the participant's head, with sufficient pressure to compress the hair. The measurements were taken in duplicate and recorded at the nearest 0.1 cm.

This measured height together with recalled pre-pregnancy weight were used to calculate the pre-pregnancy BMI of the women where only 238 pregnant women were able to recall their pre-pregnancy weight. Weight during the first visit could not be used to calculate BMI due to late initiation of the ANC (usually at 18 weeks gestation as observed in this study). The per-pregnancy data for calculating pre-pregnancy weight may have shown biases due to either over or underestimation during recalling. The pre-pregnancy BMI was calculated by the weight of individual in kilogram per meter squares and subject with BMI < 18.5 kg/m^2 was classified as underweight, 18.5-24.9 kg/m^2 as normal, 25-29.9 kg/m^2 overweight and ≥ 30 kg/m^2 obese (WHO, 2006).

Body fat percentage was determined using a bioelectric impedance analyzer (Tanita TBF 105 Fat Analyzer™), which included adjustments for age, weight, and height (Fig. 10). The body fat percentage values were treated as continuous variables due to lack of established classification criteria for pregnancy. The presence of edema was also assessed through physical or clinical observations by qualified ANC personnel.

Figure 10: Measurement of body fat percentage

Blood pressure was measured using a GT-868UF Geratherm™ machine on the left mid-upper- arm, while the participant was sitting and relaxed for 10 minutes before the actual measurement. Two measurements of blood pressure were done at an interval of five minutes and the average was recorded. Blood pressure was classified using the Standard treatment guidelines and essential medicines list categories of systolic 140 to 159 mmHg or diastolic 90 to 99 mmHg (MoHSW, 2013).

3.6.6 Assessment of knowledge on hyperglycemia in pregnancy among pregnant women

Knowledge on HIP was assessed using a questionnaire which was administered through face to face interviews. Information collected on knowledge included respondents' views on the meaning, symptoms, consequences, and risk factors for HIP. Common practices used to screen and manage HIP in their previous pregnancies, such as testing methods, follow up after diagnosis, and management practices were also assessed using questionnaire which included both closed- and open-ended questions. This information was assessed to know the previous experiences of the women on the services provided to get evidence to recommend for an intervention. This information helps to understand other sources of health information and how knowledge can influence behavior change during implementation of screening and management strategies. Moreover, as the study aimed to develop a tool that can be used by both healthcare providers and women themselves, it was important to understand their knowledge about HIP for effective implementation of the tool.

The researchers recorded verbal responses or ticked responses if matched with provided alternatives or wrote the response under the 'others' option if not matched with the provided options. Responses were coded and knowledge was determined by the percentages of women who answered the questions correctly. The assessment was done by a research scholar based on the responses obtained from the questions. The interpretation of knowledge was done based on the scores obtained, that is, those who answered correctly were interpreted as having adequate knowledge and were graded with a score of 1 for each question which were then converted into percentage. Hence, excellent knowledge was regarded as $\geq 75\%$ correct, good knowledge between 51% and 74% correct; average between 26% and 50% as well as poor knowledge $\leq 25\%$ (Dhyani *et al.*, 2018).

3.6.7 Development of the risk scores

All women with DIP were excluded from the data to develop a risk score for identification of women with or at risk of GDM. Variables collected as risk factors for GDM were analyzed for descriptive statistics to check for missing data or any abnormal distributions. Cross-tabulation analysis was carried out to identify relationships among variables for categorical data. Variables found to have a relationship with GDM from previous research evidence and confirmed by cross-tabulation were entered into a logistic regression model for analysis.

Univariate analysis of each variable in relation to GDM was done to assess their individual contribution to the development of GDM.

All variables with a p-value of < 0.05 were entered in a model. Multivariable analysis was performed, and the estimated coefficients and p-values were compared with those in the univariate analysis, whereby all non-significant predictors (p value > 0.1) were eliminated at this stage and a new model with significant predictors was set. Backwards elimination as described by Harrell (2015) was used as it starts with a full model (includes all variables) and eliminates non-significant variables one by one.

Performance of the new model was compared with the full model and the process repeated until the model contained significant predictors only. For the model to be applicable, each risk factor was scored based on the estimated coefficients whereby the increase in number of the scores indicated high risk of GDM (Caliskan *et al.*, 2004). The risk scores were calculated, indicating the risk factors and their corresponding scores multiplied by ten (10) to remove decimals to get integers for easier interpretation and application in ANC settings and for individual use. The sum of the score was calculated for each participant by adding the score for each significant variable in the risk model and a total GDM risk score was calculated as the sum of all individual scores.

Performance of the model was assessed using discrimination assessment which looked at whether estimated risks were different for patients with and without GDM. This was done using the c-statistic, known as the area under the receiver–operating characteristics curve (AU-ROC) for binary outcomes. This was done with the probability that, a randomly selected patient experiencing an event (which is GDM in this case) has a higher predicted probability than a randomly selected patient not experiencing the event (Wynants *et al.*, 2017).

The clinical utility of the model was assessed using the Net Benefit (NB) to obtain the threshold for decision making (Wynants *et al.*, 2017). This assessment was conducted based on the net proportion of true and false positive values at a selected threshold whereby the higher the net benefit for the model the higher the utility of the model.

3.7 Statistical analysis

Data collected were entered, cleaned, edited and analyzed using the Statistical Package for Social Science™ (SPSS™) Version 20 and R-Test™ version 3.61.

3.7.1 Demographic data

Demographic attributes were assessed using means, percentages, and frequencies obtained using SPSS. For example, means, frequency and percentages for maternal age, gestational age and income were reported.

3.7.2 Anthropometrics data

Percentages were obtained from SPSS to describe the prevalence of overweight, obesity, hypertension and edema. Means were calculated for weight, height, MUAC and body fat. The comparisons for these continuous variables were done using t-test.

3.7.3 Prevalence of hyperglycemia in pregnancy, insulin resistance and associated risk factors

Descriptive statistics were used to obtain percentages for the prevalence of HIP, GDM, DIP, and IR. The means were calculated for OGTT, fasting blood plasma and insulin concentration values which were compared using the t-test for the women with and without conditions. The associations among variables started with descriptive statistics to detect missing values followed by Chi-square test to compare different categorical variables for women with and without HIP and IR at $p < 0.05$. Variables assessed included overweight and obesity using MUAC and BMI categories, family history of diabetes, edema, hypertension, gestational age, maternal age, proteinuria, etc. The outcomes, which were IR and HIP, were dichotomized into two categories which were either having the condition or not having the condition. Multiple logistics regression by binary logistic was used to find associations of different factors with HIP and then with IR separately. Univariate analysis was run for each factor association with HIP and IR separately. All factors with $P < 0.05$ were entered in the multivariate analysis using stepwise backward elimination (Harrell, 2015). Crude and adjusted odd ratios were obtained for each factor associated with HIP and/or IR at $p < 0.05$ (Wynants *et al.*, 2017).

3.7.4 Knowledge on hyperglycemia in pregnancy

Data about knowledge on HIP were analyzed using SPSS where frequencies and percentages were obtained to classify women as having poor, moderate, or high knowledge on HIP. Factors influencing knowledge were assessed using logistic regression where both univariate

and multivariate analyses were run. The confounders of knowledge, such as age, parity and income, were included in the multivariate analysis and significance was set at $p < 0.05$.

3.7.5 Risk score data

All women with DIP were excluded from the analysis to develop a tool based on GDM cases. Chi-square test was used for comparing the selected categorical variables and student *t-test* for the continuous variables between women with and without GDM. Blood glucose values were dichotomized as having GDM or not having the condition. Binary logistic regression was used and univariate analysis was done for each variables independent association with GDM where crude odd ratios were obtained (Wynants *et al.*, 2017).

All variables with $p < 0.05$ were entered in the multivariate analysis where adjusted odd ratios and regression of coefficients were obtained (Harrell, 2015). All variables with $p < 0.1$ remained in the final model to avoid exclusion of important variables which potentially contributes to the development of GDM. The confidence intervals in each analysis were obtained and recorded. The final risk score model was developed based on the regression coefficients of each variable. The performance of the model was analyzed using AUC, specificity and sensitivity at a selected threshold which could give reasonable values. Utility of the model was assessed using the Net Benefit (NB) which was obtained by different combination of true and false positive values. This was analyzed in R-statistic 3.61 by running the decision curve function.

3.8 Ethical consideration

The study was approved by the Tanzania National Institute for Medical Research (NIMR) and was given ethical clearance certificate with a reference number NIMR/HQ/R.8a/Vol.IX/2694 (Appendix 3). Participants signed an informed consent which clearly explained the aim, procedure, benefits and potential negative effects of the study (Appendix 2). Anonymity was ensured using numbers to represent the names of the women during data handling and confidentiality by having a specific room where research activities were carried out. Each woman could enter alone or with a spouse or any person of her choice.

CHAPTER FOUR

RESULTS AND DISCUSSION

4.1 Results

A total of 500 pregnant women were recruited whereby 94% (n = 468) consented to participate in the study. All 76 pregnant women with HIP were referred to the doctor for further actions and followed up by phones to understand their conditions and actions taken for more advices.

4.1.1 Demographic characteristics of participants

A total of 468 pregnant women participated in the study at Ngarenaro and Kaloleni Health Centers. The mean age of pregnant women was 28 years (SD ± 5.84), of which 65.6% were ≥ 25 years old. Majority of the women were married (93.8%, n=459), and over half had attended primary school education (58.8%, n=275). About 56% (n=261) of the pregnant women were self-employed, primarily in small business earning an average income of < 250 000 Tanzanian Shillings (TSH) per month (approximately < 110 United States Dollars) (Table 1).

Table 1: Demographic characteristics of participants (N=468)

Respondent Variables	Frequency	Percent
Education levels		
Informal education	8	1.7
Primary level	275	58.8
Secondary level	164	35.0
College/University	21	4.5
Marital status		
Single	16	3.4
Married or Cohabiting	439	93.8
Divorced/Separated	13	2.8
Occupational status		
Formally employed	46	9.8
Self employed	261	55.8
Unemployed	161	34.4
Income per month (TSH)		
<250 000	255	54.5
250 000-450 000	33	7.1
≥500 000	13	2.8
Don't know	167	35.7
Age		
< 25 years	164	35.0
≥ 25 years	304	65.0

The mean gestational age during the first ANC visit was 18 weeks (SD ± 5.62) and 28.5 weeks (SD ± 3.82) at the commencement of this study. Nearly, 38% (n=177) of the pregnant women were ≥ 28 weeks of gestation at the time of entry to the study with 50.4% (n=236) reported as second or third gravidity (Table 2).

Table 2: Demographic and selected maternal characteristics of the women (N=468)

Respondent Variables	Frequency	Percent	Mean (±SD)
Gestational age at first visit			
<12 weeks	57	12.2	
12-24 weeks	363	77.6	18 (SD ± 5.62)
25-36 weeks	48	10.2	
Gestational age at study commencement			
24-28 weeks	291	62.2	28 (SD ± 3.82)
>28 weeks	177	37.8	
Gravidity			
Prime	142	30.3	
Second and third	236	50.4	3 (SD ± 1.20)
Fourth and above	90	19.2	

4.1.2 Anthropometric measurements of pregnant women

About half of the pregnant women were able to recall their pre-pregnancy weight. The mean of the self-reported pre-pregnancy weight was 67 kg (SD ± 12.5). This weight was used to determine pre-pregnancy BMI of the pregnant women. The measured mean height was 159 cm (SD ± 6.3), body fat 33.7% (SD ± 7.2), and MUAC 27 cm (SD ± 3.8). About 10.3% (n=48) of the women were hypertensive and 20.3% (n=95) had edema (Table 3).

Table 3: Anthropometry of the pregnant women (N=468 and N=238 for pre-pregnancy weight)

Variables tested	Frequency	Percent	Mean (SD)
Body fat percentage			33.4 (SD ± 7.8)
Self-reported pre-pregnancy weight (kg) (n=238)			67 (SD ± 12.5)
Height (cm)			159 (SD ± 6.3)
Hypertension			
Yes	48	10.3	
No	420	89.7	
Edema			
Yes	95	20.3	
No	373	79.7	

Pre-pregnancy BMI of the pregnant women was determined in which, 25.2% (n=60) were classified as overweight and 22.7% (n=54) obese. About 36% (n=164) of the women had MUAC ≥ 28 cm which is also an indicative of overweight or obesity (Fig. 11).

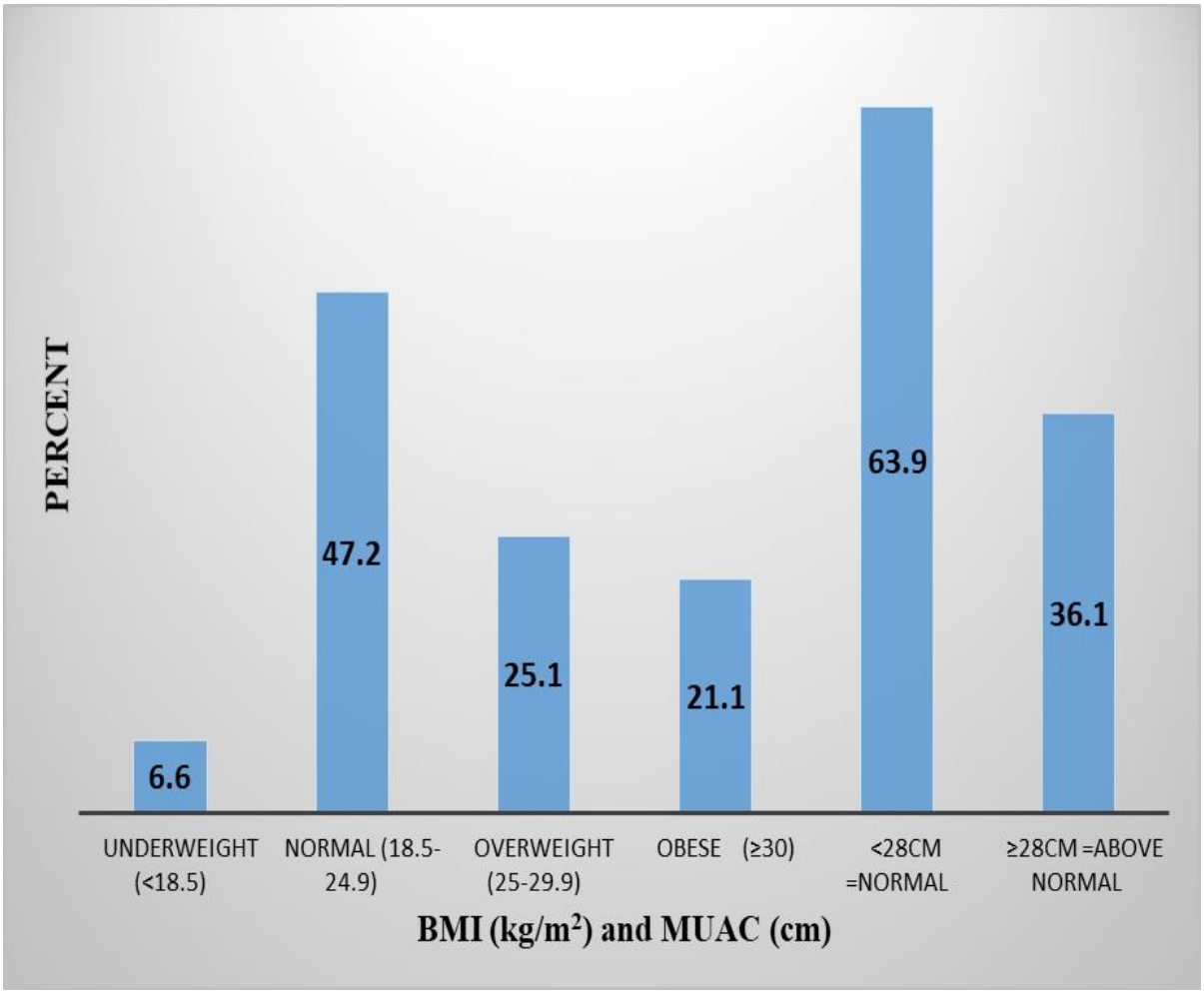


Figure 11: Nutrition status classified by body mass index (BMI) and mid upper arm circumference (MUAC) measurements

4.1.3 Prevalence of hyperglycemia in pregnancy among pregnant women

(i) Laboratory glucose tests

All pregnant women who participated in the study (100%, n=468) completed fasting blood glucose tests and 97.8% (n=446) underwent the OGTT procedure. Among the assessed pregnant women, 10.9% (n=51) reported to have one or more symptoms of diabetes such as extreme tiredness, diaphoresis (excessive sweating), and polydipsia (excessive thirst). Urine glucose test revealed that 0.9% (n=4) of the pregnant women had diabetes while 8.5% (n=40) had trace amount of glucose in the urine. Generally, HIP was prevalent in 16.2% (95% CI: 13-19.9) of the participated pregnant women of which GDM was 13% (n=61) and DIP was 3.2% (n=15) using the WHO (2013) criteria (Table 4).

Table 4: Laboratory tests for glucose and urine protein among pregnant women (N=468)

Variables Tested	Frequency	Percent
Glucose testing		
Completed fasting glucose tests	468	100.0
Completed OGTT	446	97.8
Glucose status		
Normal	392	83.8
HIP	76	16.2
DIP	15	3.2
GDM	61	13.0
Having any symptoms of diabetes		
Yes	51	10.9
No	417	89.1
Glucose test in urine		
Positive	4	0.9
Negative	424	90.6
Trace	40	8.5

(ii) Mean glucose comparisons during pregnancy

The overall mean for fasting blood glucose was 4.5 mmol/L (SD ± 1.3), with the HIP sub-group having a mean of 6.4 mmol/L (SD ± 1.5), yielding a significantly higher ($p<0.001$) mean compared to the non-HIP group (4.2 mmol/L, SD ± 0.9). The overall mean for OGTT was 5.5 mmol/L (SD ± 1.06) and significantly higher ($p<0.001$) among the HIP (8.3 mmol/L, SD ± 1.3) compared to the non-HIP group (5.5 mmol/L, SD ± 0.1) (Table 5).

Table 5: Mean blood glucose comparisons between women with and without hyperglycemia in pregnancy (N=468)

Variables Tested	Frequency	Mean	SD	P-value
Fasting blood glucose				
General fasting blood glucose	468	4.5	±1.3	
Normal (< 5.1 mmol/L)	397	4.2	±0.9	<0.001*
HIP (≥ 5.1 mmol/L)	71	6.4	±1.5	
OGTT				
General OGTT values	446	5.6	±1.06	
Normal (< 8.5 mmol/L)	436	5.5	±0.1	<0.001*
Glucose intolerance (≥ 8.5 mmol/L)	10	8.3	±1.3	

*significant at $p<0.05$

(iii) Comparisons of the selected characteristics between women with and without hyperglycemia in pregnancy

Chi-square analysis was run to identify categorical variables which are associated with HIP (Table 6).

Table 6: Comparison of selected characteristics between women with and without hyperglycemia in pregnancy

Variable	With HIP	Without HIP	P-value
MUAC			
< 28cm (Normal)	37(12.4%)	262(87.7%)	0.003*
≥ 28cm (overweight/obese	39(23.1%)	130(76.9%)	
BMI pre-pregnancy			
Underweight or Normal	19 (15.3%)	105(84.7%)	0.251
Overweight or Obese	24 (21.1%)	90(78.9%)	
Family history of diabetes			
Yes	35(44.9%)	43(55.1%)	<0.001*
No	41(10.5%)	349(89.5%)	
Previous delivery to ≥ 4kg baby			
Yes	48(47.1%)	54(52.9%)	<0.001*
No	10(4.4%)	219(95.6%)	
Maternal age			
<25 years	24(14.4%)	143(85.6%)	0.414
≥ 25 years	52(17.3%)	249(82.7%)	
Symptoms of T2DM			
Yes	25 (49.0%)	26 (51.0%)	
No	51(12.2%)	366(87.8%)	<0.001*
Previous stillbirth (>20weeks of gestation)			
Yes	10 (15.9%)	53(784.1%)	0.467
No	48(17.9%)	220(82.1%)	
Previous neonatal death(within 28 days of life)			
Yes	1 (10.0%)	9 (90.0%)	0.538
No	29(20.1%)	115(79.9%)	
Hypertension			
Yes	14(29.2%)	34(70.8%)	0.550
No	62(14.8%)	358(85.2%)	
Insulin resistance			
Yes	19(38.8%)	30(61.2%)	<0.001*
No	25(13.7%)	158(86.3%)	
Protein in urine			
Yes	1(25.0%)	3(75.0%)	0.254
No	65(15.3%)	359 (84.7%)	
Trace	10(25.0%)	392(75.0%)	
Gestational age			
24-28 weeks	49(16.8%)	242(83.2%)	0.554
>28 weeks	27(15.3%)	150(84.7%)	

*Significant at $p < 0.05$

The results shown that, HIP was significantly higher ($p < 0.000$) among women with family history of T2DM (44.9% vs 10.5%, $p < 0.001$); MUAC ≥ 28 cm (23.1% vs 12.4%, $p = 0.003$); history of previous macrosomic delivery (47.1% vs 4.4%, $p < 0.001$); symptoms of T2DM (49.1% vs 12.2%, $p < 0.001$), and IR (38.8% vs 13.7%, $P < 0.001$) (Table 6).

The observed prevalence of HIP did not differ significantly among pregnant women with, history of previous stillbirth, high gestational age (> 28 weeks), neonatal death and delivery through caesarean section, hypertension, advanced maternal age, protein in urine (proteinuria), smoking and alcohol intake habits ($p > 0.05$) (Table 6).

(iii) Factors associated with hyperglycemia in pregnancy

Selected risk factors were analyzed using multiple logistic regression analysis to determine their association with HIP. A significant association was observed in women with high body fat percentage (AOR 1.3, 95% CI: 1.3-1.4), family history of T2DM with (AOR 7.0, 95% CI: 3.1-15.6) and history of delivery macrosomic babies ≥ 4 kg at birth (AOR 2.0, 95% CI: 1.4-5.3) in the first model (Table 7).

The second model replaced body fat percentage with MUAC and the association remained consistently significant in all factors of the first model with the addition of MUAC (AOR 1.2, 95% CI: 1.1-1.3) (Table 7).

The width of interval gives an indication for precision of the point estimate. Hence, the wide ranges in CIs observed for family history of T2DM and fetal macrosomia may be due to the random distribution effects, meaning that the sample population was not sufficient to give inferences. However, the information is useful and can act as a starting point for additional research with a large sample size.

Table 7: Odd ratios of select risk factors for hyperglycemia in pregnancy

Risk factors	Crude OR(95%CI)	P-value
Body fat percentage	1.3(1.2-1.4)	<0.001*
MUAC	1.2(1.2-1.3)	<0.001*
BMI	1.0(1.0-1.1)	0.294
Family history of T2DM		
No	1	
Yes	6.9(4.0-12.0)	<0.001*
Previous delivery ≥ 4 kg baby		
No	1	
Yes	5.9(3.1-11.0)	<0.001*
Delivery(< 37 weeks of gestation)		
No	1	
Yes	1.2(0.4-3.8)	0.779
Birth modality		
Normal delivery	1	
Caesarian section	1.1(0.6-1.7)	0.858

	Model 1		Model 2	
Risk factors	**Adjusted OR(95%CI)**	**P-value**	**Adjusted OR(95%CI)**	**P-value**
Body fat percentage	1.3(CI:1.2-1.4)	<0.001	NA	
MUAC	NA		1.2 (CI: 1.2-1.3)	<0.001*
Family history of T2DM				
No	1		1	
Yes	6.9(CI: 3.1-15.6)	<0.001	6.0(CI: 3.0-12.0)	<0.001*
Previous delivery to ≥ 4kg babies				
No	1		1	
Yes	2.3(CI: 1.0-5.3)	0.049	3.5(CI: 1.7-7.4)	0.001*
Association of HIP and the presence of one or more symptoms for T2DM				
Symptoms of T2DM				
No	1		1	
Yes	2.8(CI: 1.5-6.9)	0.023	3.7(CI: 2.6-4.2)	0.002*

Note: Univariate analysis also included history of neonatal death, blood pressure smoking habit, gravidity /parity and alcohol intake, maternal and gestational age, with no significant association with HIP. In multivariate analysis, body fat was replaced by MUAC in model 2.The abbreviation NA means not applicable in the particular model. *Significant at p<0.05

4.1.4 Insulin resistance among pregnant women

The prevalence of IR was observed to be 21.3% (n=49) and 9.6% had high levels (≥ + 2) of protein in the urine (proteinuria) among 230 pregnant women who were assessed. The overall mean of IR level was 2.2 ± 1.74 of which IR cases had a significantly ($p < 0.001$) high mean of 4.4 (±2.15) compared to the normal women with a mean of 1.4(±1.15) (Table 8).

Table 8: Laboratory tests for proteinuria and insulin resistance among pregnant women (N=230)

Variables Tested	Frequency	Percent	Mean (SD)
Insulin resistance status			
Insulin level	230	100.0	2.2 (± 1.74)
Normal	181	78.7	1.4(±1.15)
IR cases	49	21.2	4.4(±2.15)
Protein in urine			
Positive	22	9.6	
Negative	145	63.0	
Trace	63	27.4	

(i) Factors associated with insulin resistance in pregnancy

Multiple logistic regression analysis was performed to determine the associations among selected risk factors with IR. Insulin resistance was significantly associated with high body fat percentage (AOR 1.7, 95%CI: 1.5-2.0), family history of T2DM with (AOR 2.8, 95% CI: 1.2-6.3), protein in urine (proteinuria) (AOR 3.4, 95% CI: 1.1-10.7), presence of edema (AOR 3.0, 95% CI: 1.3-6.7), and hypertension (AOR 2.5, 95% CI: 1.1-5.6) (Table 9).

Maternal age, MUAC, pre-gestational BMI, previous delivery of baby ≥ 4 kg were not associated with IR after adjusting for other risk factors ($p > 0.05$). Moreover, IR was significantly associated with HIP ($p < 0.001$) (Table 9).

The wide CI indicates that a large range of possible values must be included in order to be 95% confident that the parameter lies within the CI. Hence, CIs for family history of T2DM and the presence of protein in urine suggests that the sample population is not large enough to make inferences, but recognizes that this insight is practically useful and indicates the need for additional research (Table 9).

Table 9: Association of select factors with insulin resistance

Risk factors	Crude OR (95%CI)	P-value	Adjusted OR (95% CI)	P-value
Body fat percentage	1.8(1.4-2.1)	0.001*	1.7(1.5-2.0)	0.023*
Age of woman	1.1(1.0-1.1)	0.079	NA	
MUAC	1.1(1.0-1.2)	0.362	NA	
Hypertension				
No	1		1	
Yes	2.9(1.6-4.9)	0.001*	2.5(1.9-4.6)	0.025*
Family history of T2DM				
No	1			
Yes	2.2(1.1-4.6)	0.031*	2.8(1.2-6.3)	0.016*
Previous ≥ 4 kg babies				
No	1		1	
Yes	2.4(1.0-5.6)	0.049*	1.2(1-1.2)	0.045*
BMI				
< 25 kg/m^2	1			
≥ 25 kg/m^2	0.5(0.2-1.5)	0.100	NA	0.100
Protein in urine				
Negative	1		1	
Positive	3.5(1.3-9.8)	0.017*	3.4(1.1-10.7)	0.033*
Edema				
No	1			
Yes	3.5(1.7-7.4)	0.001*	3.0(1.3-6.7)	0.010*
Relationship between IR and HIP				
IR as risk factor for HIP	3.8(1.9-7.7)	0.001*	NA	

Note: The univariate analysis also included gestational age, preterm delivery (<37 weeks of gestation) as well as stillbirth and neonatal death with no significant association with IR. The abbreviation AOR means Adjusted Odd Ratio, CI - Confidence Interval, NA means Not Applicable for multivariate analysis and IR –Insulin Resistance. *Significance at $p < 0.05$

4.1.5 Knowledge on hyperglycemia in pregnancy among pregnant women

(i) Knowledge about hyperglycemia in pregnancy

Among the interviewed women, very few knew about the existence of HIP (10.7%, n=50) and 36% (n=18) correctly defined HIP as diabetes with first recognition during pregnancy. Few participants were able to mention the effects of HIP (23%, n=14), such as stillbirth, neonatal death, delivery of a microsomal infant (≥ 4 kg) at birth, and development of diabetes mellitus later in life for the mother and the newborn. Moreover, few women (26%, n=13) knew some symptoms for HIP, such as extreme tiredness, diaphoresis (excessive sweating), and polydipsia (excessive thirst). In addition, 30% (n=15) of the women knew the causes/risk factors for HIP, and mentioned family history of T2DM and history of delivery big babies to be predictors for HIP (Table 10).

Table 10: Participants' knowledge about hyperglycemia in pregnancy (N=468)

Variables tested	Frequency	Percent
Knowledge on the existence of HIP		
Yes	50	10.7
No	418	89.3
Know the meaning of HIP		
Yes	18	36.0
No	32	64.0
If yes what is HIP		
Diabetes first occurring in pregnancy	18	36.0
Do not know the meaning	32	96.2
Know the symptoms of HIP		
Yes	13	26.0
No	37	74.0
If yes what are the symptoms of HIP		
Frequent urination	6	46.0
Tiredness	3	23.0
Frequent thirsty	4	31.0
Know the effects of HIP		
Yes	14	23.0
No	36	77.0
If yes what are the effects of HIP		
Overweight baby	2	14.2
Diabetes later in life to mother and child	6	42.9
Prenatal death	6	42.9
Understand the risk (causes) of HIP		
Yes	15	30.0
No	35	70.0
If yes what are the causes of HIP		
Family history of T2DM	12	80.0
Previous delivery to > 4kg babies	3	20.0
Reported sources of information about HIP		
During ANC	12	24.0
Different media (Internet, TV, what-sap etc.)	38	76.0

(ii) Factors influencing awareness about hyperglycemia in pregnancy among women

Knowledge about HIP was significantly associated with education level (AOR 13.7, 95% CI: 4.07-46.15) for secondary and (AOR 5.5, 95% CI: 1.78-16.76) for college/university levels. After adjusting for income, occupation, age and gravidity, knowledge remained significantly associated with education levels. The wide CI in the level of education means that the factor occurs in a small proportion of women who may not be the representative, thereby creating uncertainties as to whether the estimate of the parameter is precise (Table 11). However, it important to note that the obtained information is still valuable and calls for additional studies such as longitudinal or population-based approaches.

Table 11: Participants' attributes associated with awareness of hyperglycemia in pregnancy

Risk factors	n	Crude OR(95%CI)	P-value	Adjusted OR(95%CI)	P-value
Education levels					
Primary /informal	283	1		1	
Secondary	164	25.5(10.4-62.5)	<0.001*	13.7(4.1-46.2)	<0.001*
College/university	21	12.6(5.2-30.6)	<0.001*	5.5(1.8-16.8)	0.003*
Gravidity					
Prime	142	1		1	
Second and third	236	1.46(0.67-3.21)	0.341	1.2(0.2-2.5)	0.567
Fourth and above	90	2.37(0.92-6.16)	0.050	2.1(0.5-4.7)	0.076
Maternal age					
< 25years	164	1		1	
≥ 25years	304	1.3(0..4-2.4)	0.088	1.1(0.6-1.8)	0.956
Employment status					
Unemployed	161	1		1	
Non-formal employed	261	0.1(0.1-0.3)	0.824	0.14(0.1-0.4)	0.638
Formally employed	46	1.1(0.5-2.3)	<0.001*	1.0 (0.3-2.5)	0.631
Income level (Tshs)					
<250 000	255	1		1	
250 000-450 000	33	7.1(1.6-31.7)	0.011*	2.1(1-47.0)	0.638
>450,000	13	4.7(1.4-21.3)	0.045*	0.6(0.1-12.0)	0.680
Not sure	167	0.1(0.1-0.3)	0.905	0.1(0.0-0.5)	

Note: Large Confidence Intervals (CI) may be due to a small number of women falling in the category. Abbreviation: OR–Odd ratio. *Significant at $p < 0.05$

(iii) Practices reported by women on hyperglycemia in pregnancy screening and management

During the assessments for practices in screening, and managements of HIP, about 8.1% (n= 38) of the pregnant women reported to have been screened for diabetes in their previous pregnancies using urine samples with five (13.2%, n=5) reporting positive results in their previous pregnancy. The few women who were diagnosed with diabetes were provided with counseling and referred to the doctor/regional hospital for further actions but no follow-up from the ANC (Table 12).

Table 12: Women's reported practices on hyperglycemia in pregnancy screening and management (N=468)

Variables Tested	Frequency	Percent
Tested glucose in previous pregnancies		
Yes	38	8.1
No	266	56.8
Not sure	164	35.1
Testing method used		
Urine	38	100.0
Blood	0	0.0
If tested what was the status		
Normal	33	86.8
High/detected	5	13.2
If high were you treated		
Yes	3	60.0
No	2	40.0
If yes, how were you treated		
Counseled and refereed to hospital	3	100.0
Medication	0	0.0
Followed up after diagnosis		
Yes	0	0.0
No	5	100.0

4.1.6 Development of the risk scores

The risk score for identification of women with or at risk of GDM was developed using logistic regression analysis (binary logistic) with stepwise backward selection procedure. Before analysis was done, all women with DIP were excluded from the analysis as the aim was to develop a tool for identification of women at risk of GDM which is the highly increasing type of HIP.

(i) Odd ratios and regression coefficients from univariate analysis

From the univariate logistic regression model, potential predictors for the development of GDM among pregnant women included; increased MUAC, body fat percentage, history of stillbirth in previous pregnancy, family history of T2DM and delivery model (Caesarean section) which may indicates a history of big babies in previous pregnancies. In addition to history of delivery macrosomic babies which may indicate that women had high level of glucose in her previous pregnancy which was transferred to the fetus, and IR at $P < 0.05$. On the other hand, hypertension during pregnancy and before pregnancy and after delivery, edema, smoking habits, alcohol intake, preterm delivery, gravidity, maternal age ≥ 25 years and proteinuria were not significantly associated with HIP at $p > 0.05$ (Table13). Insulin

resistance was not included in the final model due to costs associated with laboratory analysis.

Table 13: Univariate analysis of risk factors associated with gestational diabetes mellitus

Variables	B	Crude OR	CI	P-value
Mothers age ≥ 25yrs	0.10	1.01	0.96-1.05	0.846
Macrosomic (≥ 4kg)	1.09	2.99	1.63-5.48	<0.001*
T2DM history	1.66	5.27	2.88-9.63	<0.001*
MUAC	0.47	1.60	1.44-1.77	<0.001*
Body fat	0.49	1.65	1.46-1.86	<0.001*
Parity	0.09	1.10	0.46-2.64	0.835
Preterm delivery(< 37weeks)	0.13	1.14	0.32-4.02	0.837
Stillbirth	1.33	3.78	1.34-10.63	0.012*
Neonatal death	-19.44	0.00	0.00-0.01	0.999
Blood pressure in pregnancy	0.32	1.38	0.73-2.60	0.327
Blood pressure before pregnancy	-19.36	0.00	0.00-0.01	0.999
Alcohol intake	0.09	1.10	0.18-6.57	0.917
Smoking habits	-19.35	0.00	0.00-0.08	0.999
Presence of edema	-0.01	0.99	0.50-1.96	0.967
Proteinuria	0.25	1.28	0.34-4.84	0.715
Presence of glucose in urine	1.03	1.11	0.10-12.04	0.931
IR	1.77	6.76	5.67-8.22	<0.001*

Note: The word “No” was used as reference in categorical variables. Univariate also included stillbirth and neonatal death in the current pregnancy which had no significant association withn GDM *Significant at p< 0.05

(ii) Adjusted odd ratios, regression coefficients and scores from multivariate analysis

From multivariate model, factors found to be predictors of GDM were MUAC ≥ 28 cm (AOR 1.28 95% CI 1.08-1.56), body fat percentage (AOR 1.77, 95% CI 1.37-2.294), family history of type 2 diabetes (AOR 8.34, 95% CI 1.91-36.43), and previous history of delivery macrosomic babies (AOR 7.99, 95% CI 1.95-32.79) (Table 14).

Then a cut off point for body fat percentage was developed using the ROC and found that the risk for GDM is increasing with the body fat of ≥ 38%. Backward elimination method removed hypertension, preterm delivery, stillbirth and maternal age which were not significantly associated with GDM ($p > 0.1$). The significant variables were used to develop a risk score model to identify women with and /or at risk of GDM (Table 14). The risk for GDM increased among woman with 2 to 49 scores (Table 14).

Table 14: Multivariate analysis and risk scores

Variables	B	OR	CI	P-value	B x 10
Macrosomic	2.00	7.99	1.95-32.79	0.004*	20
T2DM history	2.12	8.34	1.91-36.43	0.005*	21
MUAC	0.24	1.28	1.080-1.58	0.019*	2
Body fat	0.57	1.77	1.37-2.29	<0.001*	6
Total points					**49**
R^2 of 0.80 and ROC 0.97	NA	NA	0.95-0.99	<0.001*	NA

Different threshold values for the risk of HIP

Threshold value	Sensitivity	Specificity	PPV	NPV
0.2	0.98	0.46	0.68	0.97
4	0.96	0.23	0.57	0.89
7	0.93	0.13	0.54	0.75
10	0.91	0.11	0.53	0.65

Note: Significant p≤ 0.1. The abbreviation OR means odd ratio, CI confidence interval, NA-not applicable , PPV-Positive predictive value, NPV- Negative predictive value

Among the risk factors involved in the model, family history of T2DM contributes much on the development of GDM followed by tendency of delivery macrosomic babies, high body fat percentage and lastly increased MUAC (Fig. 12).

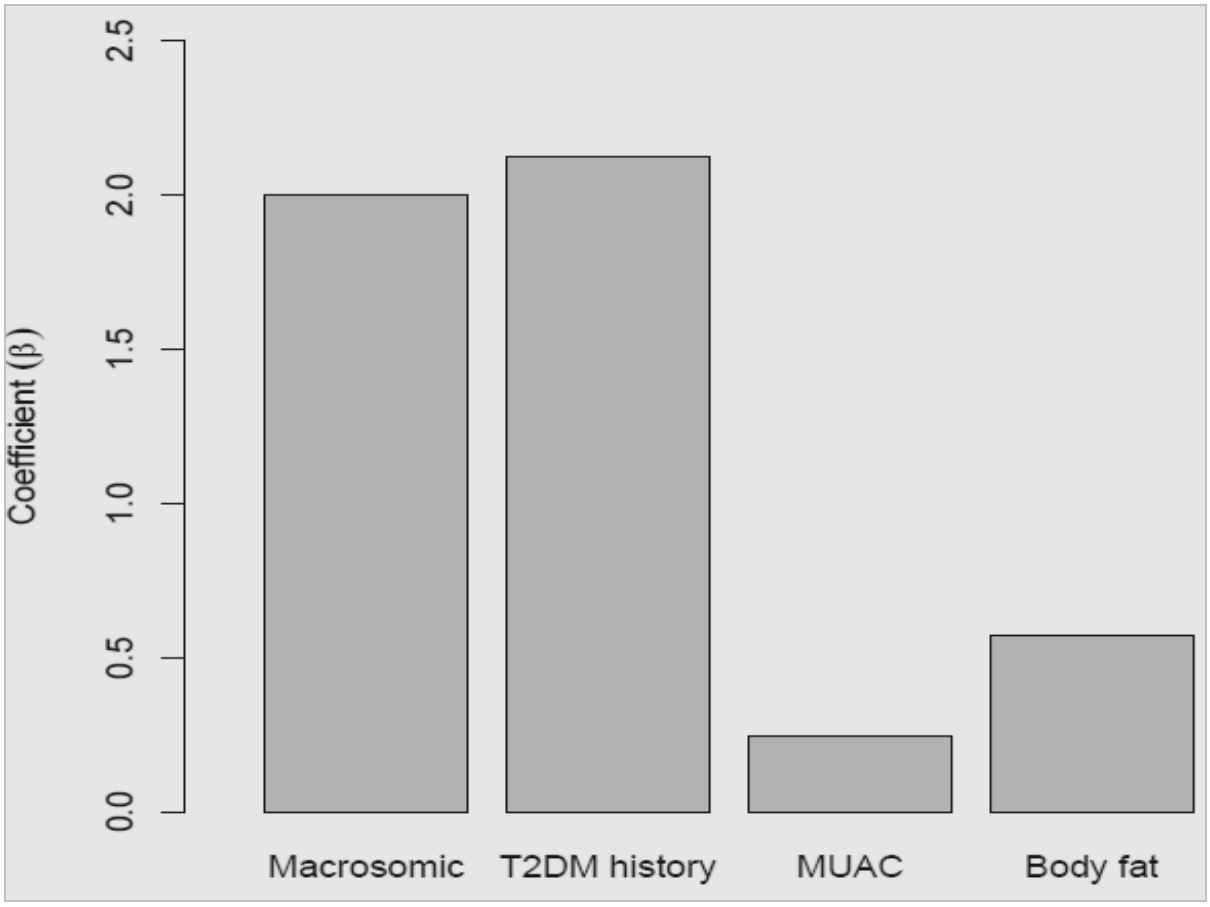


Figure 12: Contributions of each risk factor in the model

(iii) Performance of the developed model

The threshold of 0.2 was selected as cut off for the performance of the model to reduce the number of false negatives and identify most of the women at risk of the condition. The model was found to perform well in the studied ANC setting with an AUC of 0.97 (95% CI 0.96-0.99, $p < 0.001$) (Fig. 13), sensitivity of 0.98, specificity of 0.46 as well as PPV of 0.68 and NPV of 0.97 at a selected cut off of 0.2. Moreover, the regression has the pseudo-R squared = 80.03% which implies that the model is a good predictor of GDM (Table 14).

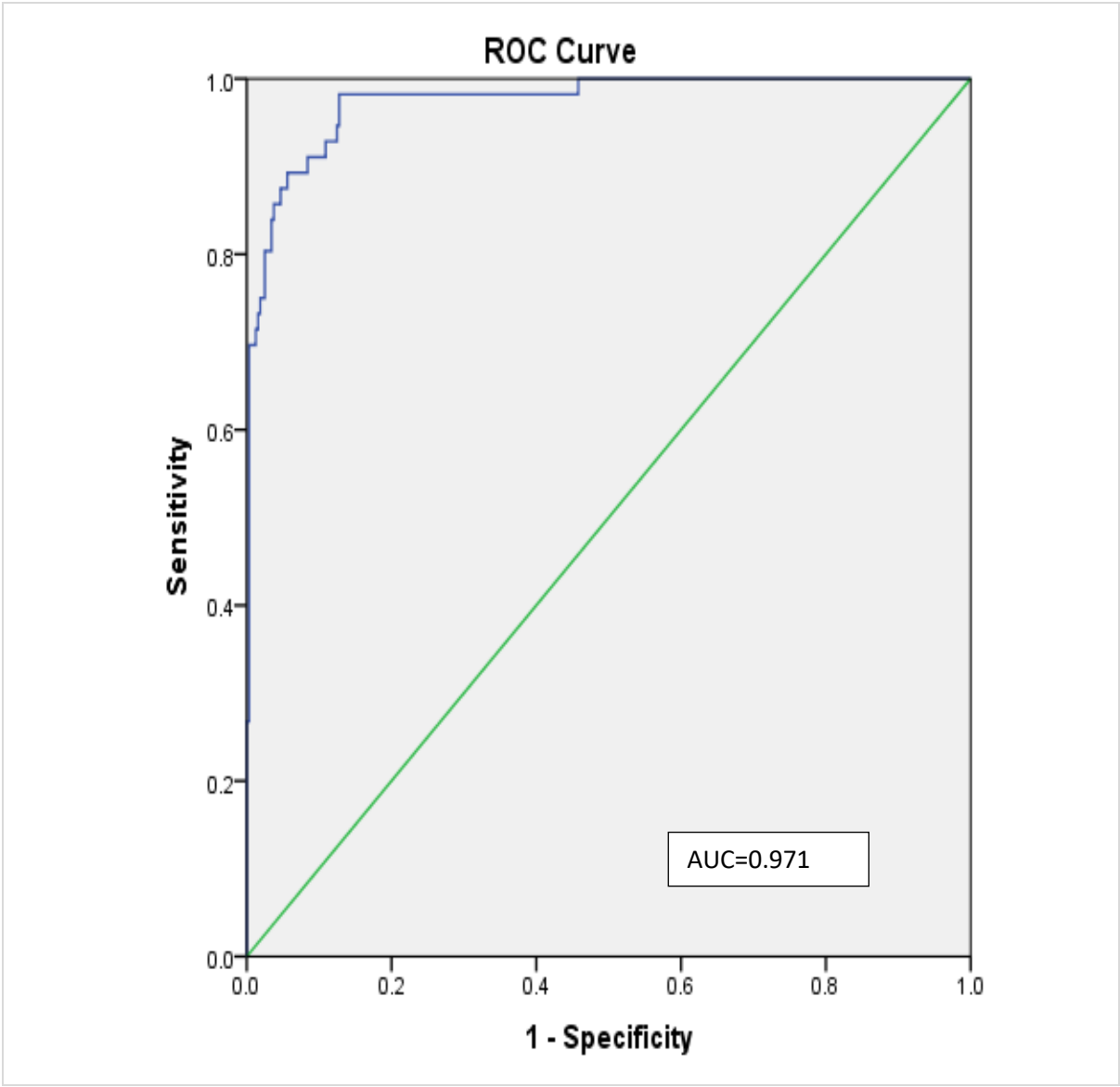


Figure 13: Receiver–operating characteristics curve (ROC) for performance of the risk score model

(iv) Comparison of performance of the risk score and other models

The performance of the risk score model was significantly higher with AUC of 0.97 (95%CI 0.95-0.99, p < 0.001) compared to that of fasting glucose test with AUC of 0.96 (95%CI 0.92-0.99, p < 0.001), and OGTT with AUC of 0.64 (95% CI 0.56-0.72, p = 0.002). Urine glucose test model performed poorly with an AUC of 0.54 (95% CI 0.45-0.63, p = 0.38 as it could not discriminate women with GDM and those without the condition (Fig. 14).

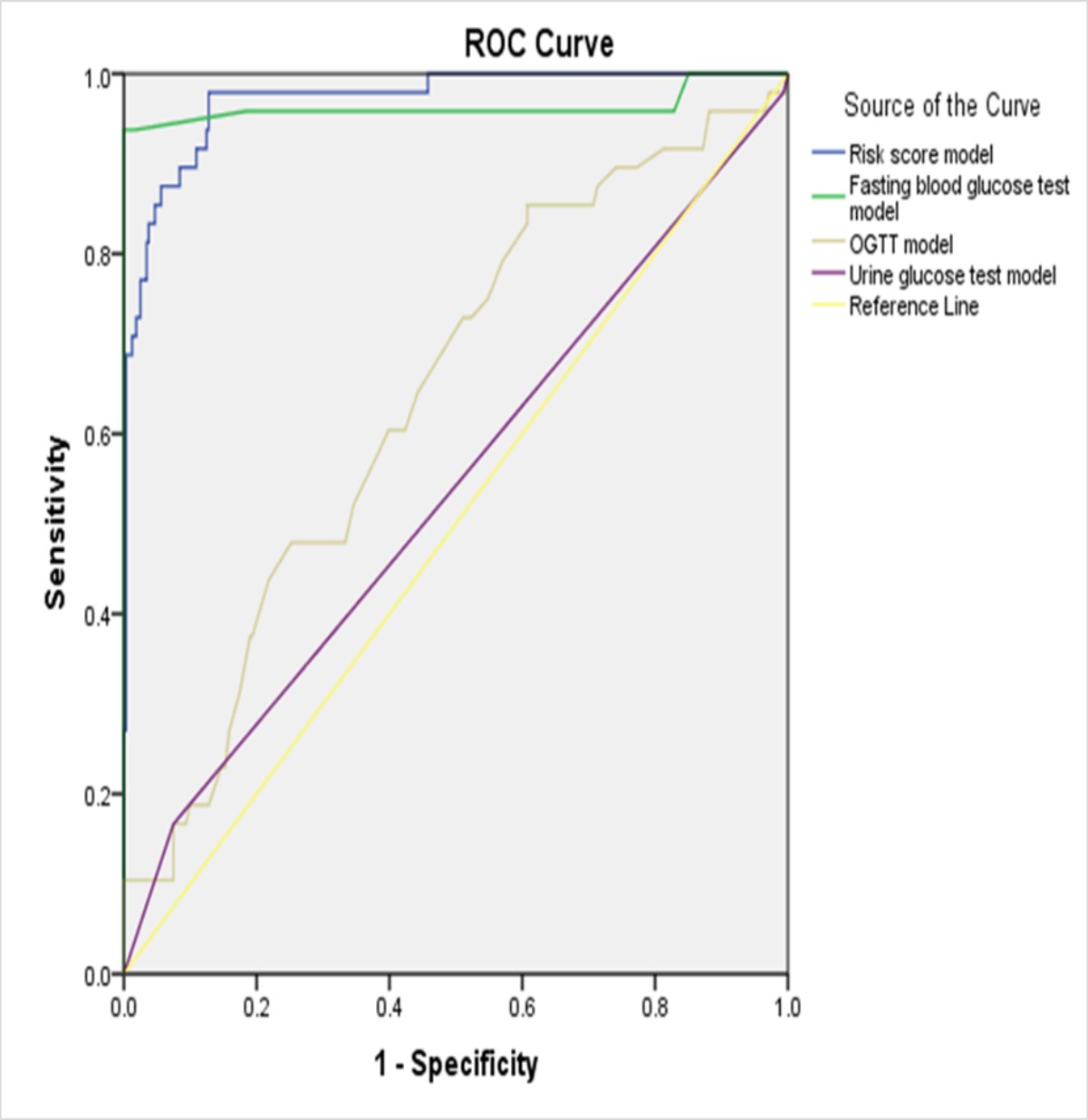


Figure 14: Receiver–operating characteristics curve for performance of the risk score, urine glucose and fasting and oral glucose tolerance test models

(v) Clinical utility of the model

Clinical utility of the model was assessed using the Net benefit (NB) curve which shows that, in different combinations of true and false positive values, there is high benefit of screening for GDM using the risk score model at any chosen threshold. For-example the NB of using risk scores is 83%, while universal screening for all women is 80% at the threshold of 0.2. When the threshold was chosen at 0.6, the NB of GDM screening using the risk score model was still high (80%) compared to universal screening for all women which was 62% (Fig. 15). This implies that, when risk score is used more pregnant women with high risk of GDM benefit from the screening program.

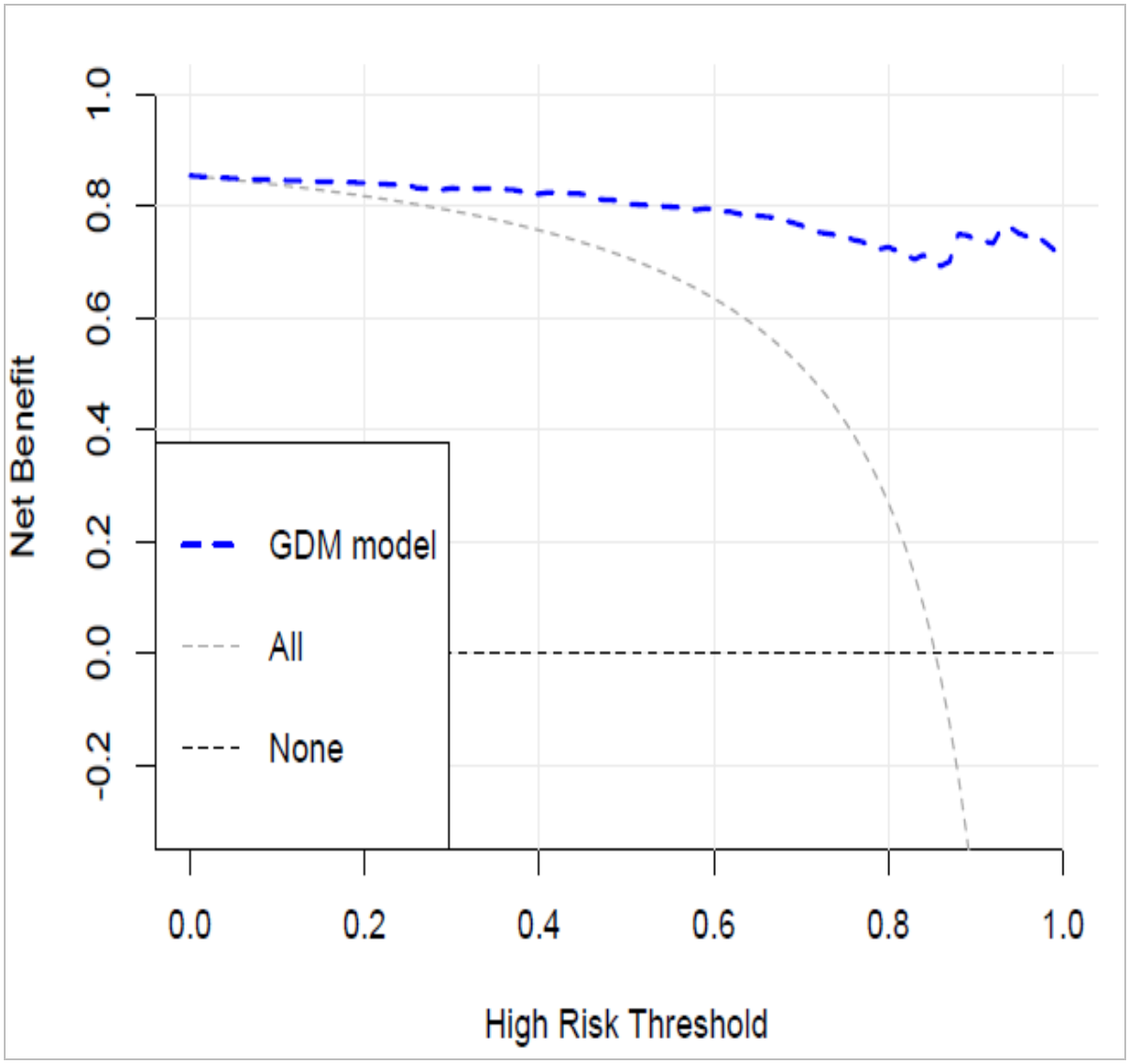


Figure 15: Net benefit curve for the clinical utility of the model (threshold probability)

(vi) The risk factors checklist

The predictors used to develop risk score in addition to the risk factors for IR were simplified into a simple checklist which involved macrosomic babies as a result of high maternal glucose levels during pregnancy, high MUAC ≥ 28 cm and body fat ≥ 38%, family history of T2DM as well as edema, and hypertension which are risk factors for IR (Table 15). In this case, having one or more of the risk factors indicated in the checklist, exposes a woman to the risk of developing GDM which indicates the need for further testing to confirm.

Table 15: The risk factors checklist

	Risk factors for GDM
1	Tendency of delivery macrosomic babies (≥ 4 kg)
2	Family history of T2DM
3	High MUAC ≥ 28 cm
4	High body fat ≥ 38%
5	Edema and/or hypertension

Note: The occurrence of preeclampsia manifested by edema and hypertension is a risk factor for IR which is associated with early GDM

4.2 Discussion

4.2.1 Overview

The current study was conducted among pregnant women in Arusha District to establish the prevalence of HIP and develop a simplified method for identification of women with /or at risk of GDM in Tanzania's ANC settings with limited recourses. This will enhance self-care and evidence-based treatment for appropriate and efficient use of the limited resources. The study also established the prevalence of IR, and knowledge about HIP among pregnant women in the selected ANC centers.

4.2.2 Prevalence of hyperglycemia in pregnancy and associated risk factors among pregnant women

The overall prevalence of HIP was 16.2%, of which 3.2% had DIP and 13% GDM according to WHO (2013) criteria. The observed prevalence of HIP may increase burden to the health system if no immediate actions are taken. The need exists to explore the associated modifiable risk factors including body fat percentage to enhance self-care practices and prevent poor pregnancy outcomes as well as T2DM later in life. A similar study conducted in Kilimanjaro Region, Tanzania using the same WHO (2013) criteria reported that the

prevalence of DIP was 3% and 19.5% had GDM (Njete *et al.*, 2018) which is higher than the current study. The differences observed may be due to nature of the diets, cultural differences in food preparation, and care during pregnancy, as well as after delivery which need further explorations. A similar study in Nigeria reported that the prevalence of GDM was 15.7% and DIP was 4.8% according to WHO (2013) criteria (Imoh *et al.*, 2017). In India likewise, HIP was prevalent in 18.9% of the studied population where by 16.3% had GDM and 2.6% had DIP (Nielsen *et al.*, 2016) using the same WHO (2013) criteria. In these studies, the prevalence of GDM is higher than DIP. As long as GDM disappears after delivery if managed, early interventions could help to prevent poor pregnancy outcomes and its progression to T2DM later in life.

The prevalence of HIP in the present study was significantly associated with high body fat percentage, family history of T2DM, MUAC ≥ 28 cm and previous delivery of ≥ 4 kg babies at birth. Increased body fat percentage and MUAC are indicatives of overweight and obesity which are positively associated with development of HIP. Excess body fat and a high proportion of large adipocytes may significantly contribute to IR later in pregnancy. Adipose tissue produces numerous factors (adipocytokines), most of which act as hormones. For example adiponectin is the main adipose-specific protein which may have a role in the pathogenesis of obesity. As obesity is a predisposing factor for development of diabetes mellitus in general and GDM in specific, this might explain the indirect involvement of a decreased adiponectin in the pathogenesis of diabetes mellitus. Moreover, obesity is linked to increased circulating levels of leptin and the inflammatory markers of TNF-α and C-reactive protein as well as decreased levels of adiponectin, which are associated with IR and risk of GDM (Kautzky-Willer *et al.*, 2001; Retnakaran *et al.*, 2003; Retnakaran *et al.*, 2004; Williams *et al.*, 2004).

On the other hand, BMI obtained from the recalled pre-pregnancy weight was not significantly associated with HIP even after been replaced for MUAC and/or body fat percentage in the models, making it a weak determinant of HIP. A major limitation with recalled weight before pregnancy is that, women may over or under-estimated their pre-pregnancy weight which may cause bias. In this case, body fat percentage together with MUAC can be used instead of BMI as determinants of HIP due to their independent association with HIP which helped to reduces biases of recalled weight.

In the current study, almost half of the pregnant women could not recall their pre-pregnancy body weight making it difficult to estimate pre-pregnancy BMI and pregnancy weight gain. This may be due to fact that majority of Tanzanians, including women, do not have tendency of assessing their nutritional status regularly unless in the case of the diseases and/or advised by the doctor. This finding is supported by Mwanri *et al.* (2014) who reported that BMI could not be estimated for most of the women, due to failure to recall their pre-pregnancy weight. Another similar study reported that, less than half of the pregnant mothers had an ability to recall their pre-gestational weight (Saldana *et al.*, 2004).

Although weight during pregnancy can be estimated with a recorded weight within fifteen weeks of pregnancy (Saldana *et al.*, 2004), women in the current study started first ANC visit at a mean gestational age of 18 weeks making their pregnancy weights to be indeterminate. A similar study reported that, since most of the women appeared late to the ANC with a mean gestational age of 20 weeks, it was difficult to obtain their pre-gestational weight (Gale *et al.*, 2007). Hence, information on changes in body fat content is required due to its independent association with HIP and easy of estimations during pregnancy. This is further supported in a previous study which report that the risk of GDM was independently associated with high body fat percentage, similar to the findings in people with T2DM (Iqbal *et al.*, 2007). Similarly, a study conducted in China reported that the percentage body fat was the strongest risk factor for GDM after adjusting pre-pregnancy BMI (Wang & Luo, 2019). With these associations, it is important to utilize these simple factors to identify pregnant women at risk for HIP so that prevention measures, such as lifestyle modifications, can be implemented to prevent poor pregnancy outcomes (Forsbach-Sanchez *et al.*, 2005).

Women with a history of delivery macrosomic babies (≥ 4 kg) at birth were at twice the risk of HIP compared to their counterparts even after adjusting for body fat percentage, pre-pregnancy BMI, gestational age and MUAC. This may be attributed by a high maternal glucose level which was transferred to the fetus. This finding reveals how maternal health status is the determinant of health of the newborn. This occurs due to fetal hyperinsulinemia, which results from maternal fetal transfer of glucose (Xiong *et al.*, 2001). It can also be due to elevation in plasma concentrations of placental hormones like progesterone, human chorionic somatomamotrophin and cortisol, which are designed to provide energy and nutrients for the developing fetus by providing more glucose, resulting in dysregulation of glucose metabolism (Asare-Anane *et al.*, 2013; Fetita *et al.*, 2006). Another study in South

Africa found that a previous history of delivery a baby weighing ≥ 4 kg at birth was an independent predictor of developing GDM (Adam & Rheeder, 2017). This finding means that a woman whose pregnancy resulted to a child with high birth weight, is at an increased risk of GDM in progressive pregnancies (Ross, 2006).

In this study, women with family history of diabetes were almost seven times at greater risk of HIP compared to their non-affected counterparts meaning that HIP can be influenced by genetic predisposition and/or lifestyle practices, such as dietary intake and low physical activities. Another study showed that, GDM is considered to result from interaction between genetic and environmental risk factors (Shaat & Groop, 2007). Pregnancy triggers a series of metabolic imbalances that lead to a diabetic state in women who are already genetically predisposed to develop diabetes (Reece *et al.*, 2009). Of note, GDM and T2DM share a similar genetic background (Kwak *et al.*, 2012), which might be a reason to why women with strong first-degree family history of T2DM are at high risk of GDM. Hence, genetic predispositions to T2DM or GDM should not be ignored. Other studies concur with the current finding that family history of diabetes remained significantly associated with GDM even after adjustment for other co-variates (Whelton *et al.*, 2017; Leng *et al.*, 2015).

Some women with HIP reported having one or more symptoms of T2DM, such as extreme tiredness, diaphoresis, polydipsia and increased frequent urination. These symptoms were found to have a strong independent association with HIP even after adjusted for MUAC, BMI, gestational age and family history of T2DM. Considering the asymptomatic nature of GDM (ADA, 2010), these women may have pre-existing T2DM which was not diagnosed before pregnancy because, 3.2% (n=15) of the women had high glucose cut off points which indicated the presence of DIP. This may be attributed by a high prevalence of T2DM without access to screening services before pregnant hence, increasing their risk for pre-existing undiagnosed diabetes in pregnancy.

Therefore, there is a need to promote pre-pregnancy preparations that include regular screening for diabetes for earlier efforts to be taken to prevent the development of HIP. Hyperglycemia in pregnancy has few or no symptoms and should be diagnosed by screening during pregnancy (Al-Noaemi & Shalaye, 2011). Another study reported that overt symptoms of GDM/HIP are rare and may be difficult to distinguish from normal pregnancy symptoms creating a need for confirmatory OGTT (ADA, 2010). Hyperglycemia in pregnancy can be influenced by first generation family history of T2DM and, when undiagnosed and

unmanaged, can lead into recurrent GDM in subsequent pregnancies and/or T2DM later in life (IDF, 2013; Leng *et al.*, 2015). Hence, symptom clusters with risk factors can be used for identification of women who need screening for HIP especially in low income countries where universal screening is not possible due to resource constraints.

4.2.3 Prevalence of insulin resistance and its determinants among pregnant women

The prevalence of IR was present in 21.3% (n = 49) of the 230 studied women with significantly higher incidence among women with HIP compared to non-HIP. This finding may reflect that IR is a normal condition in pregnancy but may become dominant leading to HIP, especially among women with increased risk for diabetes. Another similar study reported that women with GDM are more likely to experience IR than their non-GDM counterparts (Elkind-hirsch *et al.*, 2010). Furthermore, increased serum insulin level at screening in early pregnancy can predict GDM because, the higher the serum insulin level, the earlier the manifestation of GDM (Bitó *et al.*, 2005).

Insulin resistance was significantly associated with high body fat percentage meaning that increased fat deposition exposes pregnant woman to IR condition; however, MUAC and pre-pregnancy BMI were not associated with IR after adjusting for other risk factors. This divergence may reflect that pre-pregnancy BMI was determined for few pregnant women as the majority could not recall their pre-pregnancy body weight and determination of weight at early stage of pregnancy was not possible due to late start of ANC attendance. Another reason could be that the recalled weights are sometimes under-reported (i.e., most obese/overweight women report low weights) (Saleem *et al.*, 2013).

Pregnancy is associated with increased maternal adiposity and storage of carbohydrates and fat, as an evolutionary adaptation to facilitate successful lactation; but, the deposition within skeletal muscle and liver cells is a major contributory factor to IR (Ravikumar *et al.*, 2005). Several studies have supported this finding, such as a study from Japan which reported a significant relationship between HOMA-IR and body fat percentage in patients with a normal or below normal BMI level (Sasaki *et al.*, 2016). Similarly, a study from Turkey reported that body weight and BMI did not reflect body composition, particularly body fat, which is considered to be closely related to IR (Gur *et al.*, 2014). Svensson *et al.* (2016) in Sweden reported that body fat mass and the proportion of very large adipocytes were strongly associated with gestational IR.

Women with a family history of T2DM experienced three times the risk of IR than their counterparts. This finding may reflect that GDM and T2DM share a similar genetic background, which may clarify why women with strong first-degree family history of T2DM are at high risk of GDM (Kwak *et al.*, 2012). Another similar study found family history of diabetes and hypertension to play important roles in IR syndrome (Velasquez-Mieyer *et al.*, 2005).

Maternal age was not significantly associated with IR after adjusting for body fat percentage, family history of T2DM, hypertension, presence of edema, and proteinuria. This is because, IR was also prevalent among younger women where 13 out of 49 women with IR were below 25 years of age. This finding could be explained by overweight and obesity, which often increases with age however, more recent trends have shown that women become obese and overweight at a younger age as in this study where 10 out of 47 obese/overweight women were below 25 years of age. Another similar study reported that the prevalence of overweight/obesity among young adults (18 to 25 years old) in developing countries is increasing mostly among females (Poobalan & Aucott, 2016).

This increases their chance for developing NCDs at younger age, such as diabetes mellitus and cardiovascular diseases. Another study reported no significant difference in age of the mothers in IR case groups (Sonagra *et al.*, 2014). Contrary to the current study's finding, Karakelides *et al.* (2010) reported that age affects insulin sensitivity, meaning that increase in age, leads to progressive increase in IR which is a proxy for GDM and T2DM. Moreover, age of onset of diabetes and pre-diabetes is declining while age of childbearing is increasing. Overweight and obesity is increasing among women of reproductive age according to Tanzania National Nutrition Survey (MoHCDGEC *et al.*, 2018) making more women to enter pregnancy with some risk factors that make them vulnerable to IR and GDM (Hod *et al.*, 2015).

Pregnant women with hypertension had almost three times increased risk for IR than those with normal blood pressure levels. Most of the pregnant women with IR were also found to have HIP, which is associated with development of pregnancy hypertension. A similar study concurs with these findings that diseases, such as hypertension and diabetes, are associated with existence of IR (Catalano, 2010). Hyperinsulinemia may predispose a woman to hypertension by increasing renal sodium reabsorption and stimulation of the sympathetic nervous system (Reaven, 1995). Furthermore, the features of the IR syndrome may persist

many years after pregnancy raising the possibility of increased risk for future cardiovascular disease which is manifested by hypertension. Thus, interventions to reduce IR may reduce risk of both hypertension during pregnancy and later life cardiovascular complications (Seely & Solomon, 2003).

Likewise, pregnant women with edema which is normal condition but was also observed in the arms and faces with an addition of proteinuria, experienced three times the risk of IR as compared to their counterparts even after adjusted for body fat percentage, family history of T2DM, hypertension and age. As the presence of edema, proteinuria and/or hypertension indicate the risk for preeclampsia, women with risk for preeclampsia may also experience IR. A study from Iran found that IR is considered a risk factor for preeclampsia pathogenesis meaning that preeclampsia is associated with increased IR before the onset of the disease (Abhari, 2014). In addition, research done at Kermanshah in Iran reported that women who developed preeclampsia had higher fasting insulin levels at the second trimester, before the appearance of clinical signs of preeclampsia, as well as fasting insulin level progressively increases when disease develops (Malek-Khosravi & Kaboudi, 2004). These findings show that preeclampsia and IR have a casual and effect relationship.

Hence, identification of women with IR and exploration of associated risk factors can be a starting point towards the prevention of GDM as well as T2DM later in life. Although IR has been found to be significantly associated with several risk factors, the CI of some variables were wide which may be due to a relatively small sample of 230 pregnant women. This may affect results as it implies that there is not enough information to confidently conclude that the observed outcome is within the population parameters, although the results are still practically meaningful. Hence, additional research with a larger sample is needed (Sim & Reid, 1999).

4.2.4 Knowledge about hyperglycemia in pregnancy among pregnant women

This study assessed knowledge of the pregnant women on HIP for appropriate interventions to be planned to prevent short and long-term effects of HIP to the mother and her newborn through self-care. It also included sources of information and general practices of screening and managing HIP to understand how pregnant women are screened for diabetes/GDM and managed as part of the antenatal care.

The majority of the pregnant women in this study had poor knowledge on the existence of HIP, which may increase the likelihood of associated effects as these women may continue with poor lifestyle choices regardless of their condition. This finding is in line with the behavior change model under the Health Belief Model which explains that, after having knowledge on different aspects of a health condition, behavior change occurs when people feel to be vulnerable and perceive the consequences of the condition as severe. Finally, individual's behavior can change if they realize that taking action may either prevent or reduce the risk of the condition at an affordable cost (Irwin, 1974; Janz & Marshall, 1988).

Low knowledge about HIP in the studied pregnant women may reflect that, the health system is not prioritizing HIP in the ANC as a risk factor for poor pregnancy outcomes as opposed to HIV, malaria, and tuberculosis which are given significant attention in current FANC guidelines. The standard treatments and essential medicines list guidelines include GDM screening using fasting plasma blood and 2 hours OGTT (MoHSW, 2013). This guideline also recommends the condition to be managed before and throughout pregnancy along with control of glucose levels by diet, oral hypoglycemic and/or insulin. The blood sugar should be maintained within the range of 4-6 mmol/L throughout pregnancy and during labour the glucose needs to be checked after every 4 hours to detect any signs of hypoglycemia and managed it accordingly (MoHSW, 2013). Also, the same guidelines recommend monitoring of the blood sugar after delivery to adjust insulin requirements (MoHSW, 2013).

Although there is sufficient information on GDM screening and management in some guidelines, these guidelines are seldom incorporated into the ANC services to meaningfully impact accessibility and affordability of this important intervention. It is imperative that the health care system integrate these guidelines into the ANC so that they can be consistently applied by the health care providers who typically adhere to such guidelines.

The disintegrated information in the health system limits the health care providers in promoting and attending this pregnancy challenge in the ANC programs. This finding was consistent with a similar study in North Karnataka where most of the women had poor knowledge about GDM (Dhyani *et al.*, 2018). However, a study conducted in Samoa reported that a high proportion of women (58%) were aware that GDM can occur initially during pregnancy and 23% indicated uncertainty and the remaining 19% were not aware of the disease at all (Price *et al.*, 2017).

Knowledge about HIP in the current study was significantly associated with level of education where the majority of women with knowledge had attained secondary or college/university levels of education. On the other hand knowledge on HIP was not associated with occupation, income, age and gravidity after adjusting for education levels. The possible explanation is that educated women can easily search for information from different sources and may have obtained HIP knowledge at school either through training or sharing of experiences. A similar study from Ghana reported that pregnant women with higher levels of education were more aware of the risk factors associated with GDM and, possibly, its management and outcomes (Azu & Essel, 2017).

In the current study, the level of income and occupation were not associated with knowledge after adjusting for education because most of the educated women were also employed and have high income compared with their counter parts. This finding mirrors a study from the urban areas of Chidambaram where no significant association between occupation and GDM knowledge was indicated (Lakshmi *et al.,* 2018).

It is also observed in this study that, age of the respondent was not associated with knowledge on the existence of HIP which may be due to fact that most of the young women were educated which might have influenced their level of knowledge. Another similar study supported that age of the woman was not significantly associated with knowledge about GDM (Elmekresh *et al.,* 2017).

Majority of pregnant women in this study have low knowledge on the effects of HIP to the mother or the newborn because very few understood that HIP can cause stillbirth, diabetes later in life to the mother and the newborn, as well as childhood and adult obesity. Low knowledge on effects of HIP may complicate the implementation of diagnosis, prevention, and management interventions as women may not see the importance of regular screening and prevention. This is because behavior change is greatly influenced by an understanding on the possible consequences of the condition. The current finding is supported by Bhavadharini *et al.* (2017) that most of the participants were unaware of the possible effects of GDM on the mother or the new born. Similarly, knowledge on the effects of GDM was poor as most of the women did not know its consequences after pregnancy and the increased risk for T2DM in future (Elamurugan & Arounassalame, 2016; Shriraam *et al.,* 2013).

Most of the participants in this study were not informed on the risk factors for HIP, while this is a very important aspect of self-care as it can help in earlier self-identification for immediate action to prevent adverse pregnancy outcomes and long-life health effects. A similar study in India reported that, although a greater proportion of the women was aware of the conditions of diabetes mellitus (DM) and GDM, knowledge about the risk factors, causes of GDM, and future risk for T2DM was low (Shriraam *et al.*, 2013). The same study stressed that proper precautions and self-care can be taken if women have good knowledge about the risk factors and the consequences that they may face due to untreated GDM (Shriraam *et al.*, 2013).

The main source of information about HIP in the current study was reported to be different media, such as newsletters, radios, internet and television, what sap although of note very few women reported to have received the information from ANC. Most of the women declared that it was their first time to hear about HIP during the introduction of the current study. This finding affirms that most pregnant women do not have accessible important information regarding critical health issues.

The appropriate source of information was expected to be the ANC but, it was the least used source, which is likely attributable to lack of HIP information within the ANC programs. This insight creates a need to incorporate HIP in ANC guidelines to enable healthcare providers include it in their day-to-day education programs for easier access by pregnant many women. The findings from the current study are in line with studies in India and Samoa which reported that, although it is encouraging to see the role played by mass media in creating awareness about GDM, the healthcare providers were mentioned as a source of information by very few women (Price *et al.*, 2017; Shriraam *et al.*, 2013). Another study reported that although the physicians and healthcare providers were mentioned as the source of information by only 19.4% of the studied women, the rest got it from the mass media or other sources however health care providers are still the most preferable source of information (Elmekresh *et al.*, 2017).

Hence, health care providers should be a reliable source of information to provide knowledge among antenatal women by including HIP in their routine health care education programs (Shriraam *et al.*, 2013). Another study in Bangladesh reported that most of the GDM women obtained knowledge from their neighbors (47.6%) and family (42.9%) whereas both medical

professionals and neighbors (30%) provided knowledge among normal pregnant women (Monir *et al*., 2018).

Majority of the women in the current study reported to been rarely screened for HIP in their previous pregnancies unless for those who shown to have symptoms where the common screening method used was glucose test in urine. A large proportion of pregnant women reported to have never being tested for GDM in their previous pregnancies implies that, HIP testing and management is not given priority in the ANC programs in Tanzania. Hence, many women may have undiagnosed GDM which can result into unfavorable pregnancy outcome and or later progress into T2DM.

The women who were detected with glucose in urine in their previous pregnancy declared that they were referred to the doctor with no follow up from the ANC. This gap yields a need for monitoring and follow-up of these women to ensure that management is done appropriately. This finding is supported by a similar study done in 30 health facilities in Tanzania where urine tests for protein and glucose were commonly performed, but blood glucose testing was rarely done unless in the case of positive urine tests, suspect symptoms, or known diabetes diagnosis (Ramaiya *et al.*, 2018). It was reported that some health facilities have never found any woman with glycosuria, which is likely due to low sensitivity of urine test strips in detecting GDM cases (Ramaiya *et al.*, 2018).

Also, in some facilities, incidence of HIP was very low likely due to missed opportunities caused by limited screening for diabetes and poor documentation. Similar to the current findings, Utz *et al.* (2017) found that the majority of the pregnant women are referred to either a general practitioner or a specialist after diagnosis of GDM. Another study conducted in rural India was inconsistent with these findings as pregnant women were screened for GDM using blood samples and monitored at least once weekly (Appajigol & Bellary, 2015). Although referrals are common due to lack of enough specialists for diabetes care in many developing settings, the additional costs may increase the rate of lost to follow-up and drop out (Beran & Yudkin, 2006; Nielsen *et al.*, 2012). Hence, pregnant women can adhere to early diagnosis, follow up and general self-care interventions if they know their conditions and costs associated with unmanaged GDM.

4.2.5 Simple method for identification of women with/at risk of gestational diabetes mellitus

The current study developed a risk score for Tanzania's ANC settings to enhance self-care and evidence-based treatment. The observed high prevalence of HIP especially in a form of GDM may increase burden to the health system if no instant measures are taken. This created a need to explore for the associated risk factors to develop a simple method for selective screening to give priority to the high risk women due to limited recourses.

The developed risk score involved maternal and clinical characteristics, such as high MUAC ≥ 28 cm, body fat ≥ 38%, family history of T2DM and history of delivery macrosomic babies (≥ 4 kg) at birth. Macrosomic delivery is a pregnancy outcome which implies that, more glucose was transferred from the mother to the fetus, resulting into more weight gaining for the fetus. The healthcare interventions on screening and managing GDM can target women with these risk factors to reduce their risks of developing GDM. In this case family history of T2DM, was identified as being a more important predictor for GDM followed by tendency of delivery macrosomic babies, body fat ≥ 38% and lastly MUAC ≥ 28 cm with the lowest score.

This risk score was found to perform well with an AUC of 97%, implying that the developed risk score can strongly discriminate the randomly selected women who are experiencing GDM from those not experiencing the condition. Furthermore, this risk score model was compared with fasting, OGTT and urine glucose test models and found to perform better than the other three models followed by the fasting and OGTT models, while urine glucose test model was invaluable. This implies that, if urine sample is used as a solely method to screen for GDM, most of the pregnant women with GDM would be left undiagnosed.

This is observed in the current study whereby only 0.9% of the pregnant women with GDM were identified using urine samples. This is supported by a study done in Tanzanian health facilities which revealed that glucose testing using urine samples is a common practice in ANC however, due to its insensitivity, a large proportion of women with or at risk of GDM remain undiagnosed (Ramaiya *et al*., 2018). Another study supports that, as in most low-and middle-income healthcare settings, reagent-strip glycosuria testing is a routine ANC practice in Ghana and diagnostic decision is made based on its outcome (Agbozo *et al.*, 2018).

Furthermore, the utility of the risk score model was assessed using a net benefit (NB) curve and the NB of using the risk scoring model was compared with the NB of testing all patients or testing no patient. In this case, it was found that the risk score model has higher NB at any given threshold compared to universal and/or not testing any woman. This implies that, the model has high clinical value in the studied population as most as the women (more than 80%) with high risk can benefit from the screening program. Another study reported that the presence of risk factors followed by 1-hour OGTT and FPG models were more sensitive compared with glycosuria, random blood glucose and glycated hemoglobin, which were highly insensitive and diagnostically poor, and hence missed majority of the GDM cases (Agbozo *et al.*, 2018).

The developed tool has an ability to identify about 98% of the pregnant women with positive result and 46% of truly negative women at the selected threshold of 0.2. This means that it can correctly identify most of the women with or at risk of GDM in these ANC settings to allow additional testing to few women for further actions to be taken to prevent short- and long-term health effects to the mother and the newborn. The application of this tool will also potentially increase efficient use of the scarce resources to enhance treatment based practices to give priority to the high risk women to reduce costs and inconveniences. Several similar studies have been conducted to develop selective screening methods and found that the strategies perform well in reducing unnecessary testing and increase early identification of women with or at risk of GDM (Sweeting *et al.*, 2017; Harrison *et al.*, 2015; Fawole *et al.*, 2014; Teede *et al.*, 2011; Caliskan *et al.*, 2004; Zheng *et al*., 2019; Artzi *et al*., 2020). These results encourage the use of selective screening for early identification of women at risk of GDM and/or in areas with limited resources.

Most of the already published selective strategies have been developed using variety of risk factors for example a similar study was conducted in Tanzania and developed a selective screening tool which involved MUAC ≥ 28 cm, stillbirth and family history of diabetes with an ability to identify 69% of the GDM women (Nombo *et al.*, 2018). The slight disparities observed in this model with the current study's model, may be due differences in diagnosis criteria where the current study used the WHO (2013) criteria with low threshold values and the previous study used the WHO (1999) criteria with high threshold values (Nombo *et al*., 2018). It might also be due to inclusion of more risk factors including body fat percentage that can replace BMI although not very well explored. Another study done in Nigeria

reported that; history of diabetes mellitus (DM), tendency of delivery to macrosomic baby, and history of previous unexplained stillbirth were predictors of GDM hence, they were included in the risk factor checklist for screening GDM (Fawole *et al.*, 2014).

On the other hand, Caliskan *et al.* (2004) developed a risk score which included maternal age, BMI and first-degree relatives with diabetes mellitus, a prior macrosomic fetus (> 4000 g) and adverse outcome in the previous pregnancies. Their score was found to have an ability for decreasing the number of women to be screened by 63%, still diagnosing 85% of cases with GDM showing a good performance of the model. This supports the current results partially, but varies as it included BMI which was difficult to determine in the current study setting. Other studies done in Nigeria and China were also contrary to these findings because they reported that the pre-gestational BMI > 25 kg/m^2 was a determinant of GDM (Nielsen *et al.*, 2016; Zheng *et al.*, 2019). This varied from the current findings as most of the women could not recall their pre-pregnancy weight and were late to start ANC with an average of 18 weeks of gestation which made it in-determinant during pregnancy. Instead, the current study used body fat percentage in addition to MUAC as a proxy for BMI because it can easily be measured during pregnant as well as post-delivery.

Also, body fat percentage is a good indicator of fat deposition compared to BMI which may be affected by weight of the fetus and the fluids which accumulate during pregnancy. A study done in India reported that the estimation of weight for determining BMI may be susceptible to certain bias as it is partly based on self-reported weight or weight measured at first antenatal care visit potentially leading to over-or under-estimation of BMI (Nielsen *et al.*, 2016).

Maternal age was not significantly associated with development of GDM in the current study which may be attributed by changes in life style that has made more young women to be overweight/obese with high risk of developing NCDs including GDM. Another similar study reported that, by definition the selective strategy detects more cases of GDM among older women with higher BMI and misses more cases among younger women with lower body-mass indexes. Therefore, it is very unlikely that this shift in detection patterns is harmful (Naylor *et al.*, 1997). Another model which was developed in China for early screening of GDM was contrary to the current developed model because age was found to be a good predictor of GDM (Zheng *et al.*, 2019). It is also reported that due to higher fertility rates in younger women, nearly half (48.9%) of all cases of HIP (that is GDM and DIP) occurred

among women under the age of 30 years (IDF, 2017). This is also supported by similar study which reported that, the age of onset of diabetes mellitus and pre-diabetes is declining (Hod *et al.*, 2015).

Insulin resistance was positively associated with GDM in this study but it could not be involved in the risk score development due to its associated diagnostic costs, as the aim of the current study was to develop a simple and cost-effective method. However, as IR was associated with hypertension and presence of edema, which are indicative of preeclampsia, these factors were included in the final risk factors checklist to involve women with IR but not yet developed GDM. A similar study reported that women with GDM are more likely to experience IR than their non-GDM counterparts (Elkind-Hirsch *et al.*, 2010).

Furthermore, increased serum insulin level at screening in early pregnancy can predict GDM as it is reported that, the higher the serum insulin level, the earlier the manifestation of GDM (Bitó *et al.*, 2005). In this case, the inclusion of risk factors for IR is important for early identification of women at risk of GDM to prevent the development of GDM, and T2DM as insulin is an indication of future diabetes. This finding makes the developed tool to be very useful in early identification of women at increased risk for GDM even before pregnancy for immediate preventive actions to be taken to prevent short and long-term health effects to the mother and her new born.

Based on the current developed tool with factors that can be assessed even before or in the early stage of pregnancy, most of the women at risk of GDM could be identified before or during pregnancy to allow timely intervention to improve maternal and neonatal outcomes. Moreover, monitoring and testing of women for GDM throughout pregnancy can be performed according to the need of the individual patient (van Leeuwen *et al.*, 2010) hence, a more personalized approach to the health care interventions. It is also reported that a better understanding of the risk factors for GDM may not only add to the knowledge of the pathways leading to GDM, but also inform and enable health care providers to focus on women at increased risk for whom earlier and repeated screening may be of greatest importance (Nielsen *et al*., 2016). Another similar study developed selective models and found that they may allow early-stage intervention in high-risk women, as well as a cost-effective screening approach that could avoid the need for glucose tolerance tests by identifying low-risk women (Artzi *et al*., 2020).

Contrary to the current findings several studies have reported that risk factors have poor predictive value and fail to identify a large proportion of women with GDM which limits their use (Adam & Rheeder 2017; Matta-Coelho *et al.*, 2019; Agbozo *et al.*, 2018). Another review was done to validate 12 published GDM risk scores and reported that the most common predictors were age, adiposity, family history of diabetes, history of GDM, ethnicity, and history of macrosomia. The reviewed scores performed only moderately therefore, requested for more research to be done before putting the scores into practice (Lamain-de Ruiter *et al.*, 2016; Huvinen *et al.*, 2018). In line with this, some meta-analysis suggest that irrespective of the method used, risk factors do not identify women with GDM well (Farrar *et al.*, 2017), but it is still important to consider these selective screening as they can help in early identification of women at risk for timely management especially in resource limited areas. Another study done in Nigeria reported that a checklist of risk factors for GDM should be included their antenatal protocols to ensure proper identification of women with GDM is done thoroughly (Fawole *et al.*, 2014).

Some researchers in India attempted to develop a risk factor based scoring variables for screening GDM, but none of the risk factors or their accumulation were strong enough to clearly discriminate between those with and without HIP in all their settings, emphasizing the need for universal screening for GDM/DIP (Nielsen *et al.*, 2016). Universal screening is highly recommended given availability of financial, material, space and human resources however it needs implementing multiple testing during pregnancy for all women which is not only costly, but operationally challenging (Nielsen *et al.*, 2016). This makes selective screening using maternal and clinical characteristics to be important especially in low income countries with limited resources.

For operationalization of the developed risk score which was simplifies into a risk factors checklist, the health system needs to integrate it into the ANC services from the point of entry with history taking and throughout during counselling and regular education programs. This tool can be effective if it is used at the first ANC and in subsequent visits as some of the risk factors can arise at the middle or late stages of pregnancy. This will increase knowledge about GDM as a risk for poor pregnancy outcomes. When a woman is identified having one of the risk factors in the checklist, can be referred to the doctor for more actions to be taken as what is done in other conditions indicated in the FANC guideline (Kearns *et al*., 2014). This can help to give priority to high risk women when resources are limited while planning

for universal screening, which needs more resources. The developed tool can also be used by women for self-identification even before pregnancy to enhance proper preconception preparations.

4.3 Limitation of the study

Although results from this study are encouraging, the study was conducted in a population which is ethnically homogenous Africans, which limits generalizability of the findings. Moreover, the study involved a small sample size that resulted in wider CIs in some of the associations among variables which may reduce the precision of the study due to distribution effect. However, the study is still useful as it is a bases for an additional longitudinal study with large sample and improved follow-up methods.

4.4 Methodological challenges in the current study

The study faced biases on data collection where participants had to recall some information such as pre-pregnancy weight which may lead into over- or- underestimation. Hence to avoid this biasness, body fat percentage and MUAC were used to assess nutrition status of the pregnant women to replace BMI. Among 24 health facilities with both ANC and delivery services, only 2 centers were selected, which may not be representative of the health facilities, leading to bias in extrapolation as we cannot feel confident that these results will serve as a parameter of the urban population. This is because, internal and external validity are undermined.

Hence, random sampling was used to reduce this biasness effect. Furthermore potential confounders between dependent and independent variables during data analysis were identified including maternal age, income and parity. These confounders were controlled by running multivariate analysis to reduce their effects on associations among variables (K1einbaum *et al*., 1982).

CHAPTER FIVE

CONCLUSION AND RECOMMENDATIONS

5.1 Conclusion

The prevalence of HIP, especially in the form of GDM, was high in urban areas of Arusha City and significantly associated with family history of T2DM, tendency of delivering macrosomic babies (≥ 4 kg), MUAC ≥ 28 cm and high body fat ≥ 38%. Likewise, the prevalence of IR was higher among pregnant women with family histories of T2DM, high body fat percentage, presence of edema, and hypertension. Screening and management for HIP is not a common practice in the antenatal services offered in Tanzania, which creates a scenario in which the condition is not given priority in the health care system as a risk for poor pregnancy outcomes.

Universal screening for IR or HIP (GDM and DIP) and early intervention may help to reduce the associated complications, but very expensive, which created a need to develop a risk score. The developed risk score was found to perform well as it was able to predict 98% of high-risk women compared to the universal screening of all pregnant women. Hence, it was simplified into a risk factors checklist for ease of interpretation and application. Conversely, knowledge about HIP was very low among the participated pregnant women and influenced by maternal education levels. The main source of information about HIP was reported to be social and mass media while care providers were expected to be the reliable source of this important health condition.

5.2 Recommendations

Hyperglycemia in pregnancy is a substantial health problem however, it has received minimal attention from the health system. This calls for the policy makers to strengthen the ANC programs to include routine HIP screening, diagnosis, management and follow-up to prevent short and long-term effects to the mother and the newborn. To be effective the national health policy needs to be amended to recommend routine screening for GDM using universal strategies with sufficient resources or selective screening when resources are limited to give priority to the high-risk women.

Hence, to adopt either universal or selective screening, different health stakeholders should join efforts to validate these findings using a large longitudinal national study with large sample size representing all regions of the country. Furthermore, a trial of the validated tool should be done in one of the zones in the country. The health system needs to integrate different health stakeholders in prevention of HIP (GDM and DIP) through regular ANC education programs using different media to enhance self-care to address the various risk factors. This can help in proper preconception preparations, care during pregnancy, and post-delivery period. The health system is fragmented which may reduce efforts to solve related conditions. Hence, there is a need for the health system to amend different NCDs strategies, programs and policies to include HIP as one of the prioritized NCDs to reduce the burden of diabetes.

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APPENDICES

Appendix 1: Research tool (Questionnaire)

THE NELSON MANDELA AFRICAN INSTITUTION OF SCIENCE AND TECHNOLOGY
(NM – AIST)

Questionnaire on prevalence of hyperglycemia in pregnancy, risk factors and simplified method for identification of pregnant women at risk in Arusha, Tanzania

S/N	Section A: General information	Fill blanks/Tick where appropriate		
1	Interviewers name			
2	Center Name (ANC name)			
3	Name of respondent (Three names)			
4	Ward			
5	Street			
6	Date of interview			
7	Consent obtained	Yes	1	
		No	2	
8	Contact phone number of respondent			
	Alternative numbers			
9	Who is the owner of the phone number?	Yours	1	
		Husband	2	
		Someone else (Mention)	3	----
10	At what gestational age did you start visiting clinic?	Write in weeks	----	
11	What is the mother's gestational age currently?	Write in weeks	-----	
12	What is your expected date of delivery?	Write the data and month	-----	
Section B: Demographic information				
13	What is your age or date of birth?	Date -----	Years	-----
14	What is the highest level of education that you have attained?	Never went to school	1	
		Primary school	2	
		Secondary school	3	
		college/university	4	

15	What is your marital status?	Never married	1	
		Married	2	
		Separated	3	
		Divorced	4	
		Widowed	5	
		Cohabiting	6	
		Refused to mention	99	
16	Which of the following describes your main work status?	Non-government employee	1	
		Self employed	2	
		Student	3	
		Home maker	4	
		Retired officer	5	
		Unemployed	7	
		Disabled	8	
		Others (mention)	9	----
17	What is your average income per month?	<250,000	1	
		250,000-450,000	2	
		500,000- 750,000	3	
		800,000-1,000,000	4	
		>1,000,000	5	
		Others (mention)	6	
		Refused to mention	99	
Section C: Risk factors for HDP (present and past records)				
18	Which birth order is this pregnancy?	First	1	
		Second	2	
		Third	3	
		Fourth	4	
		>Fourth	5	
19	What is the age of your youngest child?	Write in Months	----	
20	Have you ever delivered ≥4kg child previously?	Yes	1	
		No	2	
		I don't know	88	
21	Have you ever delivered a pre-term baby? (Delivery before 37 weeks of gestation)	Yes	1	
		No	2	
22	Have you ever got a prenatal death?	Yes	1	
		No	2	
23	If yes, how many times?	Once	1	
		Twice	2	
		Thrice	3	
		>Thrice	4	

24	Have you ever have a perinatal death?	Yes	1	
		No	2	
25	If yes, how many times?	Once	1	
		Twice	2	
		Thrice	3	
		>Thrice	4	
26	Do you have any history of diabetes in your family? (your grandfathers/mothers or your parents/sister/brother)	Yes	1	
		No	2	
		I don't know	88	
27	Did your mother have any history of HDP?	Yes	1	
		No	2	
		I don't know	88	
28	Did you measure your sugar levels in your previous pregnant?	Yes	1	
		No	2	
		I don't know	88	
29	If yes, how was it tested	Urine	1	
		Blood	2	
30	If yes what was the status?	Normal	1	
		High (diabetes)	2	
		I don't know	88	
31	If it was high, were you treated and followed up?	Yes	1	
		No	2	
32	If yes, how was it treated?	Given medication	1	
		Education	2	
		Referred to diabetic clinic for counseling	3	
33	What was the mode of delivery in your previous pregnant?	Normal delivery	1	
		Cesarean session	2	
		Others (specify)	-	
34	If it was cesarean session, what was the reason?	Big baby	1	
		Poor positioned baby	2	
		Others (specify)	3	-----
		I don't know	88	
35	Have you ever been hypertensive in your previous pregnancies	Yes	1	
		No	2	
		I don't know		
36	What was your weight during the first visit to clinic	Write in Kg	------	
		I don't know	88	
37	What is your ethnicity?	Black	1	
		White	2	

38	Are you smoking currently?	Yes	1	
		Never	2	
		Stopped after conception	3	
		Stopped before conception	4	
39	If yes how many cigarettes per day?	At least one piece	-	
		Two pieces		
		Three pieces		
		More than three pieces		
40	Are you consuming alcohol?	Yes	1	
		Never	2	
		Stopped after conception	3	
		Stopped before conception	4	
41	If yes how many bottles per day?	At least one bottle	1	
		Two bottles	2	
		Three bottles	3	
		More than three bottles	4	
Section D: Knowledge about HIP among women				
42	Do you know the existence of HIP?	Yes	1	
		No	2	
43	If yes, where did you hear about it?	During ANC visits	1	
		Social media (mention)	2	
		Others (specify)	3	--
44	Did you test glucose in this pregnancy?	Yes	1	
		No	2	
		I don't know	88	
45	If yes, how was it measured?	In the urine	1	
		Fasting blood	2	
		OGTT	3	
		Others (specify)	4	--
		I don't know	88	
46	How were the results?	Normal	1	
		Hyperglycemic	2	
		Hypoglycemic	3	
		I don't know	88	
47	Are you know the meaning of HIP?	Yes	1	

		No	2	
48	If yes can you define it?	Diabetes first detected in pregnancy	1	
		Hereditary Diabetes	2	
		Others (Specify)	3	
49	Are you are of the symptoms of HIP?	Yes	1	
		No	2	
50	If yes mention them	Frequent thirst	1	
		Frequent urination	2	
		Vision impairment	3	
		Others mention	4	-
51	Do you know the effects of HIP?	T2DM to the baby	1	
		Death of the baby	2	
		Macrosomic baby	3	
		Overweight/obesity	4	
		Others(specify)	5	-
52	Do you know the causes of HIP?	Yes	1	
		No	2	
53	If yes mention the causes of HIP?	Overweight/obesity	1	
		Previous GDM	2	
		Family history of T2DM	3	
		Genetics	4	
		Poor Eating behavior	5	
		Others(specify)	6	-
54	Do you have anything to say? Questions, suggestion, opinions			

Section E: Measurements during pregnancy

Respondent ID						
Respondent name						
Gestational week						
Weight before pregnancy						
Anthropometric	**Variables Measured**					
	SN	**Variable**	**1**	**2**	**3**	
	1	Weight				
	2	MUAC				
	3	Body fat				
	4	Blood pressure				
	5	Presence of edema	1. Yes			
			2. No			

Blood glucose tests						
	1	Fasting blood glucose				
	2	OGTT				
	3	Serum insulin level				
Urine test	4	Urine glucose				
	5	Urine Protein test				

Thank you for your corporation

Appendix 2: Consent form for the cross-sectional study

Introduction

Hyperglycemia in pregnancy (HIP) is impaired glucose tolerance with onset or first recognition during pregnancy. In most cases, blood glucose return to normal after delivery but there are higher chances for future diabetes to the mother and the child. Studies show that early identification and management of HIP prevents adverse pregnant outcomes. This study will help to establish the prevalence of HIP and its associated risk factors and develop a risk factor score system that can be used as easy, noninvasive and less cost method of screening for HIP to avoid unnecessary universal screening but save the lives of mothers and their new bones. To complete this work we will take your blood and urine samples to measure glucose, serum insulin, urine protein and anthropometric measurements as well as requesting to answer some questions in a questionnaire.

Procedure: If you consent to participate in this study, you will be requested to come tomorrow before eating anything and your blood will be drown from the venous for checking fasting blood glucose and serum insulin status. To confirm your glycaemia status, you will be given glucose solution (75 grams dissolved in 300ml of water) to drink and blood will be taken after one and two hours and tested for glucose concentration. The results of your test will be disclosed to you and its implication will be explained. Your blood will be stored and used for the purpose stated in this study only.

Benefits: By participating in this study, your blood sugar, blood pressure, insulin resistance will be measured free of charge and provided with advice and counseling. You may be referred for more tests and managements if necessary.

Risks and precautions: We will request you to remain fasting for at least eight (8) hours at night before you come for the test, not smoke or take alcohols. We will request you to wait for two hours after drinking glucose solution without eating anything. Well trained and experienced personnel will be involved during blood collection to ensure minimal discomfort. No risks are involved in drinking glucose solution; however, you might have some inconveniences like nausea, slight headache or tiredness.

Confidentiality: Any records relating to your participation will be strictly confidential. Your names will not be used in any reports from the study. The participation to this study is voluntary and may withdraw from the study at any time. You are free to ask any questions or any clarification after you have read and understood the consent form explained to you.

Participant statement

I----------have understood the above information explained to me by the investigator and I agree to take part in this study and I can withdraw with or without giving reasons.

Participant's Name:……Signature…… Date……..

Investigator's Name :……Signature ……....Date……..

Appendix 3: Ethical clearance certificate

THE UNITED REPUBLIC OF TANZANIA

National Institute for Medical Research
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P.O. Box 9653
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Tel: 255 22 2121400
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University of Dodoma, Faculty of Arts and Social Sciences
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40478 Dodoma

NIMR/HQ/R.8a/Vol. IX/2694

19th February 2018

Safiness Msollo
Nelson Mandela African Institution of Science and Technology
C/o Dr. Haikaeli David Martin
Nelson Mandela African Institution of Science and Technology
P.O. Box 447
Arusha

RE: ETHICAL CLEARANCE CERTIFICATE FOR CONDUCTING MEDICAL RESEARCH IN TANZANIA

This is to certify that the research entitled: Risk factors scores for identification of women with hyperglycemia during pregnancy in Arusha urban Tanzania (Msolo S. *et al)* whose local supervisor is Dr. Haikaeli David Martin of Nelson Mandela African Institution of Science and Technology has been granted ethical clearance to be conducted in Tanzania.

The Principal Investigator of the study must ensure that the following conditions are fulfilled:

1. Progress report is submitted to the Ministry of Health, Community Development, Gender, Elderly & Children and the National Institute for Medical Research, Regional and District Medical Officers after every six months.
2. Permission to publish the results is obtained from National Institute for Medical Research.
3. Copies of final publications are made available to the Ministry of Health, Community Development, Gender, Elderly & Children and the National Institute for Medical Research.
4. Any researcher, who contravenes or fails to comply with these conditions, shall be guilty of an offence and shall be liable on conviction to a fine as per NIMR Act No. 23 of 1979, PART III Section 10(2).
5. Site: Arusha

Approval is valid for one year: 19th February 2018 to 18th February 2019.

Name: Prof. Yunus Daud Mgaya

Signature
CHAIRPERSON
MEDICAL RESEARCH
COORDINATING COMMITTEE

Name: Prof. Muhammad Bakari Kambi

Signature
CHIEF MEDICAL OFFICER
MINISTRY OF HEALTH, COMMUNITY DEVELOPMENT, GENDER, ELDERLY & CHILDREN

CC: RMO of Arusha
DMO/DED of Arusha urban