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Gestational Diabetes Mellitus in Ghana: Validity of Screening Tests, Prevalence, Maternal Risk Factors and Pregnancy Outcomes

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DEDICATION

To my children especially Nevin, whom I had to leave with his 'grandmother-turn-mother' when he was only three months old to start my doctoral study; and to all who strive to improve maternal health especially in resource-constrained settings, may our efforts lead to better health outcomes!

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LIST OF ABBREVIATIONS

ACOG	American Congress of Obstetricians and Gynecologists
ADA	American Diabetes Association
ANC	Antenatal Care
AUC	Area Under the Curve
BMI	Body Mass Index
BW	Birth Weight
CDA	Canadian Diabetes Association
CI	Confidence Interval
CS	Cesarean Section
DOR	Diagnostic Odds Ratio
FIGO	International Federation of Gynecology and Obstetrics
FFQ	Food frequency questionnaire
FPG	Fasting Plasma Glucose
GDM	Gestational Diabetes Mellitus
GHS	Ghana Health Service
GI	Glycemic index
HAPO	Hyperglycemia and Adverse Pregnancy Outcomes
HbA1c	Glycated Hemoglobin
HIP	Hyperglycemia In Pregnancy
IADPSG	International Association of Diabetes in Pregnancy Study Groups
LBW	Low Birth Weight
LGA	Large for Gestational Age
LR	Likelihood Ratios
MUAC	Mid-Upper Arm Circumference
NICE	National Institute for Health and Clinical Excellence
NICU	Neonatal Intensive Care Unit
OGTT	Oral Glucose Tolerance Test
OR	Odds ratio
PI	Ponderal Index
PPH	Postpartum Hemorrhage
PV	Predictive Value
RBG	Random Blood Glucose
ROC	Receiver operating characteristic
SVD	Spontaneous Vaginal Delivery
T2D	Type II Diabetes
WHO	World Health Organization

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1 INTRODUCTION

Note: The doctoral student has published some aspects of this chapter in the underlisted publications. For details, see pages 109-111.

- Accuracy of glycosuria, random blood glucose and risk factors as selective screening tools for gestational diabetes mellitus in comparison with universal diagnosing. http://dx.doi:10.1136/bmjdrc-2017-000493
- Gestational diabetes using diverse diagnostic criteria, risk factors including dietary intakes, pregnancy outcomes and postpartum glycemic status: a nested case-control study in Ghana. https://doi.org/10.1101/582239

This doctoral research focuses on the prevalence of gestational diabetes, validity of screening tests, clinical risk factors and associated maternal and perinatal pregnancy outcomes including short-term postpartum glycemic status of women diagnosed. This introductory chapter is organized into three sections. The first section gives an overview on the epidemiology of gestational diabetes mellitus (GDM) highlighting the global and regional trends, challenges with screening, implications of recent updated diagnostic guidelines and the effect of GDM on quality of materno-fetal health.

In the second section, literature on hyperglycemia in pregnancy is reviewed narrowing down to gestational diabetes: the disease burden, pathophysiology, risk factors, maternal and offspring outcomes, screening and diagnostic tests, management and prevention strategies. The third section describes the context-specific rationale for conducting the study, the objectives set out to be achieved and the research questions and hypotheses that supports these study objectives.

1.1 Epidemiology of Gestational Diabetes Mellitus

In recent years, gestational diabetes mellitus (GDM) has risen considerably globally and Africa is no exception. GDM is a glucose intolerance that affects 1–14% of all pregnancies (American Diabetes Association, 2015). In 2017, 16.2% live births experienced hyperglycemia in pregnancy of which 86.4% was accountable to GDM, that is, diabetes first recognized in pregnancy (Cho et al., 2018). Over 90% of cases occur in low and middle-income countries (Guariguata et al., 2014). In Africa, prevalence of hyperglycemia in pregnancy has increased considerably from negligible levels to almost 30% in some settings within the past four decades (Macaulay et al., 2014, Hall et al., 2011, Adam and Rheeder, 2017). With 14% prevalence in sub-Saharan Africa (Mwanri et al., 2014), health systems in many developing settings need restructuring to tackle the surge. However, consideration of gross variations in screening and diagnostic procedures and reference criteria used are necessary when interpreting these trends.

Screening denotes scheduled measurement of blood glucose in all pregnant women whether asymptomatic or symptomatic, and whether 'at risk' or not, followed by diagnostic testing in screen-positive clients. However, specific screening procedures and outcomes that should indicate diagnostic testing remain controversial (National Institute for Health and Care Excellence, 2015, World Health Organization, 2013, American Diabetes Association, 2015). Despite recent diagnostic criteria by various health regulating and advisory bodies, opinions are divided on selective verses universal screening, and the diagnostic thresholds (Agarwal, 2018, Cundy et al., 2014). Selective screening, also known as routine screening, is where only pregnant women identified from screening to be at high risk are booked to perform diagnostic testing to evaluate their actual glycemic status. Universal screening is where all pregnant women are tested irrespective of their risk status.

In line with evidence from the hyperglycemia and adverse pregnancy outcome study (HAPO) (Metzger et al., 2008), and recommendations from the International Association of Diabetes and Pregnancy Study Group (IADPSG) (Metzger et al., 2010a), the World Health Organization (WHO) updated its clinical guidelines for detecting hyperglycemia in pregnancy in 2013 (World Health Organization, 2013). Similarly, the American Diabetes Association (ADA) updated its guidelines in 2015 (American Diabetes Association, 2015). The WHO recommends one-step diagnosing using fasting plasma glucose (FPG) between 5.1-6.9 mmol/L (92-125 mg/dl) or 75-gram oral glucose intake followed by 1-hour postprandial glucose ≥10.0 mmol/L. However, the 2-hour oral glucose tolerance test (OGTT) between 8.5-11.0 mmol/L (153-199 mg/dl) performed ideally between 24-28 weeks is preferred by the WHO. Conversely, the National Institute for Health and Care Excellence (NICE) considers 2-h 75-g OGTT performed between 24-28 weeks as the 'gold standard'. Compared to the current guidelines by the WHO/IADPSG/ADA, NICE's criteria for 2-h OGTT is 0.7 mmol/L lower (≥7.8 mmol/L) whereas their fasting plasma glucose threshold is 0.5 mmol/L higher (≥5.6 mmol/L) (National Institute for Health and Care Excellence, 2015). Meanwhile, the 1999 WHO diagnostic criteria for FPG was ≥7.0 mmol/L whereas 2-h was OGTT ≥7.8 mmol/L, same as the current NICE guideline. There are concerns that lowering diagnostic thresholds would unnecessarily increase GDM prevalence and burden weaker health systems in low-resource settings (World Health Organization, 2013, Cundy et al., 2014). Random glucose or 2-h OGTT ≥11.1 mmol/L at any time during pregnancy is suggestive of clinical (overt/pre-existing) diabetes (World Health Organization, 2013, IADPSG Consensus Panel, 2010).

In Ghana, GDM screening entails dipstick glycosuria urinalysis, tested at every antenatal care (ANC) visit. Values between 1+ and 2+ on two occasions or 3+ and 4+ on one occasion warrant OGTT (Ghana Ministry of Health, 2010). But dipstick (reagent-strip) urine testing for glucose is not without challenges. During pregnancy, renal threshold for glomerular glucose reabsorption is reduced, leading to increased glycosuria at some point in about 50% of all pregnancies (Alto, 2005). However, hyperglycemia without detectable glycosuria is not unlikely (Cersosimo et al., 1997). Using glycosuria as routine screening test could result in missed (false negative) opportunities for diagnosis and management. Although in Ghana, fasting plasma glucose is recommended at the first ANC booking, and at 28-32 weeks, no diagnostic cut-offs are provided in the standard treatment guidelines. Adherence to screening and diagnostic protocol is not only discretionary on the healthcare provider but also dependent on the level of healthcare. Making diagnostic decision based on maternal risk factors is often the norm. However, there is no clear guideline on the profile of risk factors or the number of risk factors that should indicate diagnostic testing. Macrosomia (birthweight >4.0 kg), a cardinal adverse neonatal outcome associated with GDM, identifies 3% (Agbozo et al., 2016) pregnant women to be at risk of GDM.

Predisposing factors like ethnicity, first-degree relatives with diabetes, advanced maternal age, short maternal stature, macrosomia and previous bad obstetric history are non-modifiable risks. Focusing on modifiable risk factors like obesity, high parity, gestational weight gain, sedentary lifestyle, excess carbohydrate intake, abnormal lipid profile and hypertension could reduce the incidence (Ashwal and Hod, 2015, Mwanri et al., 2014, Metzger et al., 2008, Kampmann et al., 2015, Hod et al., 2015). Amid the nutrition transition, the double burden of undernutrition and obesity resulting from lack of dietary counseling, unhealthy dietary intake, urbanization and sedentary behaviors is fueling ‘uterine diabetogenic environment’ and insulin resistance (Hod et al., 2015).

Adverse outcomes linked to GDM include preeclampsia, postpartum hemorrhage (PPH), obstructed labour, cesarean delivery, macrosomia, birth trauma, birth asphyxia, neonatal hypoglycemia and perinatal mortality (Wendland et al., 2012, O’Sullivan et al., 2011, Metzger et al., 2008). GDM affects breastfeeding (Hod et al., 2015), increases risk of childhood obesity, metabolic dysfunctions and cardiovascular complications in mother-offspring dyads (Eades et al., 2015, Kampmann et al., 2015, Hod et al., 2015) and leads to long-term neuropsychiatric morbidity in the offspring (Sacks et al., 2016). Increasing obesity and pre-disposition for diabetes have triggered an inability to withstand the metabolic stress

of pregnancy. However, in rural areas in Ghana, prevalence of maternal obesity (4.3%) (Agbozo et al., 2018) and type II diabetes (4.0%) (Sarfo et al., 2017) are low. Unlike type II diabetes, risk factors and adverse pregnancy outcomes associated with GDM are not well established in Ghana. Extrapolated data indicated 0.5% prevalence in 2004 but a decade on, the prevalence has risen to 9.3% (Oppong et al., 2015). Given that this study was conducted in the national referral hospital, lower prevalence is hypothesized in lower level facilities.

Many studies in Africa have assessed risk factors, but evidence on short-term outcomes is limited. In this doctoral research, a cohort of pregnant women was prospectively followed to assess socio-demographic, anthropometric, dietary, obstetric and physiologic factors that increased predisposition to GDM, short-term adverse birth outcomes and postpartum glycemia. Prevalence of GDM in primary and secondary healthcare settings in Ghana was assessed using the current WHO and NICE diagnostic criteria. Accuracy of screening tests (dipstick glycosuria, random capillary whole blood glucose, and presence of maternal risk factors) were tested and validated against the diagnostic tests (glycated hemoglobin (HbA1c), fasting venous plasma glucose, 1-hour and 2-hour postprandial OGTT). Effectiveness of universal and selective screening approaches were tested and diagnostic thresholds that optimized sensitivity and specificity was evaluated from coordinates of the receiver operating characteristic curve.

1.2 Review of Literature on Hyperglycemia in Pregnancy

Hyperglycemia in pregnancy is the most prevalent metabolic disorder occurring during pregnancy. Globally, prevalence is rising due to increasing diabetes mellitus resulting from lifestyle changes, shifts from consumption of whole grains to refined and high fat foods, increasing obesity, physical inactivity and more pregnancies in older women (National Institute for Health and Care Excellence, 2015). Hyperglycemia in pregnancy is divided into two broad categories: (1) diabetes in pregnancy and (2) gestational diabetes mellitus.

Diabetes in pregnancy, also referred to as clinical or overt diabetes, presents in pregnant women previously diagnosed with either type I or type II diabetes. GDM which is hyperglycemia first detected in pregnancy, is a pregnancy-specific glucose intolerance (National Institute for Health and Care Excellence, 2015) considered to be a transient form of type II diabetes. The rapid onset is triggered by the metabolic and hormonal changes of pregnancy (American Diabetes Association, 2013). GDM is therefore any degree of

carbohydrate or glucose intolerance that is not clearly overt diabetes, and results in hyperglycemia of variable severity with onset or first recognition during pregnancy (American Diabetes Association, 2010, WHO, 2006a).

1.2.1 Prevalence of GDM

Among all forms of hyperglycemia in pregnancy, gestational diabetes accounts for 87.5%, type I diabetes accounts for 7.5% and type II diabetes accounts for 5% (National Institute for Health and Care Excellence, 2015). Prevalence depends on the population studied and the diagnostic procedures used. Over 90% of all cases of hyperglycemia in pregnancy is estimated to occur in low- and middle-income countries (Guariguata et al., 2014). In 2013, the global prevalence of hyperglycemia in pregnancy in women aged 20–49 years was 16.9%. South-East Asia had the highest prevalence (25.0%) while North America and Caribbean had the lowest prevalence (10.4%) (Guariguata et al., 2014). In America for instance, 1-14% of all pregnancies are complicated by GDM (American Diabetes Association, 2015) but in certain populations, the prevalence is much higher. Prevalence in Qatar and India are 16.3% (Bener et al., 2011) and 17.9% (Seshiah et al., 2007) respectively. In the Atlantic Diabetes in Pregnancy study in Ireland involving 5,500 pregnant women, 12.4% (2010 IADPSG criteria) and 9.4% (1999 WHO criteria) were diagnosed with GDM (O'Sullivan et al., 2011).

On the African region, type II diabetes accounts for over 90% of all diabetes. Systematic reviews suggest that GDM prevalence has risen considerably from 0-14% between 1979 and 2013 (Macaulay et al., 2014, Hall et al., 2011). A systematic review on GDM prevalence in Africa showed that in 1991, no GDM case was recorded in Tanzania (Macaulay et al., 2014) but this increased to 5.9% in 2013, indicating an emerging public health problem (Mwanri et al., 2014). Also, GDM prevalence in Ethiopia in 1999 was 3.7%; prevalence in Mozambique in 2002 was 11%; prevalence in South Africa in 2006 was 8.8%; prevalence in Morocco in 2009 was 7.7%, and prevalence in Nigeria in 2012 was 13.9% (Macaulay et al., 2014). However, the wide variations in test procedures, diagnostic criteria, timing of test, rural-urban disparities and level of healthcare delivery accounts for much of the differences.

Although data on GDM from Ghana is limited, the epidemiological and nutrition transitions apparent in Ghana suggest rising GDM prevalence. Shifts from consumption of traditional foods high in complex carbohydrates and fibre to refine and high fat diets and physical inactivity is promoting obesogenic environments (Popkin, 2001). This could contribute to

metabolic imbalances. The first study reporting prevalence of GDM in Ghana was conducted at the largest national tertiary healthcare facility in 2015. The study was a cross-sectional survey involved 399 pregnant women who did 2-h OGTT following intake of 75-g glucose between 24-28 weeks. Reported prevalence of GDM was 9.3% (n=37, 95% CI 6.6%-12.5%) (Oppong et al., 2015).

1.2.2 Pathophysiology of GDM, Macrosomia and Hypoglycemia

Maternal hyperglycemia is believed to be caused by excessive hypophyseal production of gonadotropins and growth factors in pre-diabetic and diabetic mothers, hypercorticism of pregnancy and genetics (Pedersen, 1954). Maternal adipose tissue and the placenta are believed to produce large amounts of diabetogenic adipokines with adipokine tumor necrosis factor alpha (TNF-α); believed to be the most significant independent predictor of maternal insulin sensitivity (Kirwan et al., 2002). Elevated pre-pregnancy insulin resistance observed in obese women is supposedly based on the role of diabetogenic adipokines in the insulin resistance pathways. Insulin resistance characterizes normal pregnancy and triggers increased insulin secretion by the pancreatic β cells. This reduces renal threshold for glucose reabsorption from the glomerular filtrate. Placenta hormones contribute to making maternal tissues progressively insensitive to insulin. In normal pregnancy, insulin secretion increases by 200-250% to make up for the 50% decreases in insulin-mediated whole-body glucose disposal needed to maintain a normoglycemic state (Barbour et al., 2007). GDM tends to develop when the pregnant woman is unable to produce adequate insulin to compensate for this normal insulin resistance.

Adipose tissue, especially the intra-abdominal omental fat, contribute to the pathophysiology of GDM (Harlev and Wiznitzer, 2010). According to the Pedersen hypothesis, maternal hyperglycemia results in excess glucose transfer to the fetus leading to fetal hyperglycemia, hyperinsulinemia and overgrowth of insulin-sensitive tissues such as adipose tissues especially around the chest, shoulders and abdomen (Pedersen, 1954). Fetal hyperglycemia triggers hypoxemic state in utero increasing risk of fetal polycythemia, hyperbilirubinemia and intrauterine fetal death (Metzger et al., 2008). When placental nutrient supply is discontinued at birth, immediate postnatal metabolic changes preserve fuel supplies for vital organ function. Plasma insulin levels fall with rapid surge of catecholamine and pancreatic glucagon release (Hussain, 2011). Although transient hypoglycemia are reflections of normal metabolic adaptation during fetal-to-neonatal transition, the peak of the fluctuations is 2-4

hours after birth and should normalize by the fourth day. Newborn who experience diabetogenic in-utero conditions face difficulty normalizing this transient hypoglycemia (Hawdon, 2012, Metzger et al., 2010b).

1.2.3 Risk Factors and Predictors for GDM

Both current and previous studies have assessed factors associated with increased risk for GDM (National Institute for Health and Care Excellence, 2015, Ashwal and Hod, 2015, Metzger et al., 2008, Kampmann et al., 2015, Berkowitz et al., 1992). Significant demographic and anthropometric risks include maternal age above 25 years, high parity, ethnicity (Native Americans, Asians, Hispanics, and African-American women), obesity, short maternal stature and high gestational weight gain. High pre-pregnancy body mass index (BMI) and the BMI at 28 gestational weeks are strongly correlated to increased insulin resistance at 28 weeks (Metzger et al., 2008). Physiologic and genetic risk factors include abnormal lipid profile, hypertension in pregnancy, first-degree relatives with diabetes and prior GDM. Previous poor obstetric outcomes like previous cesarean delivery, history of stillbirth, miscarriage, unexplained perinatal/neonatal death, macrosomic birth and congenital malformations have all been found to be independent risks.

Secondary analysis of data on singleton live births in the US between 1995 and 2003 provides some insights on ethnicity and GDM risk among US-born and foreign-born women (Savitz et al., 2008). Ghanaian-born women had 6.9% risk for GDM. Peruvians had the least risk while Bangladeshi had the highest risk. Data on 2,056 pregnant women in Qatar shows that women with GDM were significantly older (35-45 years age group) (Bener, 2012, Bener et al., 2011). Others were family history of diabetes, high parity and obesity. Similar risks have been reported in sub-Saharan Africa. In Tanzania, GDM prevalence was found to be higher for women who had a previous stillbirth, family history of type II diabetes and mid-upper arm circumference (MUAC) >28 cm (Mwanri et al., 2014). In Zambia, the predictors were high BMI, prior macrosomic birth and history of diabetes (Liu et al., 2013). Studies in Ghana have found obesity, stillbirth, first-degree relatives with diabetes, more than two miscarriages, previous caesarean delivery and parity above two live children as significant predictors for GDM (Oppong et al., 2015, Asare-Anane et al., 2014). Also, low density lipoprotein and total cholesterol were significantly higher in women with GDM (Asare-Anane et al., 2013).

1.2.4 Maternal and Child Outcomes

The HAPO study demonstrated that risk for adverse maternal, fetal and perinatal outcomes continuously increased as a function of maternal glycemic index between 24–28 weeks of gestation (Metzger et al., 2008). Adverse maternal outcomes include pre-eclampsia and cesarean deliveries and neonatal effects include macrosomia, large for gestational age and shoulder dystocia (O'Sullivan et al., 2011, Wendland et al., 2012, Vambergue and Fajardy, 2011). A systematic review to assess adverse maternal and perinatal outcomes in 44,829 untreated pregnant women diagnosed with GDM showed increased risk of adverse outcomes such as with macrosomia, large for gestational age, perinatal mortality, pre-eclampsia and cesarean delivery (Wendland et al., 2012). Macrosomia, a key adverse outcome, increased likelihood for cesarean delivery, fresh stillbirth, low Apgar score and admission to neonatal intensive care unit (NICU) in Zambia. (Liu et al., 2013)

Uncontrolled GDM has implications on long-term risk of type II diabetes. Follow-up between 6 weeks postpartum to 28 years post-gravidity shows a cumulative incidence of diabetes ranging from 2.6-70% (Kim et al., 2002). Adjustment for lengths of follow-up shows similar rates of progression. Despite the adjusted odds for diabetes increasing at 3 years (5.4), 3-6 years (16.6) and 10 years of diagnosis (8.2), the risk is substantially highest during the 3–6 years after GDM (Song et al., 2018). A Scottish cohort study between 1994-2004 on women diagnosed with GDM reported 25% (n=41) prevalence of type II diabetes from 4 months to 16 years between diagnosis of GDM and follow up (Eades et al., 2015). To determine the long-term implications of GDM, women diagnosed in the UK from 1995-2003 were followed up till 2009. Risk of developing diabetes was 6.9% at 5 years and increased to 21.1% at 10 years following the initial diagnosis of GDM (Sivaraman et al., 2013). Significant associations were found between fasting and post-prandial glucose levels during pregnancy and future risk of diabetes. However, it was not associated with age, gestational age at diagnosis, numbers of previous and subsequent pregnancies.

Likewise, offspring of women diagnosed with diabetes during pregnancy are at higher risk for long-term metabolic outcomes, cardiovascular diseases and increased adiposity at a younger age. Epigenetic mechanisms are thought to play a role (Ma et al., 2015, Landon et al., 2015). A clinical trial in Germany analyzed differences in offspring anthropometrics among pregnant obese women with or without GDM and normoglycemic lean women. Findings show that pre-pregnancy obesity combined with GDM was associated with newborn hyperinsulinemia and increased offspring fat mass (Uebel et al., 2014). Not only does GDM

predisposes mother-offspring to type II diabetes, it also increases adiposity and lipidemia. A cohort study assessed impact of GDM on longitudinal changes in adiposity and metabolic variables in overweight Latino offspring between age 8-20 years (Davis et al., 2013). Results showed that compared with the non-GDM offspring, the GDM offspring had greater increases in total body fat, steeper declines in acute insulin response and disposition index across the Tanner stages. The associations were independent of ethnicity, sex, breastfeeding status, family history of diabetes, and changes in body composition.

1.3 Detection of GDM

1.3.1 Universal Versus Selective Screening for GDM

A 3-pronged approach has been proposed for screening GDM; (1) selective screening, (2) risk stratification and (3) universal screening (Ashwal and Hod, 2015). Screening denotes scheduled assessment of GDM risk and measurement of blood glucose in asymptomatic pregnant women followed by diagnostic testing of screen-positive women. Universal screening is screening of all pregnant women irrespective of symptoms and glycemic status and booking all for diagnostic testing to assess likelihood for GDM (Tieu et al., 2014). Selective (risk factor-based) screening is the assessment done at the first prenatal visit. History is taken on pre-pregnancy or first trimester body mass index (BMI), parity, previous pregnancies and outcomes, family history of diabetes, etc. Screening tests include glycosuria, random blood glucose, fasting blood glucose, 50-g glucose challenge test and glycated hemoglobin (HbA1c) (NICE, 2015). Whether to screen for GDM or not, and the screening approach to use remain controversial.

The risk factor-based screening approach shown in **Table 1** stratifies risks as low, average and high (Ashwal and Hod, 2015). Some have proposed selective screening where risk is stratified according to severity and only the high-risk group selectively booked for diagnostic testing (Ashwal and Hod, 2015, National Institute for Health and Care Excellence, 2015). Depending on the woman's risk level, an appropriate diagnostic action is taken. Indications for OGTT based on independent risk factors and clinical measurements include the following (National Institute for Health and Care Excellence, 2015):

- Glycosuria ≥ 1+ on more than one occasion or ≥ 2+ on one occasion
- Macrosomia in current pregnancy
- Previous macrosomia (<4.5 kg, or above the 95th percentile for gestational age)
- Previous gestational diabetes
- First-degree relative with diabetes
- Asian ethnic background
- Previous unexpected perinatal death
- History of polycystic ovary syndrome
- Obesity (BMI >30 kg/m²) or booking or weight above 100 kg
- Polyhydramnios
- Fasting blood glucose > 6.0 mmol/L or random blood glucose >7.0 mmol/L

Table 1. Screening for gestational diabetes using the risk stratification approach

	Low risk	**Average risk**	**High risk**
Risks groups	1. Normal pre-pregnancy and pregnancy weight (not overweight) 2. Age <25 years 3. No T2D in first-degree relatives 4. No history of abnormal glucose metabolism 5. No prior poor obstetric outcome 6. Not from high risk ethnic group	1. Not classified as low/high risk 2. Detected as high risk at early pregnancy but did not have GDM in early pregnancy	1. Obesity 2. First degree family with T2D 3. Prior history of GDM 4. Known glucose intolerance outside of pregnancy 5. Glycosuria
Diagn-ostic action	No challenge test is required for screening or diagnosis of diabetes	Challenge test is required at 24–28 weeks	Single OGTT or 2 stage GCT & OGTT in early pregnancy. If negative, repeat at 24–28 weeks

GDM: oral glucose tolerance test; GCT: glucose challenge test; T2D: type II diabetes

In the midst of the epidemiological transition, WHO cautions the use of selective screening as there is possibility of under-diagnosis thereby missing the opportunity to manage women who might need treatment (World Health Organization, 2013). Essence of universal screening has been reaffirmed in an observational study in Nigeria where selective versus universal screening was assessed. Singleton pregnant women (n=1059) were screened for GDM between 24-32 weeks using the 2010 IADPSG criteria. If selective screening were used, about 20% of the GDM cases would have been missed (Olagbuji et al., 2015). In the US, the screening universal group was found to be less likely of being diagnosed with GDM (RR [relative risk]: 0.44 95% CI [confidence interval]: 0.26-0.75) than the selective screening group (Tieu et al., 2014). Low-risk women are less likely to benefit from universal screening (Tieu et al., 2014). This has generated concerns about the economic burden universal screening will put on health systems. The new criterion is expected to increase the number of

women identified with GDM (World Health Organization, 2013) and health systems need to be prepared to manage the implications of the high prevalence.

1.3.2 Global Guidelines on GDM Screening and Diagnosis

Until the landmark HAPO study in 2008, which was a large-scale multinational prospective observational study involving 25,000 pregnant women, GDM did not receive much global policy attention. GDM detection is attributed to Matthews Duncan. In 1882, Duncan observed a possibility of hyperglycemia during pregnancy, which did not normalize after delivery (Coustan, 2013). In 1964, OGTT was identified as a diagnostic test to detect GDM. Pregnant women (n=752) were tested for GDM through intake of 100-g glucose and the 3-hour postprandial glucose measured (O'Sullivan and Mahan, 1964). Thereafter, various guidelines for detecting GDM evolved.

Notable were the National Diabetes Data Group (NDDG) in 1979 (National Diabetes Data Group, 1979), the criteria by Carpenter and Coustan in 1982 (Carpenter and Coustan, 1982) and the 1999 WHO consultation report on the definition, diagnosis and classification of diabetes mellitus (WHO, 1999). In the past decade, these guidelines were updated to bring global uniformity in the diagnosing and improve sensitivity and specificity of the diagnostic tests. Example is the 'clinical guideline on the management of diabetes and its complications in pregnancy from pre-conception to the postnatal period' by NICE in 2008 (NICE, 2008).

The Hyperglycemia and Adverse Pregnancy Outcomes (HAPO) study formed basis for the current globally endorsed criteria on the definition, diagnosis and classification of diabetes in pregnancy and GDM (Metzger et al., 2008). Based on the HAPO study, the International Association of Diabetes and Pregnancy Study Groups (IADPSG) developed recommendations for the diagnosis and classification of Hyperglycemia in Pregnancy (IADPSG Consensus Panel, 2010). It was adopted by WHO in 2013 as the 'Diagnostic Criteria and Classification of Hyperglycemia First Detected in Pregnancy". Similarly, the American Diabetes Association (ADA) updated its diagnostic guidelines based on IADPSG recommendations (American Diabetes Association, 2015). It is expected that with the new diagnostic criteria, more women would be diagnosed with GDM as a reflection of the increasing prevalence of type II diabetes (World Health Organization, 2013).

Presented in **Table 2** are some common diagnostic criteria and thresholds. The NICE guideline considers 75-g OGTT conducted at 24–28 weeks as the 'gold standard' test for GDM (National Institute for Health and Care Excellence, 2015). The WHO guideline focuses on prognostic accuracy rather than diagnostic accuracy (World Health Organization, 2013) and hence does not endorse any gold standard test per se. Most guidelines recommend 24-28 weeks as the optimum timing for diagnostic testing using fasting plasma glucose (FPG), 1-hour and 2-hour OGTT. Cut-offs are based on mean glucose values at which odds of adverse pregnancy outcomes reach 1.75 times (IADPSG Consensus Panel, 2010).

Table 2. Global guidelines for diagnosing gestational and overt diabetes

Diagnostic criteria	Random plasma glucose		Fasting plasma glucose		1-hour 75g post prandial OGTT		2-hours 75g post prandial OGTT		Test time (weeks)
	mmol/L	mg/dl	mmol/L	mg/dl	mmol/L	mg/dl	mmol/L	mg/dl	
Gestational diabetes									
ADA 2015[a]			≥5.1	≥ 92	≥10.0	≥ 180	≥8.5	≥153	24-28
IADPSG 2010			≥5.1	≥92	≥10.0	≥180	≥8.5	≥153	24-28
NICE 2015			≥5.6	≥100			≥7.8	≥140	24-28
WHO 2013			5.1-6.9	92-125	≥10.0[b]	180[b]	8.5-11.0	153-199	20-28 preferred
Clinical diabetes									
IADPSG 2010	11.1[c]	200[c]	7.0	126					Early prenatal
WHO 2013	≥ 11.1[d]	200[d]	≥ 7.0	126			≥ 11.1	200	Anytime

Tests with blank spaces imply that no diagnostic cut-offs have been recommended. [a] This criterion is according to the one-step strategy. The two-step" approach is 50-g OGTT screening followed by 100-g OGTT for those who screen positive (American Diabetes Association, 2015). [b] There is no established WHO criterion for the diagnosis of GDM based on 1-hour post-load value **(World Health Organization, 2013)**. [c] When random plasma glucose test is used, diagnosis should be confirmed using fasting plasma glucose or glycosylated haemoglobin **(IADPSG Consensus Panel, 2010).** [d] Diagnosis based on random plasma glucose test results should be made in the presence of diabetes symptoms **(World Health Organization, 2013)**.

1.4 Management and Prevention of GDM

Gestational diabetes is associated with adverse maternal and neonatal consequences (Metzger et al., 2008, Wendland et al., 2012) including long-term metabolic risks (National Institute for Health and Care Excellence, 2015). Testing and management using non-pharmacological and pharmacological methods could improve outcomes (Landon et al., 2009). Although evidence on the clinical importance of non-pharmacological management is not so strong

(Hartling et al., 2013, Colberg et al., 2013), management is shown to improve glycemic control. Treatment may consist of lowering blood glucose concentration alone or in adjunct with special obstetric care. Treatment options include lifestyle modifications (dietary changes, physical activity), use of oral hypoglycemic agents (metformin or glibenclamide) and insulin therapy. Likewise, WHO recommends GDM management with interventions which promote lifestyle changes like nutritional counseling and exercise and cautions the use of insulin therapy unless clinically indicated (World Health Organization, 2013). The recommendation is that in mild cases of GDM where glucose values overlap with the thresholds recommended, 80–90% of these women could be managed with lifestyle therapy alone (American Diabetes Association, 2013).

1.4.1 Biomarkers for GDM

Research is ongoing to understand the role of maternal serum biomarkers in predicting the risk of gestational diabetes (Nanda et al., 2011, Nagalla et al., 2015, Zhu et al., 2015, Rasanen et al., 2013, Singh et al., 2015). Aside known maternal risk factors, serum biomarkers like adiponectin, follistatin-like-3, sex hormone binding globulin, oxidative stress associated with levels of high-sensitivity C reactive protein (hs-CRP) and high fluorescence reticulocytes at fasting, and hs-CRP in 1-h OGTT, proteomic and glycosylated fibronectin are significantly associated with GDM.

In recent times, gut microbiota of both GDM women and their newborns is shown to alter with more metabolic and inflammatory taxa, suggesting a potential effect on metabolic health in later stages in life (Su et al., 2018, Ferrocino et al., 2018). The current epidemiological transition necessitates that screening for GDM be combined with maternal characteristics and serum biomarkers as it will provide a holistic approach to understanding the pathophysiology of GDM and interventions needed to reduce the incidence and ameliorate materno-fetal complications. However, many of these biomarkers are expensive and difficult to perform in low-income settings.

1.5 Conceptual Framework and Current State on GDM

Except for GDM detection using biomarkers and the management strategies, all other aspects related to GDM conceptualized in **Figure 1** were directly investigated in the study. The literature review has shown a global rising prevalence of GDM. High prevalence in some

low-income settings are worrying considering the low investments in healthcare and inadequate preparedness to respond to the condition. Although the increasing prevalence has been attributed to rising diabetes mellitus, obesity, physical inactivity and more pregnancies in older women, lowering of diagnostic cut-offs in recent guidelines is largely accountable.

The screening procedure is chaotic, because the screening tests are not clearly defined and there is no global non-consensus on the approaches to use. Opinions are divided on whether to test all pregnant women (universal screening) or screen all pregnant and test the 'at risk' group (selective screening). The argument of the universal screening proponents is based on not missing any pregnant women who might need management and specialized care to avert pregnancy complications. The argument of the selective screening proponents is based on cost implications of testing all pregnant women some of whom have no risk factor whatsoever and the associated over-medicalization of obstetric care. Evidence is not strong on the pregnancy outcomes, but a trajectory of GDM to type II diabetes has been established in the long term. Pharmacological treatment is initiated when glycemic control is not achieved from non-pharmacological management.

The first gaps identified in the literature are the dearth of evidence on the prevalence of GDM in lower level facilities and among rural and peri-urban dwellers in low-income settings; diagnostic validity of some screening tests as well as the birth outcomes and glycemic status in the short and long-term postpartum period. Also missing is lack of evidence on the cost effectiveness of universal versus selective screening; effectiveness of interventions to prevent and manage GDM during pregnancy and during postpartum in low-income settings; low-cost biomarker tests for early prediction of GDM and gut microbiome profile of GDM-affected mother-offspring pairs. This study attempts to fill the first gaps identified.

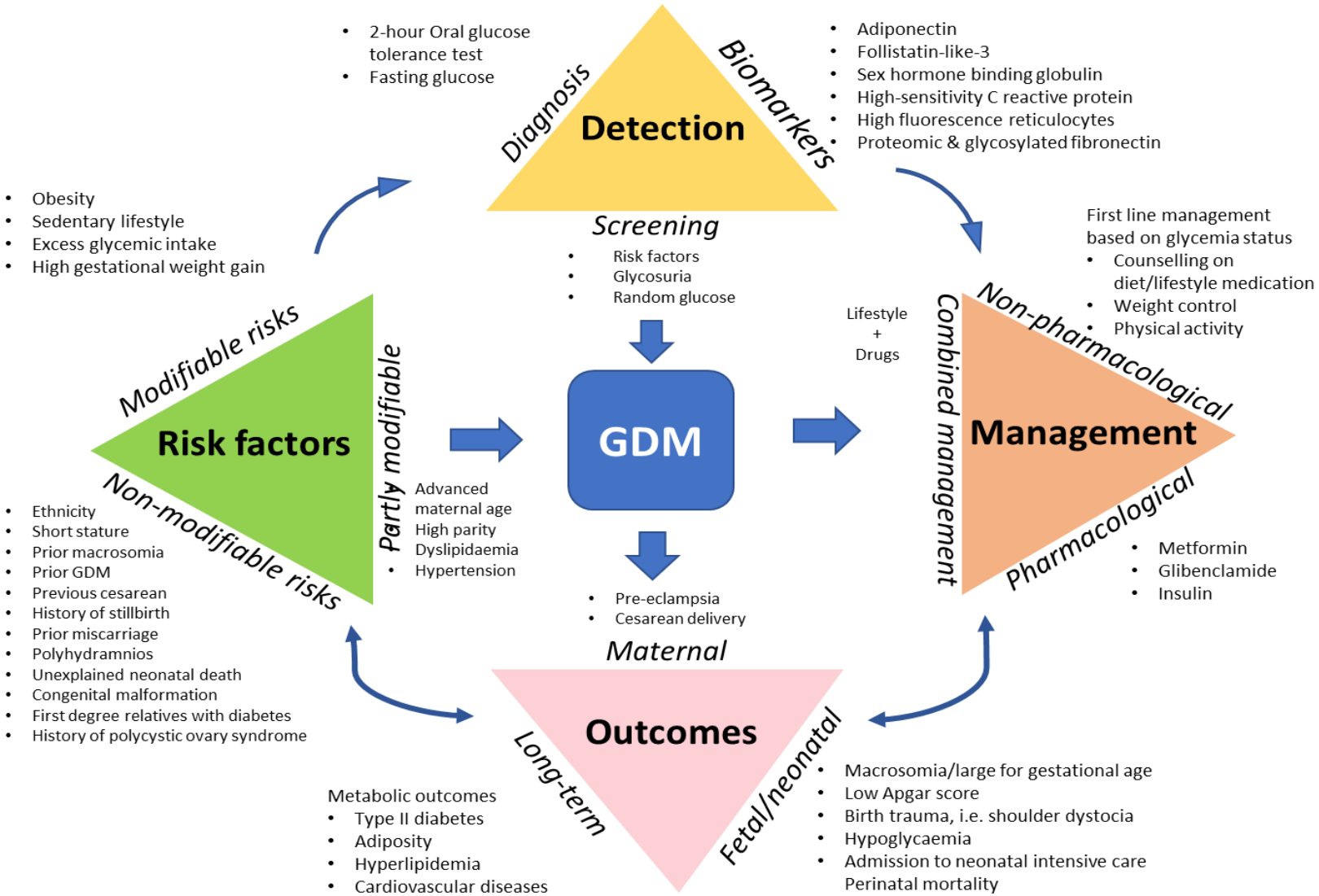

Figure 1. Conceptual framework on the public health spectrum of GDM

1.6 Problem Statement

1.6.1 Background of Ghana – the Study Context

Ghana is a lower middle-income West African country sharing borders with Togo to the East, Cote d'Ivoire to the West and Burkina Faso to the North. It is bordered to the South by the Atlantic Ocean, covering a coastline of 539 km while the country covers a total land area of 227,540 km^2. The median age of the 24,658,823 population is 20.5 years and about 55% is in urban centers (Ghana Statistical Service, 2013). Per the population density, Ghana has 10 administrative regions sub-divided into 6 metropolitan, 49 municipalities and 261 districts. Life expectancy is 60 years for among males and 63 years among females (Ghana Statistical Service, 2015). Presented in **Table 3** are the key economic and health indicators for Ghana.

Table 3. Key economic and health indicators for Ghana

Economic or Health Indicator	Results
Gross domestic product	24.6%
Gross domestic product growth	8.5%
Inflation	9.8%
Average lending interest rates	16.2%
Main economic activity - agriculture	45%
Women in reproductive age (15-49 years)	45.3%
Mean size of households	3.5
Females educated above secondary level	6.3%
Females currently employed	73.4
Median age at first birth for women age 15-49 (years)	21.4
Total fertility rate (children per woman)	4.2
Mean no. of children ever born to women age 40-49	4.8
General fertility rate (per 1,000 women age 15-44)	143
Crude birth rate (per 1,000 population)	30.6
Women age 15-49 currently pregnant	7.1%
Teenage pregnancy (15-19 years)	11.3%
Use of any modern contraceptive method	31.7%
Unmet need for family planning	29.9%
Antenatal care from a skilled provider	97%
Births attended by a skilled provider	74%
Four or more antenatal care visits	87%
Median pregnancy duration at first antenatal visit (months)	3.6
Perinatal mortality rate (per 1,000 pregnancies)	38
Neonatal mortality rate (per 1,000 live births)	29
Infant mortality rate (per 1,000 live births)	41
Under-5 mortality (per 1,000 live births)	60
Maternal mortality ratio (per 100,000 live births)	310
Lifetime risk of maternal death	1%
Percentage of maternal deaths	7%

Source: (Ghana Statistical Service, 2015, Ghana Statistical Service, 2018, African Development Bank, 2019)

1.6.2 GDM in Ghana and the Diagnostic Procedure

GDM screening and diagnosis is not uniform in Ghana but based primarily on glycosuria

Selective screening for GDM is a risk assessment strategy routinely used in Ghana Health Service facilities. The procedure used in screening and diagnosing GDM in Ghana is presented in **Figure 2**. At the first antenatal visit, the pregnant woman is interviewed to determine the risk for GDM by assessing age, body weight at first ANC visit, previous pregnancies, previous diagnosis of GDM, and family history of diabetes. In addition, at every antenatal visit, glycosuria is tested using a qualitative rapid urine dipstick test to detect the presence of glucose in urine. Corresponding colour changes represent negative, trace, +1, +2, +3 and +4 urine glucose. Clients in the high-risk category are identified based on risk factors and/or +1 glycosuria test result on one or two screening occasions. These clients usually perform a GDM confirmatory test. However, type of diagnostic test depends on level of healthcare and could be fasting or random glucose using capillary whole blood or venous plasma and OGTT.

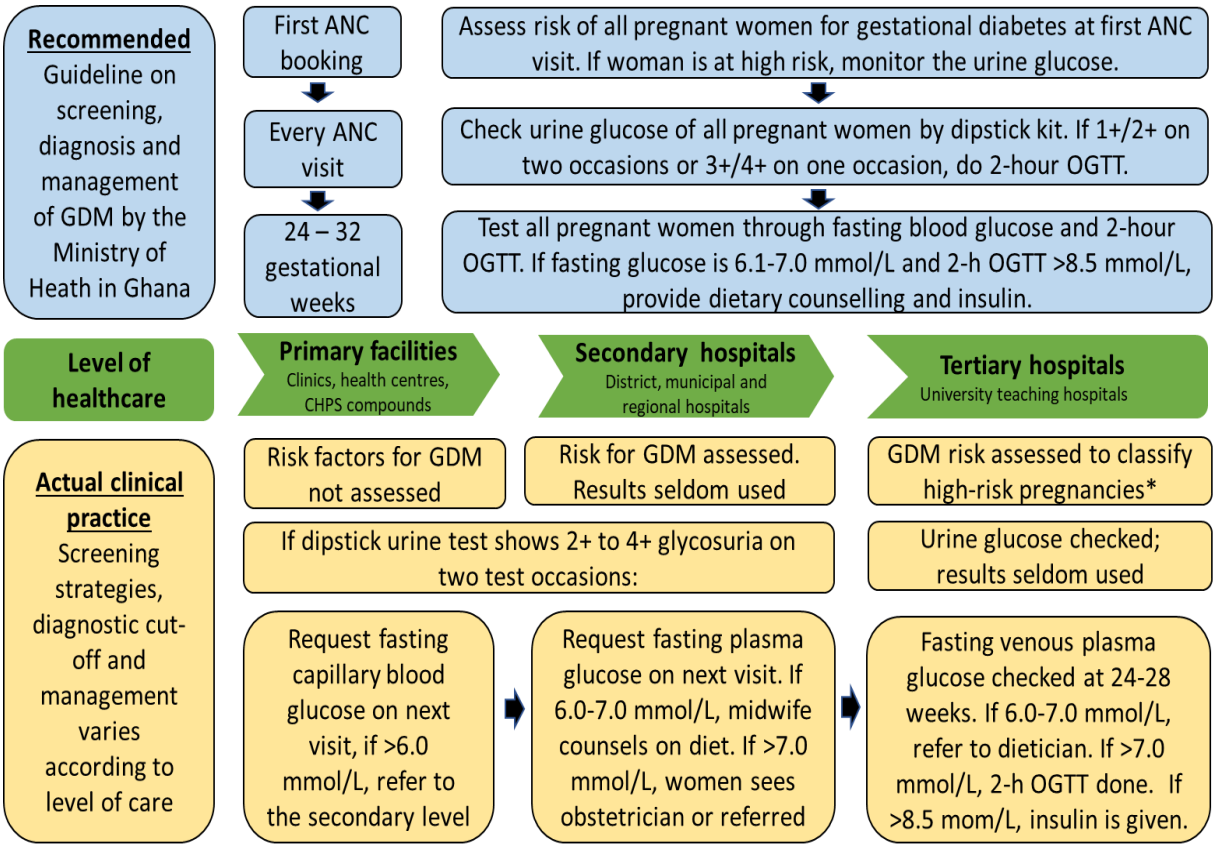

Figure 2. Procedure for screening and diagnosing gestational diabetes in Ghana Health Service hierarchy of facilities.

*Note: *The standard treatment guideline currently used in Ghana does not indicate what monitoring entails.*

Glycosuria testing is unreliable during pregnancy, yet it is used

During pregnancy, renal threshold for glucose reabsorption from the glomerular filtrate reduces leading to increased glycosuria at some point in about 50% of all pregnancies (Alto, 2005). The renal threshold for glucose is highly variable with a reduction in glycemic thresholds needed for the GDM diagnosis. This may lead to a positive glycosuria despite normal blood glucose (that is, glycosuria without hyperglycemia).

Glycosuria test, aside being cheap and convenient, is useful in identifying patients with uncontrolled diabetes. However, it has low specificity due to the lower renal threshold that occurs with gestation (Hanna and Peters, 2002). Yet, there is possibility of symptomatic hyperglycemia without detectable glucose in the urine (that is, hyperglycemia without glycosuria) (Cersosimo et al., 1997). Cases could be missed should glycosuria be the only screening test thereby missing the opportunity to manage the condition and prevent adverse materno-fetal complications. Glycosuria screening for GDM has been discredited (National Institute for Health and Care Excellence, 2015), but remains the only option in primary facilities in Ghana. Some studies have suggested removal of routine urine dipstick screening for glycosuria during pregnancy (Alto, 2005) while others have suggested a re-evaluation of the test as it is a routine ANC practice (National Institute for Health and Care Excellence, 2015).

Global guidelines on GDM screening are inconsistent and Ghana has no clear policy

Currently, there are controversies regarding screening tests for GDM that should form the basis to perform a diagnostic test. Also, whether the procedure should be done for all pregnant women (universal screening) or on a selected number based on their risk levels (selective screening) is yet another issue with no international consensus. On the contrary, guidelines for diagnosing GDM and overt diabetes are clear (**Table 2**). Key guidelines include that by the International Association of Diabetes in Pregnancy Study Groups Consensus Panel (2010), World Health Organization (2013), American Diabetes Association (2015), and the National Institute for Health and Clinical Excellence (2015). These guidelines are based on the outcomes obtained from random plasma glucose, fasting plasma glucose, 1-h and 2-h post 75-g OGTT. Clinicians in Ghana rely on outcomes of routine glycosuria testing and history taking for risk assessment as indicators for diagnostic testing. Maternal history though taken at first ANC visit, is seldom used to evaluate GDM risk level. The WHO guideline on diagnosis and management of GDM is used as there is no clear policy guideline in Ghana. A

study in the US assessed glycemic status of 324 pregnant women to evaluate effects of using fasting blood glucose as screening test, and 1-h and 2-h OGTT as diagnostic tests (Herrera et al., 2015). Seven percent tested positive using fasting glucose, 37% using 1-h and 22% using 2-h OGTT. But for the screening, the 7% would have been missed.

GDM situation in Ghana is not well established

Literature consistently points macrosomia as one of the most important adverse neonatal outcomes of diabetes in pregnancy (Metzger et al., 2008, Wendland et al., 2012, Vambergue and Fajardy, 2011). Secondary data was analyzed on 4262 singleton newborns from January 2012 to December 2013 to get an overview of the magnitude of GDM in the study location. Macrosomic deliveries (birthweight ≥4 kg) was found to be 3.03% (n=129) (Agbozo et al., 2016). Analysis of antenatal records from the same health facility for 2013 showed that out of 2234 pregnant women who did dipstick urinalysis, over half (n=1175) tested positive for protein in urine whereas only 1.8% (n=40) tested positive for dipstick glycosuria. Findings from this secondary analysis of data are inconclusive making it difficult to draw any meaningful conclusion.

Until 2015, there was no published data on prevalence of GDM in Ghana. Using the 2012 diagnostic criteria of the American Diabetes Association, prevalence of GDM by 2-h OGTT was 9.3% in the largest referral hospital in Ghana (Oppong et al., 2015). As this study was conducted in a tertiary facility, generalizing findings as the true population prevalence must be done with caution. Meanwhile, prevalence of type II diabetes among adults age 18-80 years seeking outpatients services at the same hospital was 6.5% (Nelson et al., 2015). Thus, this pregnancy-related metabolic condition is emerging as a maternal problem that could pose challenges to already over-stretched health systems. Considering the lack of consensus on universal verses selective screening, GDM is hypothesized to be under-diagnosed in Ghana.

Summary of the rationale for the study

In summary, despite the recommendation to checking the fasting blood glucose of all pregnant women in Ghana as stipulated in the standard treatment guideline, GDM screening and diagnostic procedures are not uniform in Ghana and the diagnostic decision is at the discretion of the provider. Dipstick glycosuria remains the most used screening test despite its non-reliability during pregnancy. Moreover, the actual GDM situation that is

representative of the true population is not well established in Ghana, neither is there any evidence on the associated birth outcomes and postpartum glycemia. On the global front, current GDM screening and diagnostic guidelines are inconsistent leading to application of diverse tools and cut-off.

1.6.3 Study Objectives

The overall objective is to validate the diagnostic accuracy of screening tests for gestational diabetes, assess prevalence, risk factors and associated maternal and neonatal birth outcomes including short-term postpartum glycemia status.

Specific objectives

1. To estimate the prevalence of GDM using various cut-offs including WHO and NICE diagnostic criteria
2. To validate the diagnostic accuracy of glycosuria and random blood glucose compared to fasting plasma glucose and OGTT
3. To assess the risk factors for GDM using socio-demographic, anthropometric and dietary data; obstetric and medical history and macrosomia as proxy for GDM
4. To assess association of GDM with adverse maternal and newborn birth outcomes
5. To examine extent of attainment of euglycemia among GDM mothers at 12 weeks postpartum

1.6.4 Hypothesis and Research Questions

Hypothesis: The current screening tests for GDM in Ghana (urine dipstick for glucose and history taking) is missing majority of cases.

Research questions that this study intend to answer include the following:

1. What is the prevalence of GDM and overt diabetes in Ghana?
2. How accurate are the screening tools used to detect GDM?
3. Which diagnostic criteria will be most applicable in primary level facilities?
4. Is there difference in prevalence using universal and selective screening approaches?
5. What proportion of cases are missed if selective screening is applied?
6. Which maternal characteristics (adiposity, dietary, obstetric and physiologic risk factors) predict the likelihood for developing GDM?
7. What is the effect of GDM on maternal and newborn health outcomes?

8. To what extent do women diagnosed with GDM attain euglycemia during postpartum?

1.6.5 Purpose of the Study

In order to develop a national protocol on GDM screening and diagnosis and design evidence-based interventions for prevention and management, empirical evidence is needed on validity of screening tests that is applicable within the Ghanaian context, prevalence, risk factors and birth outcomes. This study aims to generate this knowledge following current global diagnostic criteria and provide background for future intervention studies.

2 MATERIALS AND METHODS

Note: The doctoral student has published some aspects of this chapter in the underlisted publications. For details, see pages 109-111.

- Prevalence of low birth weight, macrosomia and stillbirth and their relationship to associated maternal risk factors in Hohoe Municipality, Ghana http://dx.doi.org/10.1016/j.midw.2016.06.016
- Accuracy of glycosuria, random blood glucose and risk factors as selective screening tools for gestational diabetes mellitus in comparison with universal diagnosing. http://dx.doi:10.1136/bmjdrc-2017-000493
- Gestational diabetes using diverse diagnostic criteria, risk factors including dietary intakes, pregnancy outcomes and postpartum glycemic status: a nested case-control study in Ghana. https://doi.org/10.1101/582239

This methods chapter is organized into six main sections. The first section describes the geographic and health context of the study. The second and third sections describe the four observational study designs used and how the sample size of approximately 800 was obtained. The fourth and fifth sections describe the procedures used in obtaining data in the prenatal, intrapartum and postpartum phases of the study and the statistical analyses applied in interpreting the raw data generated. In the final section, the ethical considerations are highlighted. Overview of the methodology is presented in **Figure 3**.

2.1 Study Setting

2.1.1 Maternal Health Indicators of the Study Setting

The study was conducted at the maternal health departments of five state-own hospitals in the Volta region administered through the Ghana Health Service and regulated by the Ministry of Health. Data was collected from the antenatal clinic, labour ward and postnatal clinic of the study facilities. Generally, in Ghana, antenatal care (ANC), delivery and postnatal services are provided at secondary level facilities. Therefore, participants were proportionately recruited from one primary-level facility serving mainly rural communities, three secondary-level facilities serving rural and peri-urban communities, and the largest referral hospital in the region, also a secondary facility.

The facilities comprised the Jasikan district hospital, a primary level facility; three secondary facilities (district hospitals) comprising the Hohoe and Ho municipal hospitals, and the Margaret Marquart Catholic hospital. The largest of the secondary facilities was the Volta regional hospital, a 240-bed capacity hospital situated in Ho, the Volta regional capital. It serves as the regional referral facility and has now been upgraded to a tertiary facility to serve as a Teaching Hospital for the University of health and Allied Sciences.

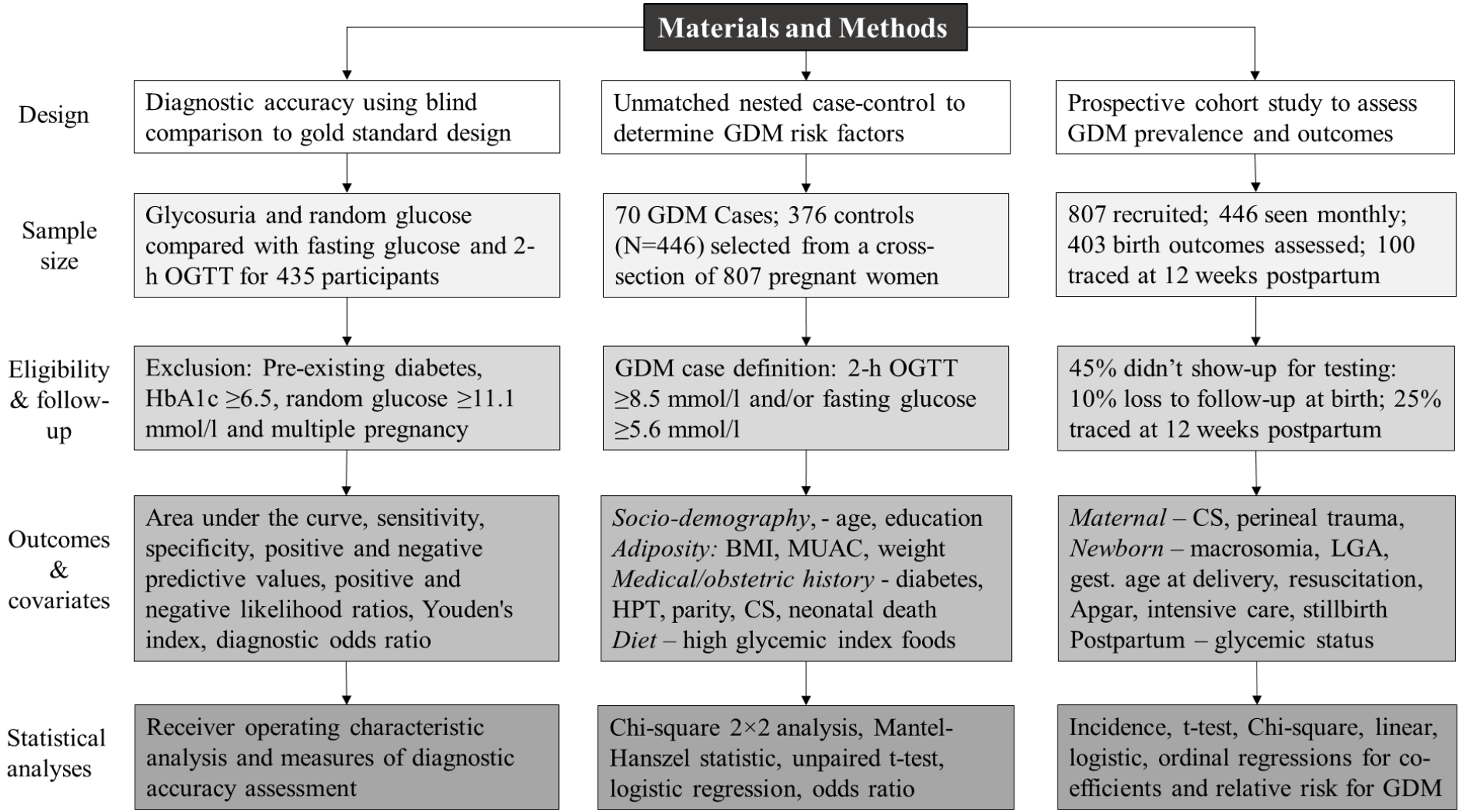

Figure 3. Summary of the study methodology highlighting the designs, sample size, eligibility criteria, follow-up, statistical analyses and outcome measures

Note: GDM, gestational diabetes mellitus; CS, cesarean section; BMI, body mass index; LGA, large for gestational age; MUAC, mid-upper arm circumference; HPT, hypertension

These study facilities were purposively selected because of their peculiar diverse characteristics (**Table 4**), which aided in providing an overview of the maternal and newborn healthcare situation in the region. Therefore, findings obtained were most likely to be generalizable to the national situation as it gives a representation of rural-urban differences and provides empirical data for comparing healthcare systems in urban and rural areas of Ghana. Also crucial in the selection of the study facilities was the ease and proximity of transporting samples to the research laboratory located in the Hohoe municipality (see section 2.4.1) where the biochemistry and hematological analyses were done.

Shown in **Table 4** is the maternal and child health profile of the study facilities and the demographic and health indicators of the region, three municipalities and one district where the study facilities are located. The primary facility is somewhat resourced to deliver the seven basic Emergency Obstetric and Newborn Care (EmONC) signal functions while the higher-level facilities provide both basic and comprehensive EmONC services and have at least one resident obstetrician. But all the facilities have skilled birth attendants particularly midwives and other crucial support staff.

Table 4. Demographic and health indicators of the Volta region and the facilities where the study was conducted

Profile	Volta Region	Ho Municipality	Hohoe Municipality	Kpando Municipality	Jasikan District
Total population	2,118,252	177,281	167,016	93,649	59,181
Rural inhabitants (%)	66.3	55.7	59.7	68.4	72.4
Women in reproductive years (15-49 years) (%)	24.4	28.1	25.2	25.1	23.5
Total fertility rate (15-49 years)	3.4	2.7	3.3	3.0	3.4
General fertility rate (1000 women 15-49 years)	99.2	74.4	96.0	87.1	98.5
Crude birth rate (per 1000 population)	24.2	20.9	24.3	21.9	22.5
Crude death rate (per 1000 population)	8.8	8.3	8.7	8.9	9.6
Infant mortality (per 1,000 live births)	57	58	51	50	53

Major health facility	Volta Regional Hospital[a]	Ho Municipal Hospital[a]	Hohoe Municipal Hospital[a]	Margret Marquart Hospital[a]	Jasikan District Hospital[a]
Bed capacity	240	130	178	152	45
ANC registrants	1,359	1,160	1,417	902	832
ANC attendance	12,128	6,256	7,073	5,290	4,236
1st trimester registrants	730	621	628	354	385
2nd trimester registrants	446	395	550	447	348
3rd trimester registrants	183	144	123	101	99
No. making 4 ANC visits	572	568	1071	794	509
No. of deliveries	1,989	1,699	2,016	1,396	669
Live births	1,972	1,687	2,030	1,407	667

Source: Ghana Statistical Service, 2013 and Ghana Health Service 2015 District Health Information Management System (DHIMS II) Data for the Volta region.

[a] These secondary facilities provide both basic and comprehensive Emergency Obstetric and Newborn Care (EmONC) signal functions and [b] the primary facility provides only basic EmONC signal functions.

Basic EmONC signal functions:

(1) parenteral antibiotics;
(2) parenteral anticonvulsants;
(3) parenteral oxtyocics;
(4) manual removal of placenta;
(5) removal of retained products (manual vacuum aspiration);
(6) assisted vaginal delivery (with vacuum extractor or forceps);
(7) neonatal resuscitation with bag and mask

Comprehensive EmONC signal functions:

(8) blood transfusion and
(9) cesarean section

2.1.2 General Information about the Volta Region

Volta Region is the third least populated region in Ghana and has 20 districts and 5 municipalities. It is located between latitudes 5° 45'N and 8° 45'N along the southern half of the eastern border of Ghana. The region lies on the eastern side of Ghana and shares boundaries with the republic of Togo. It shares boundaries with Greater Accra, Eastern and Brong Ahafo regions to the west, Northern Region to the north and the Gulf of Guinea to the south. The region is the longest of all the regions in Ghana covering about 500 km in length from south to north. Map of the study site is shown in **Figure 4**. It occupies 20,570 square km representing 8.7% of the total land area of Ghana. The vegetation includes costal grassland, mangrove swamps, guinea savannah, semi-deciduous forests, Sahel-savannah and mountainous wooded savannah in the north. Apart from the ecological diversity of the region, almost all ethnic groups in Ghana live in the region as indigenes. Although Ewes constitute the largest ethnic group in the region, there are seven other major ethnic groups speaking 56

different dialects. As a result of this uniqueness, the region is described as a "microcosm" of the country (Ghana Statistical Service, 2013).

The region has a total of 326 health institutions out of which 242 are administered by the Ghana Health Service. The doctor to population ratio in the region is one doctor to 35,871 inhabitants and the nurse to population ratio is one nurse per 1,327 inhabitants. The region has a population of 2,118,252 inhabitants with 66.3% resident in rural areas. Out of the 1,098,854 females, 45.2% are women in their reproductive years aged 15-49 years. The regional total fertility rate is 3.2 children per woman age 15-49 years while the average completed family size for women aged 12-54 years is 5.1 children per woman. Fertility rates of rural dwellers is relatively higher but there is little difference in teenage fertility in urban and rural areas. Infant mortality and under-five mortality (per 1,000 live births) for the region are 57 and 87 respectively (Ghana Statistical Service, 2013). On the other hand, the national crude birth rate (per 1,000) is 30.6 (Ghana Statistical Service, 2015). Data from the Ghana Health Service District Health Information Management System (DHIMS II) reveals that in 2014, 72,003 pregnant women registered at antenatal clinics in the Volta region. First, second and third trimester registrant were 33,149 (47%), 27,694 (39%) and 8,742 (12%) respectively. Mothers making four ANC visits were 48,007 (67%) while 48,096 live births were recorded.

Figure 4 a: Map of Ghana in relation to West Africa *(source: Google map)*

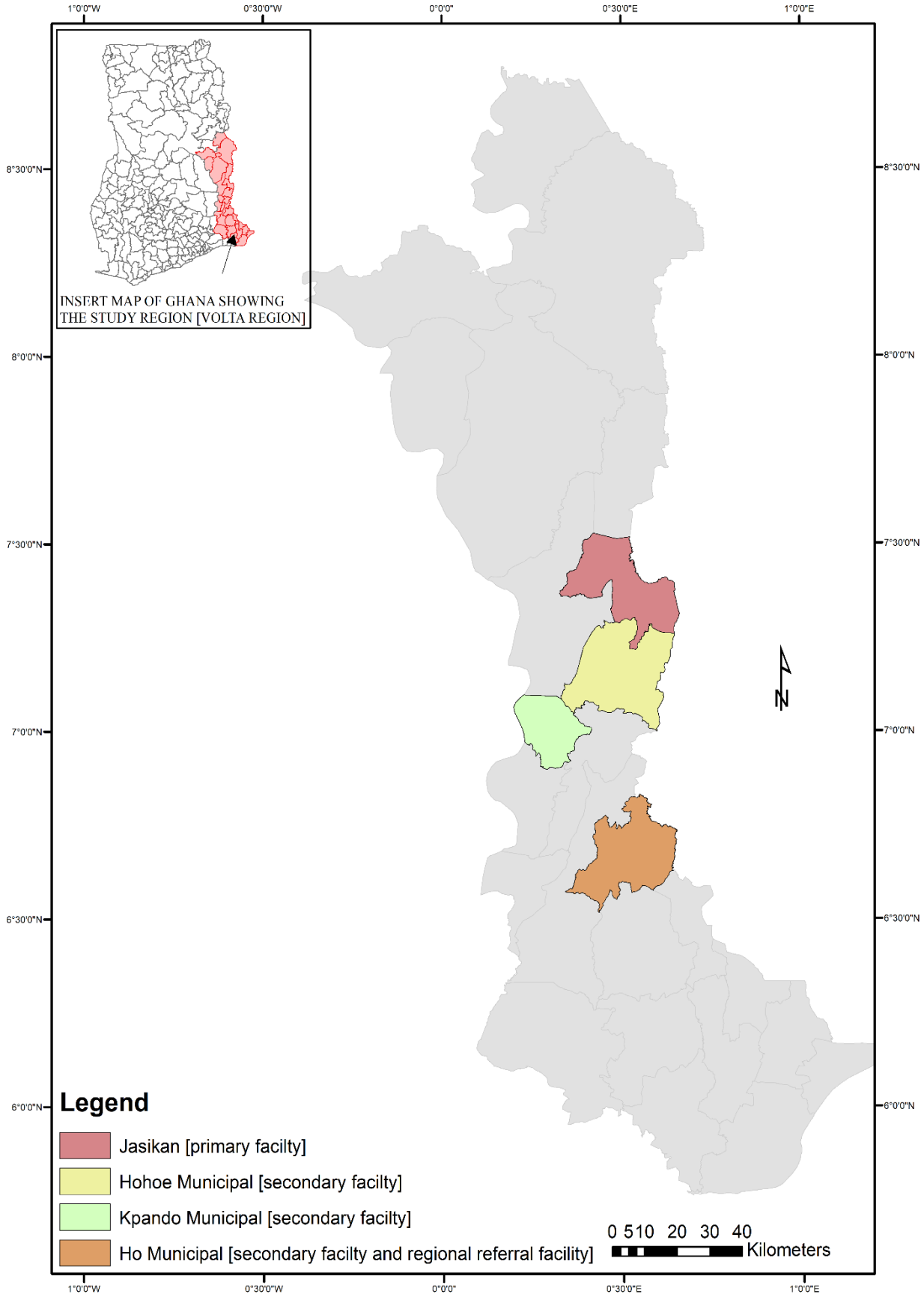

Figure 4 b. Map of the Volta region showing the specific study sites

2.2 Study Design

The study was observational and employed four main designs; cross-sectional survey; diagnostic accuracy study design, prospective longitudinal study design and unmatched nested case-control study design. The diagnostic accuracy study and the case-control study were nested in the prospective cohort study. Synopsis of the study designs used, and the corresponding number of participants enrolled is shown in **Figure 5**.

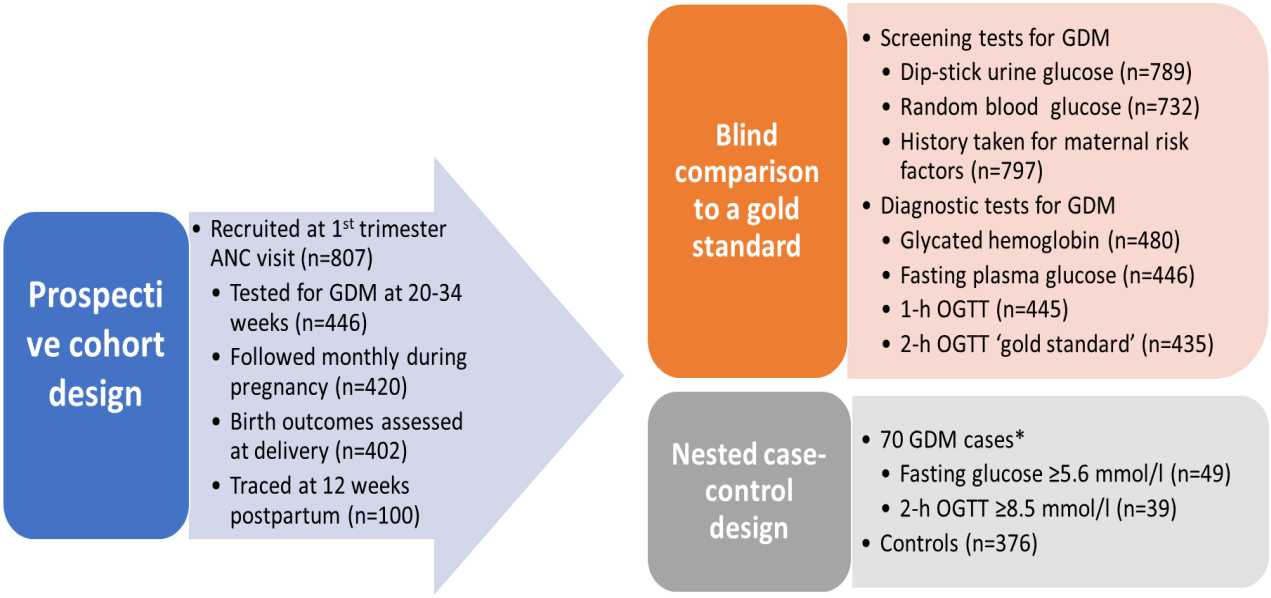

Figure 5. Synopsis of the study designs and corresponding number of participants enrolled

*Note: *Case definition used in this present was fasting plasma glucose ≥5.6 mmol/L (National Institute for Health and Care Excellence, 2015) and/or 2-h OGTT ≥8.5 mmol/L* (World Health Organization, 2013)

Cross-sectional design: To obtain information on the magnitude of GDM in the study area using newborn macrosomia as a proxy, a baseline cross-sectional survey was conducted in the Hohoe municipality between January 2013 to December 2014. Secondary medical records of 4477 deliveries documented in the labour and gynecological theatre of the Hohoe municipal hospital were reviewed, extracted and analyzed.

Blind comparison to a gold standard design: For the diagnostic accuracy study, the prospective blind comparison to a gold standard design was used. This design compares accuracy of different diagnostic tests in the same individual. The index screening tests evaluated were dipstick glycosuria test, random blood glucose (RBG) and presence of maternal risk factors. The index diagnostic tests evaluated were 1-h OGTT and HbA1c. Performance of each test within the same individual was validated against the 2-h OGTT and

fasting glucose. Findings were reported according to the Standards for Reporting Diagnostic Accuracy (STARD) guidelines (Bossuyt et al., 2015).

Longitudinal cohort design: The longitudinal cohort study involved a cohort of pregnant women who were followed through the prenatal (antenatal), intrapartum (during delivery) and postpartum periods of pregnancy. Prevalence of GDM was assessed as well as the association with maternal, fetal and newborn outcomes. Participants were tested for GDM in the second to third trimesters of pregnancy and the postpartum changes in glycemic status repeated at 12 weeks postpartum. Physiologic measurements such as glycosuria, proteinuria, blood pressure and weight were assessed at each ANC visit while birth outcomes were extracted from facilities' delivery records.

Case-control design: The unmatched nested case-control design was used to assess the risk factors that decreased or increased a pregnant women's likelihood for GDM. At enrolment, data was obtained on socio-demographic characteristics. Dietary intake, medical and obstetric history were assessed retrospectively, whereas weight, height, random blood glucose and Hb1Ac were measured at ANC registration to assess the risk for GDM.

2.3 Sample and Sampling

2.3.1 Study Population

The study population was pregnant women who attended and received antenatal care, delivery and postnatal care services at the Volta regional hospital, Hohoe and Ho municipal hospitals and the Jasikan district hospitals between May 2016 and April 2017. Pregnant women who were found at the antenatal care clinic in any of the study facilities during the data collection period who met the inclusion criteria and were willing to participate in the study were enrolled.

2.3.2 Sample Size Estimation

Due to the variability of the study designs used, two approaches were employed to calculate the required sample size. First, the sample size formula proposed by Cochran which accounts for finite population corrections and prevalence in a randomly-selected population was used to determine the minimum sample size (n) (Cochran, 1977). To assume normality of the Gaussian distribution for the study population of 516,461 (Ghana Statistical Service, 2013) women in their reproductive age (15-49 years) in the region, a confidence level of 95%

corresponding to 1.96 z-score (Z) statistics and permitted error margin (e) of 5% were used. Even though the reported prevalence of GDM in an urban tertiary teaching hospital in Ghana was 9.3% (Oppong et al., 2015), the study was conducted among peri-urban and rural dwellers where GDM prevalence was unknown. Besides, other factors such as hypertensive disorders in pregnancy, dyslipidemia, obesity, dietary patterns and micronutrient deficiencies, also known to affect pregnancy outcomes were assessed. Therefore, using estimation of risk associations as the basis, default population proportion (p) of 50% (Cochran, 1977) was used in determining the required sample size (n) as shown below.

$$n = \left[\frac{\frac{Z_\alpha^2 \times p(1-p)}{e^2}}{1+\left(\frac{Z_\alpha^2 \times p(1-p)}{e^2 N} \right)} \right] \times d \qquad = \left[\frac{\frac{1.96^2 \times 0.1(1-0.1)}{0.05^2}}{1+\left(\frac{1.96^2 \times 0.1(1-0.1)}{0.05^2 \times 516{,}461} \right)} \right]$$

$$n = 130 \times 3.2 = \boldsymbol{416}$$

Where n = Sample size

Z_α = Z score of the Gaussian distribution

N = Study population

p = Percentage proportion or prevalence

e = Margin of error (precision level)

d = Design effect

The primary and secondary facilities were each treated as separate clusters. Clustering ensured that participants in the same cluster were somewhat similar to one another. To account for variability of health service provision at each level, the effect of clustering was adjusted for, ensuring maximize statistical accuracy of GDM estimate that was nationally representative. Aided by the G*Power software (version 3.1.9.2) (Faul et al., 2007), a design effect of 3.2 was determined based on a two-tail t-test statistic with an alpha error probability of 0.05, 1-β error probability of 0.95 and an intra-cluster correlation of 0.16 derived from 0.03 coefficient of determination. This was to allow for comparison of differences among cases and controls without increasing the error margin. This way, the 5% pre-determined error margin used in calculating the sample size was evenly distributed across the two comparison groups without introducing biases. This generated a sample size of 130. The sample size was multiplied by the design effect resulting in an effective sample size of 416. An a priori statistical power analysis yielded 91%, an indication that the sample size was adequately powered. The sample size was doubled (100% increase) to approximately 800 participants to account for attrition and loss to follow-up.

In all, 807 participants were recruited in their first trimester of pregnancy. As ANC and delivery services are mainly provided at the secondary level in Ghana, 75% of the participants were proportionately recruited from secondary facilities while about 15% were each recruited from the primary and referral (tertiary) facilities. Breakdown of the sample size (n=807) per study facility is as shown below.

- One primary facility
    - Jasikan district hospital – 13.4% (n=108)
- Three secondary facilities – 73.8% (n=598)
    - Ho municipal hospital – 30.2% (244)
    - Margaret Marquart Catholic hospital – 24.1% (n=195)
    - Hohoe municipal hospital – 19.7% (n=159)
- One referral facility (currently being upgraded to a teaching hospital)
    - Volta regional hospital – 12.5% (n=101)

2.2.3 Sampling Technique

The consecutive sampling method was used in recruiting participants onto the study. This implied that every pregnant woman who visited any of the five facilities during the study period who met the inclusion criteria was enrolled. This process was sustained until the required sample size was obtained. Regarding the nested case-cohort component, all pregnant women tested for GDM and were disease-free per the case definition were purposively selected to act as controls. The case to control ratio was about 1:5, that is 70 cases to 376 controls. At delivery and 12 weeks postpartum, GDM outcomes all participants and their index offspring were purposively followed.

2.2.4 Eligibility Criteria

Any pregnant woman identified at the ANC of any of the study health facilities was approached, screened for eligibility and enrolled onto the study if she met the following criteria:

Inclusion criteria

- At recrement, gestational age of the pregnancy was supposed to be in the first trimester (up to 13 weeks) as evidenced by last menstrual period adjusted to either ultrasonography or fundal height measurement.
- The woman did not have pre-existing diabetes.
- Permanent residency within any of the study districts and intention to deliver in any of the study facilities.
- Willingness to partake in the study by signing or thumb-printing the consent form.

Exclusion criteria

- Verbal confirmation of having pre-existing diabetes. If the woman was unaware of her diabetes status, random glucose and Hb1Ac were done in the first trimester.
    - Random glucose value ≥11.1 mmol/L and HbA1c value ≥6.5% was an indication of pre-existing diabetes.
    - HbA1c is useful indicator of glycemic control and is used to determine quality of glycemic intolerance the preceding 10-12 weeks and hence is a useful test to differentiate GDM from pre-existing diabetes.
    - Pregnant women with multiple gestation.

Note:

Age was not an exclusion criterion due to evidence of increasing incidence of non-communicable diseases including metabolic disorders in both younger and older populations. Pregnant women who were teenagers were included because they were regarded as emancipated adults. Similarly, chronic ill-health was not an exclusion criterion because of the possibility of concomitant presence of GDM in immune-suppressed women.

2.4 Data Collection Instruments and Procedures

This section describes how the raw data was obtained. Administrative and clinical managers of the hospitals where the study was conducted were sensitized on the study objectives and data collection procedures and their support elicited. Obstetrics and gynecology specialists, midwives, nurses, laboratory technicians and health assistants working in the maternal and

child health unit of the study facilities were trained on the study protocol. Fifteen research assistants with academic backgrounds in Health and Allied Sciences who were conversant with the local terrain were trained and engaged on the project to assist with participant recruitment and face-to-face interviews. Three research assistants were stationed in each of the five study facilities. Data was collected concurrently from the five study sites between April 2016 to April 2017.

Phases of the study: The study was conducted in three interrelated phases; antenatal (prenatal), intrapartum (delivery) and post- postpartum (post-delivery) phases. Presented in **Figure 6** are the specific type of data collected at each phase of the study. The data collection tools used included structured questionnaires, validated food frequency questionnaire, validated Edinburgh Postnatal Depression Scale (EPDS) and data extraction sheets. The questionnaires were designed and, in some cases, adopted from the Ghana Health Service Maternal Health Records Booklet and the delivery records book. The data collection tools are found in Appendix 8.1.

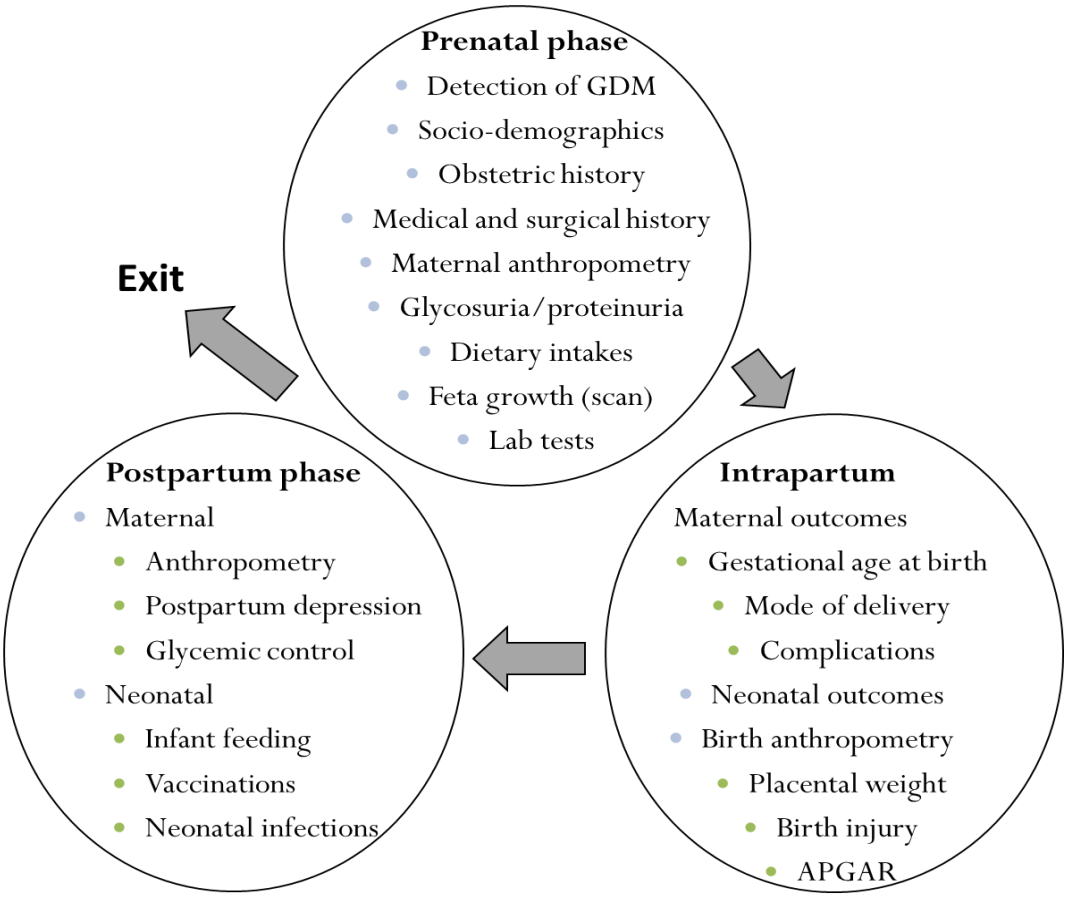

Figure 6. Phases of the study and the types of data collected

2.4.1 Prenatal Care Phase

One-on-one interviews were conducted with the 807 participants at enrolment. During the prenatal phase, the following data were collected directly from the participants.

2.4.1.1 Socio-demographic and health indictors

- Socio-demographic data: The women's age, place of residence, ethnicity, marital status, educational level and occupation of the couple, and household size.
- Obstetric history: Last menstrual period, parity (number of live births), gravida (number of pregnancies in her life-time) including spontaneous and induced abortions, and outcome of previous pregnancies (sex, mode of delivery, whether alive or dead, single or multiple delivery and any complications encountered).
- Medical history: physical assessments using glycosuria, proteinuria, blood pressure measurements, probing for known individual and family history of diabetes, previous GDM, hypertension and other cardiovascular diseases.

2.4.1.2 Maternal and fetal adiposity

Maternal anthropometry: To assess adiposity, pre-pregnancy body weight was recorded if known. Weight and height were measured in the first trimester and used to determine the body mass index (BMI). Weight at first trimester is a good proxy for pre-pregnancy weight since no substantial weight changes are expected in the first trimester (Institute of Medicine, 2009). Pregnancy weight change was monitored monthly. Pregnancy weight change was calculated by subtracting weight measurement when the woman reported at the health facility for delivery from the weight at the first ANC visit in the first trimester. BMI was estimated using weight (kg) divided by height squared (meter squared) and classified using WHO classification (WHO, 2006b). In accordance with recommendations from the Institute of Medicine on appropriate pregnancy weight gain based on a woman's BMI, the expected weight gain for each BMI group was identified as shown below. Weight gain above the threshold was considered as a GDM risk (Institute of Medicine, 2009).

	BMI	***Pregnancy weight gain (kg)***
1.	underweight (<18.5)	12.5-18.0
2.	normal weight (18.5-24.9)	11.5-16.0
3.	overweight (25.0-29.9)	7.0-11.5
4.	obese (≥30)	5.0-9.0

Mid-upper arm circumference (MUAC) was measured in the first, second and third trimesters of pregnancy and the average of two or the three closest values taken as MUAC measurement is fairly stable throughout pregnancy (Institute of Medicine, 2009). Since no optimal MUAC cutoff is currently available, measurements above the population specific cut-off values for the median MUAC value was used to estimate adiposity.

Fetal growth: To determine fetal adiposity, ultrasound scans taken in the first, second and third trimesters of pregnancy were reviewed for fetal growth parameters such as estimated fetal weight, head circumference, crown rump length and femur length. Symphysio-fundal height was measured between 20-36 weeks gestation. Excess fetal growth was suspected when the symphysio-fundal height was larger than the gestational age by ultrasound scan. Fetal and newborn growth was assessed using guidelines from the International Fetal and Newborn Growth Consortium for the 21st Century study (Papageorghiou et al., 2014, Villar et al., 2014).

2.4.1.3 Habitual dietary intakes

A validated food frequency questionnaire (FFQ) modified based on habitually consumed foods in Ghana was used to assess the dietary patterns and intakes of the participants. Dietary patterns were derived a priori. The foods were classified into nine groups according to major nutrient contribution: (1) cereals and grains; (2) roots, tubers and plantain; (3) legumes and peas; (4) nuts and seeds; (5) animal source foods; (6) green leafy vegetables; (7) other vegetables; (8) fruits; and (9) fats and oils. Information was also taken on less consumed foods and snacks, confectionaries, fizzy drinks, fruit juices, alcohol, smoking, non-nutritive pica, supplements as well as food cravings, aversions and taboos.

The FFQ had seven frequency of consumption categories ranging from (1) at least once daily; (2) 3-6 times per week; (3) 1-2 times per week; (4) 2-3 times per month; (5) once monthly, (6) rarely to (7) never. The dietary data was modified into a ten-food-group FFQ according to the FAO Minimum Dietary Diversity for Women (MDD-W) designed by the Food and Agriculture Organization (FAO, 2014). Consumption of at least five out of the ten defined food groups the previous day indicated micronutrient adequacy (FAO, 2014). The ten food groups are:

(1) staple foods (grains, white roots and tubers, and plantains);
(2) pulses (beans, peas and lentils);
(3) nuts and seeds;
(4) dairy;
(5) fleshy foods (meat, poultry and fish);
(6) eggs;
(7) dark green leafy vegetables;
(8) other vitamin A-rich fruits and vegetables;
(9) other vegetables; and
(10) other fruits

The dietary data was validated by a non-quantitative 24-hour call of foods eaten the previous day/night. Qualitative data on intake of high glycemic index (GI) foods including snacks and beverages during the day prior to the interview was obtained. Each carbohydrate-containing food consumed that contributed above 70% of the GI value was assigned a score of one. Example of these foods included white bread, polished rice, processed cassava and corn foods, ripe plantain, table sugar, pasta, pineapple, watermelons and soda drinks. To determine excess intake of high glycemic index foods, cumulative scores obtained from the high glycemic index foods consumed during the previous day were classified into three groups as follows:

1. adequate (intake of high GI foods 1-2 times per day),
2. moderate (intake of high GI foods 3-4 times per day) and
3. excess (intake of high GI foods ≥5 times per day)

2.4.1.4 Measurement of glycemic status

The one-step universal strategy recommended by the IADPSG for diagnosing GDM was followed whereby all the study participants did all the screening and diagnostic tests for GDM. (Metzger et al., 2010a). The screening and diagnostic procedures is simplified in **Figure 7**. Glycosuria, random glucose and maternal history taking for GDM risk factor assessment were considered as screening tests whereas HbA1c, and 1-hour OGTT were diagnostic. Each screening test was evaluated reference to fasting plasma glucose and the 'gold standard' 2-hour OGTT. Where thresholds for 2 out of these 4 test results were obtained, it was considered as a case of pre-existing diabetes first detected in pregnancy:

1. random blood glucose ≥11.1 mmol/L,
2. 2-h OGTT ≥11.1 mmol/L,
3. HbA1c ≥6.5% (7.8 mmol/L) or
4. Fasting plasma glucose ≥7.0 mmol/L

Screening for GDM

Dipstick glycosuria: Glycosuria urinalysis was tested at every ANC visit as a qualitative urine dipstick test using the 'Urit 5V' urine reagent strips to detect the presence of glucose in about 10 ml of urine. A colour change corresponding to trace test result or above (1+ to 4+) at any one point during pregnancy was considered to be screen positive for GDM. To be eligible for inclusion in the analysis, the woman should have performed at least one dipstick urine test each in the first, second and third trimesters.

Random capillary glucose: Between 10-20 weeks, participants were screened for GDM through random capillary blood glucose. About 0.8ul capillary blood was drawn from the middle fingertip prick and measured on the point-of-care testing devise called 'On Call Plus Blood Glucose Meter'. Random blood glucose >7.0 mmol/L was considered to be screen-positive for GDM (National Institute for Health and Care Excellence, 2015).

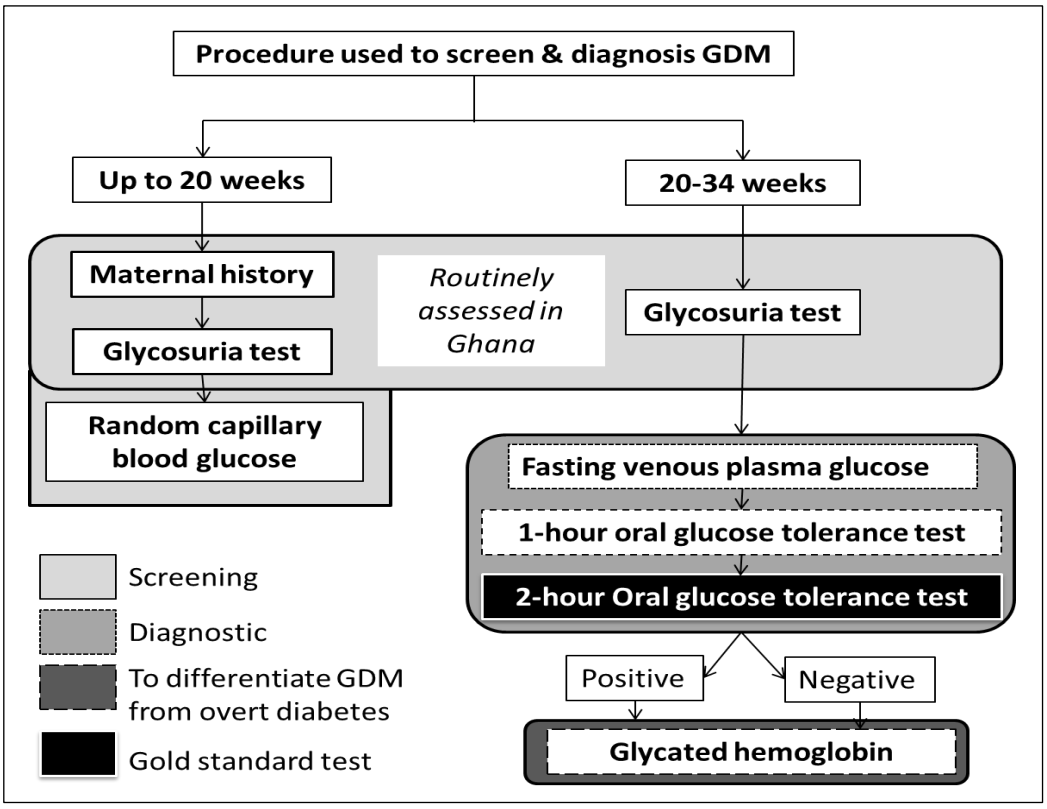

Figure 7. Screening and diagnostic procedures for GDM

Diagnosis of GDM

All participants were scheduled for diagnostic testing between 20-28 gestational weeks. Participants who failed to turn-up were rescheduled for testing between 30-34 weeks. The evening prior to the test, participants were called and reminded to fast overnight for ten to twelve hours. Upon arrival at the laboratory in the morning of the test, they were made to rest for about 15 minutes before the tests were conducted.

Fasting plasma glucose: Three millilitres of pre-prandial venous blood was drawn from the antecubital fossa. One ml of the blood was used to measure the fasting plasma glucose on a fully-automated 'Selectra ProM' clinical chemistry analyzer operating on kinetic enzymatic peroxidase-antiperoxidase principle. In accordance with the WHO (World Health Organization, 2013) and the NICE (National Institute for Health and Care Excellence, 2015) diagnostic criteria, fasting plasma glucose ≥5.1 mmol/L and ≥5.6 mmol/L were considered to be GDM diagnostic positive.

Glycated hemoglobin: HbA1c was checked irrespective of clients' fasting status using two ml of the venous blood. It was analyzed on an automated HA-8160 ADAMS analyzer operating on the ion exchange HPLC principle. Results were aligned to the Diabetes Control and Complications Trial (DCCT) method. HbA1c results ≥6.5% (7.8 mmol/L) was suggestive of GDM (National Institute for Health and Care Excellence, 2015).

Oral glucose tolerance test: After drawing the pre-prandial blood, participants were supervised to drink within three minutes 75-gram anhydrous glucose dissolved in 300 ml of water at room temperature. Post-prandial venous blood was collected at one- and two-hour intervals and plasma glucose levels checked following similar biochemical procedure as for the FPG. As per the WHO diagnostic criteria, 1-hour OGTT ≥10.0 mmol/L and 2-hour OGTT ≥8.5 mmol/L were indicative of GDM (World Health Organization, 2013). Also, the NICE diagnostic criterion based on 2-hour OGTT ≥7.8 mmol/L was indicative of GDM (National Institute for Health and Care Excellence, 2015).

2.4.1.5 GDM case definition

Diagnosis of gestational diabetes using fasting plasma glucose was in line with the NICE (National Institute for Health and Care Excellence, 2015) guideline while diagnosis using 2-h OGTT was in line with the IADPSG/WHO guidelines (World Health Organization, 2013, IADPSG Consensus Panel, 2010). Since only one abnormal value is needed for GDM

diagnosis to be made (World Health Organization, 2013, Hod et al., 2015, National Institute for Health and Care Excellence, 2015), the case definition and diagnosis of GDM was done as follows:

1. Fasting plasma glucose ≥5.6 mmol/L (National Institute for Health and Care Excellence, 2015) ***and/or***
2. 2-hour OGTT (≥8.5 mmol/L) (World Health Organization, 2013)

Basis for choosing these thresholds is the result of a previous study where fasting plasma glucose ≥5.6 mmol/L and 2-h OGTT ≥8.5 mmol/L were found to have higher diagnostic validity including higher disease prediction compared to the lower thresholds recommended by WHO for fasting glucose (≥5.1 mmol/L) and the lower threshold recommended by NICE for 2-hour (≥7.8 mmol/L) required to make a diagnosis of GDM (Agbozo et al., 2018).

Also, the recent updated guidelines whereby lower thresholds have been recommended by some health regularly bodies for GDM diagnosis has spark concerns of overdiagnosis of GDM and the resultant over medicalization of obstetric care (Cundy et al., 2014, Twohig et al., 2018, Glasziou, 2017, Moynihan, 2016, Moynihan et al., 2015, Bolognesi, 2015, Naaktgeboren et al., 2018). These informed the decision to limit to using higher and restrictive diagnostic thresholds for both fasting glucose (≥5.6 mmol/L) and 2-h OGTT (≥8.5 mmol/L) as the case definition for GDM in this study.

2.4.1.6 Other tests performed

Tests such as lipid profile (total cholesterol, triglycerides; high, low and very low-density lipoproteins), hemoglobin levels as proxy for iron status, full blood count, and blood film for malaria parasites were measured to assess the general health of the woman. Other routine tests conducted during ANC were extracted from the medical records. These included tests for hemoglobin Electrophoresis, glucose-6-phosphate dehydrogenase (G6PD) deficiency, blood group, rhesus factor, urine and stool routine examination, Venereal Disease Research Laboratory test for syphilis, Hepatitis B Virus Surface Antigen and HIV status.

2.4.1.7 Quality control

Blood samples were collected and analyzed by qualified laboratory scientists. On-the-spot tests were analyzed by midwives engaged on the project. To ensure comparability of the test results, the same brands of urine dipsticks and glucometers were used across all the study

facilities. The urine dip-stick brand was Urit Series 5V Urine Reagent Strips (Manual) manufactured by Urit Medical Electronic Group and supplied by the Ghana Health Service. The glucometer brand was On Call® Advanced Blood Glucose Monitoring System manufactured by Medical Device Safety System GmbH in Hannover, Germany. All the laboratory analyses were conducted at a central point, that is the research laboratory of the University of Health Allied Sciences located in the School of Public Health within the premises of the Hohoe municipal hospital. On-the-spot sample collection and analysis was done for random and fasting blood glucose using glucometer as well as for glycosuria and proteinuria using test trips. In cases where laboratory analysis was required (e.g. fasting plasma glucose, OGTT, lipid profile), samples were collected from participants at the respective study facilities, emptied into sodium fluoride or anticoagulant test tubes, stored in cold boxes and transported to the laboratory within a maximum of three hours for immediate analysis. Analysis of blood chemistries were done using the Selectra Pro M fully-automated Clinical Chemistry Analyzer manufactured by 'EliTechGroup'. Standard operating procedures relating to calibration, client preparation, sample collection, specimen handling and preparation, reagents, materials and equipment needed, and analysis procedures were duly followed. Test quality was ensured by running controls after every 20th test and/or in the morning of each field visit as the case might be.

2.4.2 Intrapartum Phase

At delivery, the following information were extracted from the delivery records.

Maternal information: Mode of delivery (spontaneous vaginal delivery, instrumentation, cesarean section); perineal injury; labour complications (prolong, obstructed labour, hemorrhage); pre-eclampsia and/or eclampsia.

Newborn's information: Gestational age at birth (preterm birth: below 37 weeks; term birth: 37-42 weeks; and post-term birth: above 42 weeks); newborn's anthropometry (birth-weight, length, head and chest circumferences); APGAR score at birth and after five minutes to determine respiratory distress; birth trauma especially shoulder dystocia; neonatal glucose status to assess hypoglycemia; congenital malformation; admission to intensive care and stillbirth.

- *Apgar score*

  In relation to the newborn's appearance, pulse, grimace, activity and respiration, cumulative Apgar scores at 1 and 5 minutes after birth

(1) ≥7 was considered as normal;

(2) 4 to 6 implied fairly low Apgar;

(3) ≤3 was considered as critically low and necessitated resuscitative efforts.

- *Diagnosis of neonatal hypoglycemia*

Hypoglycemia was assessed by taking capillary heel prick blood between 1-2 hours after birth into sodium fluoride micro-tube, placed immediately in a cold box and transferred to the research laboratory for analysis. Neonatal hypoglycemia was defined as glucose levels of <10th percentile, that is 2.2 mmol/L (Metzger et al., 2010b). It is recommended that intervention to increase blood glucose in newborns diagnosed with neonatal hypoglycemia should be considered if two consecutive blood glucose levels are below 2 mmol/L or a single blood glucose level is below one mmol/L (Hawdon, 2012). Hence categorization based on severity was done as follows (Tin, 2014):

  - Mild: blood glucose 2.2–2.8 mmol/L (40–50 mg/dl);
  - Moderate: 1.1–2.2 mmol/L (20–40 mg/dl);
  - Extreme: <1.1 mmol/L (20 mg/dl)

2.4.3 Postpartum phase

Twelve 12 weeks after delivery, the study participants were contacted in their homes to monitor glycemic status especially for women diagnosed with GDM. Postpartum anthropometric changes and general health of the mother-infant pairs were also assessed.

- *Maternal information*: Weight; height, MUAC; fasting plasm glucose; and assessment for postpartum depression using the validated Edinburgh Postnatal Depression Scale.
- *Infant information*: Body weight, length, head/chest circumferences and MUAC; infant feeding including breastfeeding; immunizations; infections (jaundice, sepsis, pneumonia, diarrhoea, malaria); and general wellbeing.

2.4.4 Baseline Study of the Context

The cross-sectional survey was conducted as the first step to investigate all deliveries over a 2-year period from January 2013 to December 2014 to assess the prevalence of macrosomic births. The data covered 4,359 pregnant women between the ages of 12-51 years who delivered 4,477 newborns in the Hohoe municipal hospital. All women with documented delivery record in the delivery register were reviewed. After excluding multiple births, 4262

infant-mother pairs were included in the analysis. Maternal information extracted included age at delivery, gravidity (number of pregnancies in her lifetime), parity (number of live children), number of doses of sulfadoxine–pyrimethamine taken for Intermittent Preventive Treatment (IPT) for Malaria in Pregnancy, HIV status, partner involvement during labour and the mode of delivery. Newborn information extracted included birthweight, sex and whether alive or dead at birth.

2.5 Exposure and Outcome Measures

Main exposure of interest was diagnosis of gestational diabetes in line with the case definition.

Maternal outcomes: Primary maternal outcomes were cesarean delivery and perineal trauma while the secondary outcomes were preeclampsia (defined as concomitant hypertension and proteinuria with/without edema) and post-partum hemorrhage (defined as estimated blood loss above 500 ml).

Fetal outcomes: Primary outcomes were fetal adiposity and survival. Secondary newborn outcomes were gestational age at birth and hypoglycemia.

Fetal adiposity was assessed using 3 indicators:

(1) macrosomia defined as birth weight ≥4 kg regardless of gestational age at birth;
(2) large for gestational age defined as birth weight >90th percentile per the InterGrowth study standards accounting for gestational age at birth and sex of the newborn; and
(3) Ponderal Index (PI) defined as newborn weight (g)/length (cm^3) ×100 and classified as small for gestational age (<2.0), marginal (2.0-2.5), normal (2.5-3.0.) and large for gestational age (≥3.0).

Newborn survival was assessed using 4 indicators:

(1) Apgar score at one and five minutes,
(2) newborn resuscitation,
(3) admission to neonatal intensive care unit (NICU) and
(4) perinatal death (that is, death before discharge home)

2.6 Statistical Analyses

Described in this section is how the raw data generated through the various data collection procedures were processed and analysed. Data was entered into Statistical Package for the Social Sciences (SPSS version 24) for preliminary data cleaning and management. Data analysis was conducted in STATA (version 14.2). To ensure that errors were reduced, consistency and plausibility checks were done; multicollinearity and singularity among independent variables checked; and residual scatter plots visualized to check for normality, linearity, and homoscedasticity. Also, correlation matrix was computed to identify collinearity and possible confounders while interaction terms were considered in final model selections. The data was summarized using descriptive statistics including frequencies and percentage distributions for categorical variables. Interquartile values, ranges, means ($\bar{x}$) and standard deviations (SD) were used to report continuous variables.

To make inferences from the analysis of continuous variables, paired samples t-test was used for repeated measures, one sample t-test was used to compare means of two unrelated groups whereas one-way analysis of variance (ANOVA) was used to determine whether there were any statistically significant differences between the means of more than two independent groups. To test differences between two or more groups, the inferential statistics used was Fisher's exact test for 2×2 contingency tables (pairwise comparisons). For tables with more than two rows and/or columns, Pearson's Chi-square test ($\chi 2$) was used for multiple comparisons.

Post-hoc tests using Bonferroni-corrected pairwise technique or least significant difference (LSD) was used for categorical variables with more than two response levels to adjust for the effect of multiple comparisons and determine specific variables that generated significant differences. McNemar's test aided in reducing inter-subject variability in polychotomous variables obtained at different time points. Results were statistically significant when confidence intervals (CI) excluded one and the P-value was <0.05 at 95% confidence level and 5% margin of error. A detail description of the analysis conducted is presented below.

2.6.1 Validation of diagnostic accuracy

In the exception of results from dipstick glycosuria, all the tests yielded continuous scale values. Diagnostic thresholds aided in defining positive and negative results. Changing the threshold changed the proportion of false positive and false negative diagnoses. The formulae

used in estimating the diagnostic measures is presented in **Table 5**. Number of true positive, true negative, false positive, and false negative were estimated reference to the diagnostic criteria for 2-h OGTT based on the WHO (≥8.5 mmol/L) and NICE (≥7.8 mmol/L) guidelines. Similar measures were calculated for fasting plasma glucose in accordance with the WHO (≥5.1 mmol/L) and NICE (≥5.6 mmol/L) diagnostic criteria. This was done by designing a 2 x 2 table with participants grouped according to the reference test in columns, and the categorization of disease status in rows.

Paired diagnostic accuracy was estimated using standard formulas for disease measurement to evaluate the discriminative, predictive and diagnostic properties of each test. Discriminatory and predictive abilities were determined by test sensitivity (true positive rate), specificity (true negative rate), positive and negative predictive values, and positive and negative likelihood ratios (LR). Likelihood ratios for instance compares probabilities that a person with a particular disease will have a specified test result versus the probability that a person without that disease will have the same test results. Positive and negative predictive values are measures of test performance that are used in interpreting patients' results (Raslich et al., 2007). Other predictive measures used to validate diagnostic accuracy included Youden's index, diagnostic effectiveness and diagnostic odds ratio (DOR). Except for negative LR where lower values indicate more discriminatory ability of the test, for all the disease measures estimated, higher values were indicative of more discriminatory and predictive diagnostic accuracy.

To determine overall test performance, receiver operating characteristic (ROC) curve and coordinates of the curve was obtained for each continuous glucose measurements. Test performance was evaluated based on the area under the curve (AUC). The closer the curve was to the left-hand upper border of the ROC space, the more accurate the test. Rating ranged from excellent (AUC = 0.9 to 1.0), very good (0.8 to <0.9), good (0.70 to <0.80), sufficient (0.60 to <0.70), poor (0.50 to <0.60) to invaluable (AUC <0.5) (Raslich et al., 2007) (Mallett et al., 2012). The p-value for each variable tested the null hypothesis that the true area under the ROC curve equal to 0.5 (no effect). This is the diagonal where the true positive rate equals the false positive rate. A p-value <0.05 indicated that the null hypothesis could be rejected, meaning the test was clinically relevant (Raslich et al., 2007). The lower the p-value, the better the test performance. Reference cut-offs for each test that provided analogous and clinically useful sensitivity and specificity for the study population was estimated from the coordinates of the ROC curve.

Table 5. Diagnostic validity, basic definitions and method of estimation

Diagnostic measure	Basic definition	Estimation
True positive (TP)[a]	Actual GDM cases correctly identified as having GDM	<table><tr><td></td><td>GDM</td><td>No GDM</td></tr><tr><td>Test +</td><td>TP</td><td>FP</td></tr><tr><td>Test -</td><td>FN</td><td>TN</td></tr></table>
False negative (FN)[a]	Actual GDM cases wrongly identified as not having GDM	
False positive (FP)[a]	Those without GDM wrongly identified as having GDM	
True negative (TN)[a]	Those without GDM correctly identified as not having GDM	
Sensitivity	The proportion of actual GDM positives that are correctly identified as such. Probability that a person with the target disease will test positive	$= \frac{TP}{TP + FN}$
Specificity	The proportion of actual GDM negatives that are correctly identified as such. Probability that a person without the target disease will test negative	$= \frac{TN}{TN + FP}$
Positive predictive value	Probability of having the state/disease of interest in a subject with positive result. Percent with positive result having the disease.	$= \frac{TP}{TP + FP}$
Negative predictive value	Probability of not having a disease in a subject with a negative test result. Percent with negative result not having the disease.	$= \frac{TN}{TN + FN}$
Positive likelihood ratio[b]	Ratio of probability that a positive test result occurs in subjects with the disease compared to those without disease. Useful for ruling-in diagnosis	$= \frac{\text{Sensitivity}}{1 - \text{Specificity}}$
Negative likelihood ratio[b]	Probability that a negative result occurs in subjects with the disease to probability that same result occurs in subjects without the disease. Useful for ruling-out diagnosis	$= \frac{1 - \text{Sensitivity}}{\text{Specificity}}$
Diagnostic accuracy	Discriminative ability of a diagnostic test that gives the probability that an individual will be correctly classified by a test	$\frac{TP + TN}{TP + TN + FP + FN}$
Diagnostic odds ratio[c]	It is the ratio of the odds of positivity in subjects with disease relative to the odds in subjects without disease	$= \frac{TP + FN}{FP + TN}$
Youden's index[d]	Measure of a test performance used to evaluate overall discriminative power of a diagnostic procedure and to compare test with other tests	$= (\text{Sensitivity} + \text{Specificity}) - 1$
ROC curve & area under the curve	Global measure of diagnostic accuracy that helps to estimate the discriminative power of a test. The closer the curve to the upper left-hand corner and the larger the area, the better the discrimination between those with and without the disease.	0.9-1.0: Excellent; 0.8-0.9: Very good; 0.7-0.8: Good; 0.6-0.7: Sufficient; 0.5-0.6: Bad; <0.5: Not useful

[a] Number of true positive, false negative, false positive and true negative estimated with the aid of the inserted two-by-two table.
[b] Good diagnostic tests have positive likelihood ratio >10 and negative likelihood ratio <0.1 and
[c] Higher discriminatory and predictive values indicate more diagnostic accuracy. Diagnostic odds ratio ranges from 0 to infinity with higher values indicating more discriminatory properties.
[d] Youden's index values ranges from -1 to 1
Source: (Raslich et al., 2007, Mallett et al., 2012).

2.6.2 Determinants of GDM

To assess the significant determinants for GDM, the case-control component was analyzed using the dichotomous outcome (GDM present or absent) tabulated in a two-by-two table with the predictor variables. GDM present was defined as 2-h OGTT ≥8.5 mmol/L and/or fasting glucose ≥5.6 mmol/L whereas GDM was absent when thresholds lower than this were obtained. To run the model, all the predictor variables were recategorized into dichotomous forms. For instance, formal educational was recategorized into primary level versus secondary level and above; BMI into overweight/obese versus normal/underweight, parity into more than 3 children versus 3 children and below; glycemic intake into excess versus moderate/adequate (Table 15), etc. Statistical differences between the cases and controls were tested using the Cochran-Mantel-Haenszel statistic. Unconditional univariate logistic regression model was run to generate the crude estimates of association between the predictor variables and GDM as the outcome. This regression model was used because the cases and controls were unmatched. Then correlation analysis was conducted using variables known from literature and clinical practice to increase or decrease likelihood for GDM. Variables with p-value ≤ 0.3 and factors demonstrated from literature to be associated with GDM were selected into the final regression model. Confounding factors were adjusted for by stratifying the exposure variables into sub-groups and computing the multivariate binary logistic regression to obtain the adjusted odds ratios (AOR). Fit of the logistic regression models were evaluated using Goodness-of-fit whereas R-squared (coefficient of determination) was used to determine the percent of variance explained by the regression model.

2.6.3 Associated Birth Outcomes

First, the continuous scale measurements for 2-h OGTT and fasting glucose were used as the predictor scale variables and simple linear regression analysis with the outcome variables to estimate the regression coefficients and identify the direction of a unit increase in 2-h OGTT and fasting glucose on each maternal and newborn outcome. After computing a correlation matrix to identify collinearity and noting the possible confounding factors and interaction terms, the predictor variable was categorized as binary, that is, GDM present defined as 2-h OGTT ≥8.5 mmol/L and/or fasting plasma glucose ≥5.6 mmol/L and GDM absent when 2-h OGTT and FPG fell below these thresholds. To estimate the pregnancy outcomes associated with GDM, a multivariate binary logistic regression model was run to estimate the relative risk (RR) association of GDM with pregnancy outcomes. To ensure that the final model was

significant, the model summary had a Prob > Chi^2 = 0.0000 and the Hausman test showed no evidence of violation of the independent of irrelevant alternative assumption. A p-value of <0.05 and CI excluding one were considered as statistically significant.

2.6.4 Postpartum Glycemia

Differences in the prenatal and postpartum scale fasting glucose measurements was tested using paired-comparisons t-test to analyze for significant change. To determine the extent of attainment of euglycemia at 12 weeks postpartum, postpartum glycemic outcome was categorized into a binary variable. GDM was considered to be resolved when fasting glucose at 12 weeks postpartum was less than <5.6 mmol/L whereas GDM was considered to persist when fasting glucose measurement was ≥5.6 mmol/L at 12 weeks postpartum. The binary outcome (GDM resolved and GDM unresolved) were analyzed using a two-by-two table and the difference in the two groups tested using McNemar's test.

2.7 Ethical Consideration and Consenting

All procedures pertaining to human research ethics was adhered to in accordance to the Helsinki declaration. The study was approved by the Ghana Health Service Ethics Review Committee (*GHS-ERC-GM 04/02/16*) and the Institutional Review Board of Heidelberg University Medical Faculty (*S-042/2016*). All participants including minors (less than 18 years) provided written informed consent after verbal explanation of the study protocol to every potential participant who met the inclusion criteria. Voluntary willingness to participate in the study was obtained by either signing or thumb-printing the consent form. Pregnant teenagers were included in this study but were not required to provide assent because they were considered by the ethical review committee as emancipated adults. Permission was granted by heads of the respective study facilities and the Volta regional health directorate. To ensure that quality of care for all women who sought ANC care in the study facilities was not compromised, a woman's status as a study participant was known only to the research team. Personal details of participants were taken only for the purpose of addressing them appropriately and facilitating follow-up at all phases of the study. In Appendix 8.2 is the participant information and consent form used.

2.7.1 Unintended Treatment Effect of the Study

During the study period, when a participant was identified to have any physical, social or mental health condition either through the interviews, physical assessment or diagnostic procedures that affected the wellbeing and optimum pregnancy experience, a clinical staff was notified immediately for appropriate action to be taken. Particularly at the prenatal stage of the study, a chain of communication was instituted from the research assistants to the midwife in-charge at the antenatal clinic. Through this chain, participants who were diagnosed with gestational diabetes or any other health problem were referred to the appropriate specialist for treatment. Consequently, although provision of an intervention to GDM cases was not a direct objective of this study, referral and subsequent management of diagnosed cases was expected to have a positive effect on the materno-fetal outcomes. The referral procedures instituted in provided in Appendix 8.3.

3 RESULTS

Note: The doctoral student has published some aspects of this chapter in the underlisted publications. For details, see pages 109-111.

- Prevalence of low birth weight, macrosomia and stillbirth and their relationship to associated maternal risk factors in Hohoe Municipality, Ghana. Midwifery Journal; http://dx.doi.org/10.1016/j.midw.2016.06.016
- Accuracy of glycosuria, random blood glucose and risk factors as selective screening tools for gestational diabetes mellitus in comparison with universal diagnosing. BMJ Diabetes Research & Care http://dx.doi:10.1136/bmjdrc-2017-000493
- Gestational diabetes using diverse diagnostic criteria, risk factors including dietary intakes, pregnancy outcomes and postpartum glycemic status: a nested case-control study in Ghana. bioRxiv 582239 https://doi.org/10.1101/582239

This results chapter is organized into five sections according to the study objectives. Results on the prevalence of gestational diabetes and diagnostic validity of the test instruments are described in the first and second sections respectively. Results on the associated risk factors and birth outcomes are described in the third and fourth sections respectively. The chapter closes with results on the postpartum glycemic status of cases. Number of participants enrolled in each stage of the study is shown in **Figure 8**.

Overall, 807 participants were booked for GDM testing of which 490 representing 55% reported for diagnostic testing but 446 and 435 participants performed the fasting plasma glucose test and 2-hour OGTT respectively. Also, 402 were traced at delivery and 100 followed-up at 12 weeks postpartum.

3.1 Prevalence of GDM Per Diverse Diagnostic Criteria

3.1.1 Description of Blood Glucose Values

In **Figure 9** is the comparison of interquartile glucose values for each test among primary (n=78) and secondary/referral (n=357) facility users. In comparison to secondary/referral facility users, primary facility users had significantly higher mean fasting plasma glucose (4.44±0.98 vs 5.12±0.85 mmol/L), 1-h (6.70±1.88 vs 7.20±1.83 mmol/L) and 2-h postprandial glucose (6.24±1.71 vs 6.74±1.72 mmol/L). However, no statistical differences were observed for RBG and HbA1c. Overall, mean 1-h OGTT (7.2±1.8 mmol/L) was 0.5 mmol/L higher than 2-h OGTT (6.7±1.7 mmol/L). Also, mean RBG (5.4±1.1 mmol/L) was 0.3 mmol/L higher than the fasting plasma glucose (5.1±0.9 mmol/L). Fairly strong correlation was observed between 2-h OGTT and 1-h OGTT values ($r=0.764$, $p<0.001$) and also between 2-h OGTT and fasting plasma glucose values ($r=0.643$ ($p<0.0001$) but correlation the between 2-h OGTT and random glucose values ($r=0.240$, $p<0.0001$) and HbA1c were weak.

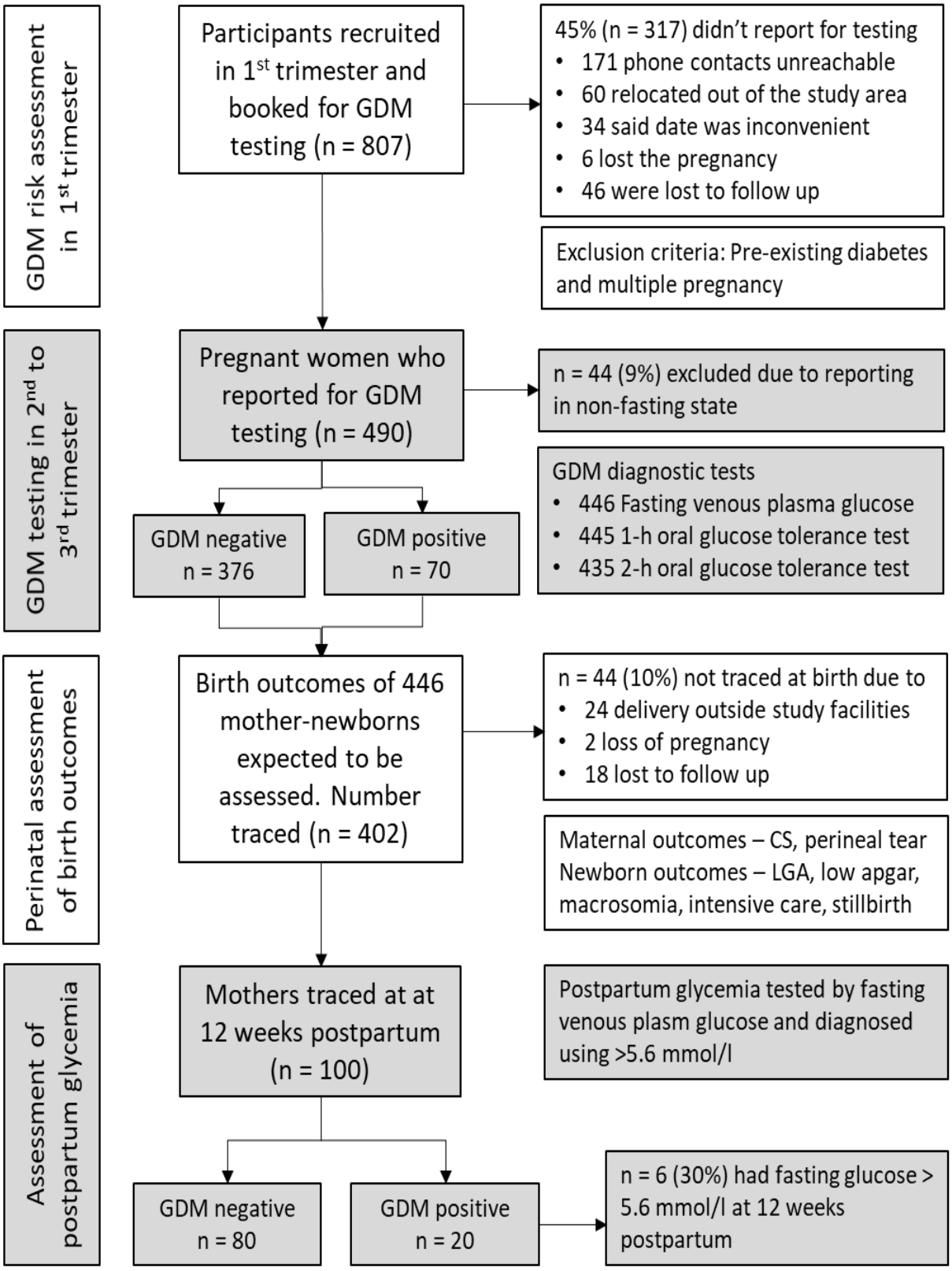

Figure 8. Number of participants followed-up at each stage of the follow-up

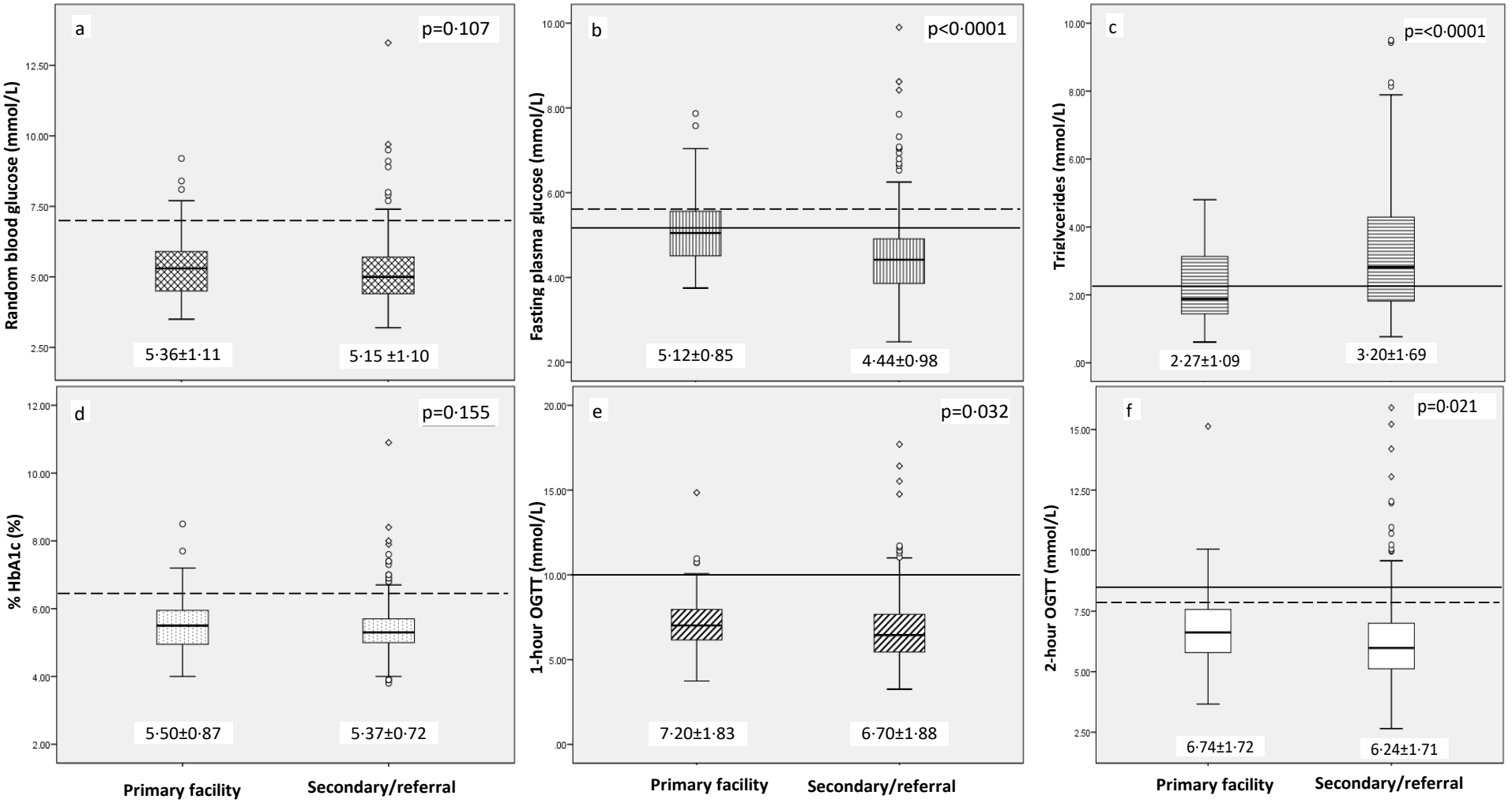

Figure 9. Box and whisker plots comparing interquartile and mean glucose values among users of primary and secondary/referral facilities

Note: The Solid line represents the WHO diagnostic criteria and dotted lines represent the NICE diagnostic criteria. The referral facility is the Regional hospital in the process of upgrade to a teaching hospital

3.1.2 Prevalence According to Common Diagnostic Criteria

The main diagnostic criteria used in diagnosing and classifying GDM were the guideline by IADPSG adopted by the WHO, International Federation of Gynecology and Obstetrics and American Diabetes Association; and the guideline by the NICE.

Fasting glucose of 446 participants and 2-hour OGTT of 435 participants were obtained. Prevalence of gestational diabetes per 2-h OGTT ≥8.5 mmol/L was 9.0% (n=39, 95% CI; 6.3-11.6) and prevalence per fasting plasma glucose ≥5.6 mmol/L was 10.8% (n=49, 95% CI; 8.1-13.9). Participants who met the case definition of 2-h OGTT ≥8.5 mmol/L and/or fasting plasma glucose ≥5.6 mmol/L were 15.9% (n=70/446; 95% CI; 12.5-19.3). Only 3.9% (n=17/433; 95% CI; 2.1-5.8) were positive for both 2-h OGTT ≥8.5 mmol/L and fasting plasma glucose ≥5.6 mmol/L whereas 15.9% (n=70/466, 95% CI; 12.5-19.3) had either FPG ≥5.6 mmol/L or 2-h OGTT ≥8.5 mmol/L being positive. Presented in **Table 6** is the prevalence of gestational diabetes according to the common diagnostic criteria.

Table 6. Prevalence of GDM according to common diagnostic criteria

Diagnostic criteria	Fasting plasma glucose positive (N=446)		2-hour OGTT positive (N=435)		Fasting glucose and/or 2-h OGTT positive [e] (n=446)
	Cut-off mmol/L	Prevalence %	Cut-off mmol/L	Prevalence %	Prevalence %
IADPSG[a]/WHO/ FIGO/ADA	≥5.1	23.8	≥8.5	9.0	26.5
NICE[b]	≥5.6	10.8	≥7.8[b]	14.3	20.3
CDA	≥5.3	16.9	≥9.0	5.1	18.9
ACOG/Carpenter & Coustan[c]	≥5.3	16.9	≥8.6	7.8	20.0
ACOG/NDDG[c]	≥5.8	8.3	≥9.2	4.4	10.6
1999 WHO	≥7.0	2.7	≥7.8	14.3	14.9
This study[d]	≥5.6	10.8	≥8.5	9.0	15.9

IADPSG: International Association of Diabetes in Pregnancy Study Groups (IADPSG Consensus Panel, 2010); WHO: World Health Organization (World Health Organization, 2013); FIGO: International Federation of Gynecology and Obstetrics (Hod et al., 2015); ADA: American Diabetes Association (American Diabetes Association, 2015); NICE: National Institute for Health and Care Excellence (National Institute for Health and Care Excellence, 2015); CDA: Canadian Diabetes Association (Diabetes Canada Clinical Practice Guidelines Expert Committee, 2018a); ACOG: American Congress of Obstetricians and Gynecologists (Committee on Practice Bulletins—Obstetrics, 2018).

[a] IADPSG criteria is adopted by WHO, FIGO, ADA, Australian Diabetes in Pregnancy Society and Brazilian Society of Diabetes. GDM is diagnosed made when one or both glucose values is abnormal.

[b] NICE cut-off for 2-h OGTT is used by the Diabetes in Pregnancy Study group in India but 2-h OGTT is done irrespective of the woman's fasting state.

[c] ACOG recommends 2-step screening. Diagnosis requires two or more elevated values on the 3-h OGTT.

[d] This study used a case definition of fasting plasma glucose (≥5.6 mmol/L) and 2-h OGTT (≥8.5 mmol/L).

[e] GDM is diagnosed made when one or both of the diagnostic cut-off values is exceeded

3.1.3 Prevalence Per Diverse Fasting Glucose and 2-h OGTT Combinations

Using the case definition of 2-h OGTT ≥8.5 mmol/L and fasting plasma glucose ≥5.6 mmol/L to determine the prevalence of gestational diabetes, varied GDM prevalence were investigated using combinations of 2-h OGTT and fasting plasma glucose. As shown in **Table 7**, it was observed, for instance that 6.7% of participants were positive for GDM based exclusively on fasting plasma glucose ≥5.6 mmol/L while the 2-h OGTT was negative (that is below the 8.5 mmol/L cut-off). Likewise, 5.0% had positive 2-h OGTT while the fasting plasma glucose was negative.

Table 7. Prevalence using diverse fasting glucose and 2-h OGTT combinations

Combinations of 2-h OGTT and fasting glucose	N	n	%
1. Either fasting positive ***and/or*** 2-h OGTT positive [a]	446	70	15.9
2. All fasting glucose positive (irrespective of 2-h OGTT results)	446	48	10.8
3. All 2-h OGTT positive (irrespective of fasting results)	435	39	9.0
4. Only fasting glucose positive but 2-h OGTT negative (both positive cases excluded)	416	28	6.7
5. Only 2-h OGTT positive but fasting glucose negative (both positive cases excluded)	416	21	5.0
6. Both fasting ***and*** 2-h OGTT positive	433	17	3.9
7. Either fasting glucose positive ***or*** 2-h OGTT positive (but not both being positive)	416	49	11.8

N: sample size; n: number of observations. [a] The NICE cut-off for fasting plasma glucose (≥5.6 mmol/L) was used to define GDM (National Institute for Health and Care Excellence, 2015) while the IADPSG/WHO cut-off for 2-hour OGTT ≥8.5 mmol /L was used to define GDM (World Health Organization, 2013).

3.1.4 Proportion of Pre-Existing Diabetes and Screen-Positive Cases

Pre-existing diabetes first detected in pregnancy was 2.0% (n=10, 95% 95% CI: 1.0-3.5). Per WHO diagnostic criteria, prevalence based on fasting plasma glucose ≥5.1 mmol/L was 23.8% (n=106, 95% CI: 19.8-27.9) while based on 1-h OGTT ≥10.0 mmol/L was 4.5% (n=20, 95% CI: 2.7-6.7). Regarding screening outcomes, almost one third (29.1%, n=130, 95% CI: 24.7-32.6) of participants had at least one risk factor for GDM, 9.1% had two risk factors while only 1.3% had three risk factors. Positive dipstick glycosuria including trace results was 31% while random blood glucose ≥ 7.0 mmol/L was 4.7%. **Figure 10** shows the prevalence based on screening and other diagnostic tests. If the WHO 1999 criteria for fasting glucose ≥7.0 mmol/L was in use, the prevalence of GDM would have been 2.7% (n=12, 95% CI: 1.1-4.3).

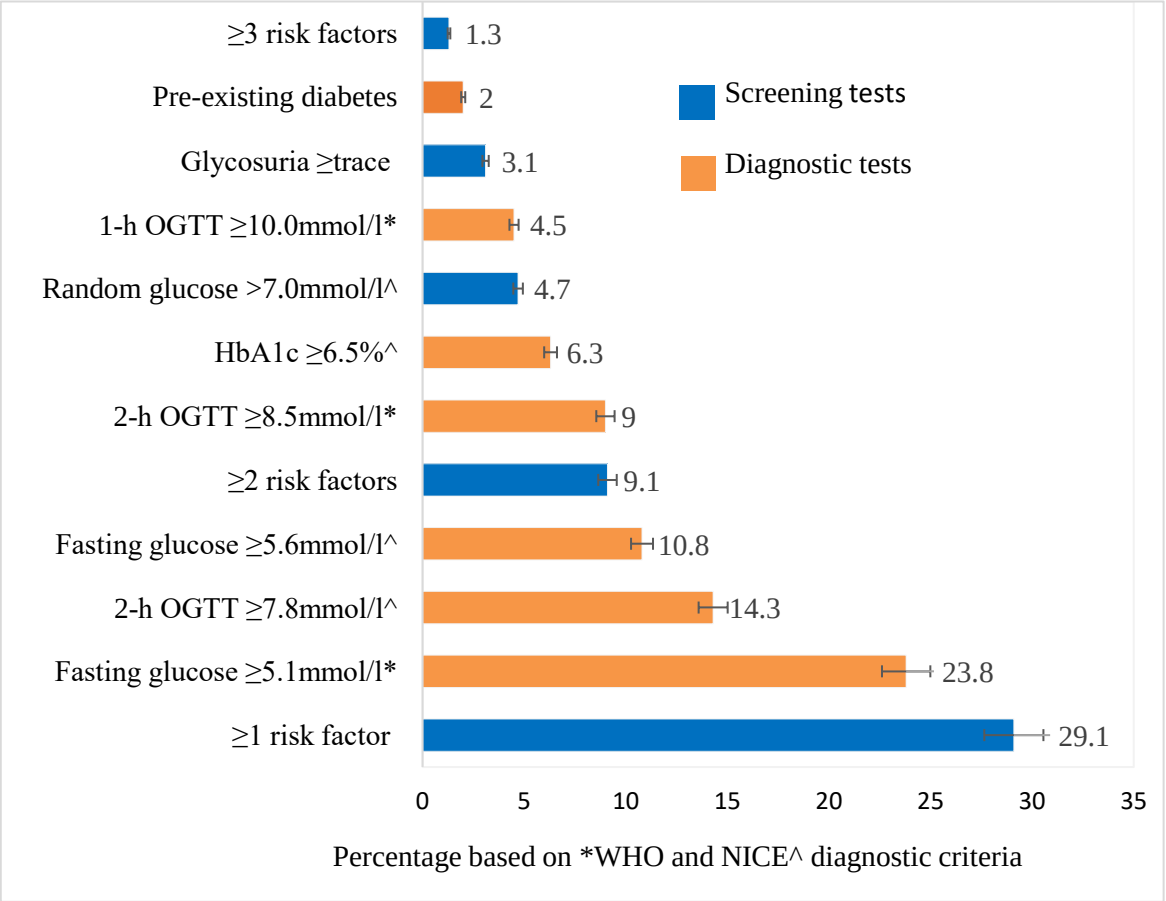

Figure 10. Percentage of participants who tested positive to the screening and diagnostic tests and the proportion who had pre-existing diabetes

Note: GDM diagnosis from 2-h OGTT (≥8.5 mmol/L) using WHO and NICE (≥7.8 mmol/L) guidelines; fasting plasma glucose using WHO (≥5.1 mmol/L) and NICE (≥5.6 mmol/l); 1-h OGTT using WHO (≥ 10.0 mmol/L); HbA1c using NICE (≥6.5% [7.8 mmol/L]).

Source: WHO guideline (World Health Organization, 2013) and NICE guideline (National Institute for Health and Care Excellence, 2015)

3.2 Diagnostic Accuracy of Test Instruments

3.2.1 Blood/Urine Glucose and Risk Per Facility Type

Presented in **Table 8** is the breakdown of diagnostic-, screen-, and risk factor-positive proportions among primary and secondary/referral facility users. Even though GDM tended to be more prevalent among primary healthcare users, no significant differences existed except for the prevalence based on fasting glucose from the WHO (48.7% vs 18.7%) and NICE cut-offs (23.4% vs 8.2%) and HbA1c (11.7% vs 5.2%). However, compared to primary facility users, significantly higher proportion of secondary facilities users were obese per the first trimester BMI (4.3% vs 13.5%) and had higher triglycerides (35.0% vs 64.4%).

Table 8. Comparison of blood/urine glucose and GDM risk profile among participants accessing antenatal care from primary and secondary facilities

Test and reference cut-off values	Mean±SD	% (n)	95% CI[e]	Facility (%)		P-value [g]
				Primary (n=77)	Second[f] (n=369)	
Diagnostic tests						
2-h OGTT ≥8.5 mmol/L [a]	6.7±1.7	9.0 (39)	6.5-12.0	10.3	8.7	0.663
2-h OGTT ≥7.8 mmol/l [b]	6.7±1.7	14.3 (63)	11.0-17.5	20.5	12.9	0.106
1-h OGTT ≥10.0 mmol/L [a]	7.2±1.8	4.5 (20)	2.7-6.7	6.4	4.1	0.368
Fasting glucose ≥5.1 mmol/L[a]	5.1±0.9	23.8 (106)	19.8-27.9	*48.7*	*18.7*	*<0.0001*[*]
Fasting glucose ≥5.6 mmol/L[b]	5.1±0.9	10.8 (48)	7.9-13.7	*23.4*	*8.2*	*<0.0001*[*]
HbA1c ≥ 6.5% [b]	5.5±0.9	6.3 (30)	4.2-8.5	*11.7*	*5.2*	*0.040*[*]
Screening tests	[d]					
Random glucose >7.0mmol/L[b]	5.4±1.1	4.7 (23)	2.9-6.7	6.2	4.4	0.562
Glycosuria ≥ trace	[d]	3.1 (15)	1.6-4.7	1.2	3.4	0.484
Risk factors						
Maternal age >35 years	28.4±6.3	13.8 (62)	10.5-17.2	13.3	13.9	>0.999
Gravidity above 5	2.7±1.5	5.4 (24)	3.4-7.7	6.7	5.1	0.577
Parity above 3 children	1.5±1.3	7.1 (30)	4.8-9.7	5.8	7.4	0.801
Body weight >90 kg [c]	63.0±13.1	3.4 (15)	1.8-5.3	1.4	3.8	0.483
Height <150 cm	161.8±8.2	4.2 (19)	2.4-6.2	5.9	3.9	0.509
BMI ≥29.9 kg/m^2	24.7±4.9	12.0 (52)	9.0-15.0	*4.3*	*13.5*	*0.027*[*]
MUAC >30 cm [c]	28.3±3.9	23.3 (103)	19.5-27.6	16.9	24.5	0.220
Family history of diabetes	[d]	6.4 (29)	4.2-8.6	8.0	6.1	0.604
Systolic BP >140 mmHg	106.6±12.4	2.0 (9)	0.7-3.3	1.4	2.1	>0.999
Diastolic BP >90 mmHg	66.2±9.4	1.8 (8)	0.7-3.1	1.4	1.9	>0.999
Proteinuria ≥1+	[d]	4.2 (19)	2.4-6.0	1.3	4.8	0.338
Triglycerides >2.25 mmol/L	3.0±1.7	59.5 (290)	55.0-63.9	35.0	*64.4*	*<0.0001*[*]

OGTT: oral glucose tolerance test; BMI: body mass index; MUAC: mid-upper arm circumference; BP: blood pressure.

[a, b] Same tests but different diagnostic criteria based on [a]WHO and [b]NICE guidelines.

[c] Maternal weight, height and mid-upper arm circumference were measured in the first trimester.

[d] The blank spaces represent categorical variables that do not have mean values.

[e] Represents the 95% CI for the positive proportions [% (n)].

[f] Included in the secondary facilities was the largest referral facility in the region (Volta regional hospital) now upgraded to a teaching hospital.

[g] Differences among primary and secondary facility estimated by Chi-square test

3.2.2 Flow of Participants through the Study

In reporting findings from the diagnostic accuracy study, the 2015 STARD guidelines (standards for reporting diagnostic accuracy studies) (Bossuyt et al., 2015) was followed. Overall, 807 pregnant women aged 15-54 years were booked for GDM screening between 12-20 gestational weeks. Even though all participants performed dipstick urine testing, 797 participants had the urine dipstick test results documented for at least three times during the pregnancy (one in each trimester) while random blood glucose was performed by 732 participants. Concerning diagnostic tests, between 20-34 weeks, fasting plasma glucose of 446 participants were tested while 436 and 435 completed the 1-hour and 2-hour OGTT

respectively. The over 300 participants missed in the follow-up diagnostic testing were as result of logistical constraints; difficulty establishing contact; relocation outside the study area; lack of interest in doing the test, spontaneous termination of the pregnancy, inability to fast overnight and difficulty tolerating the OGTT. Participants' flow through the study, proportions performing each screening and diagnostic test and the main reasons for withdrawal is shown in **Figure 11**.

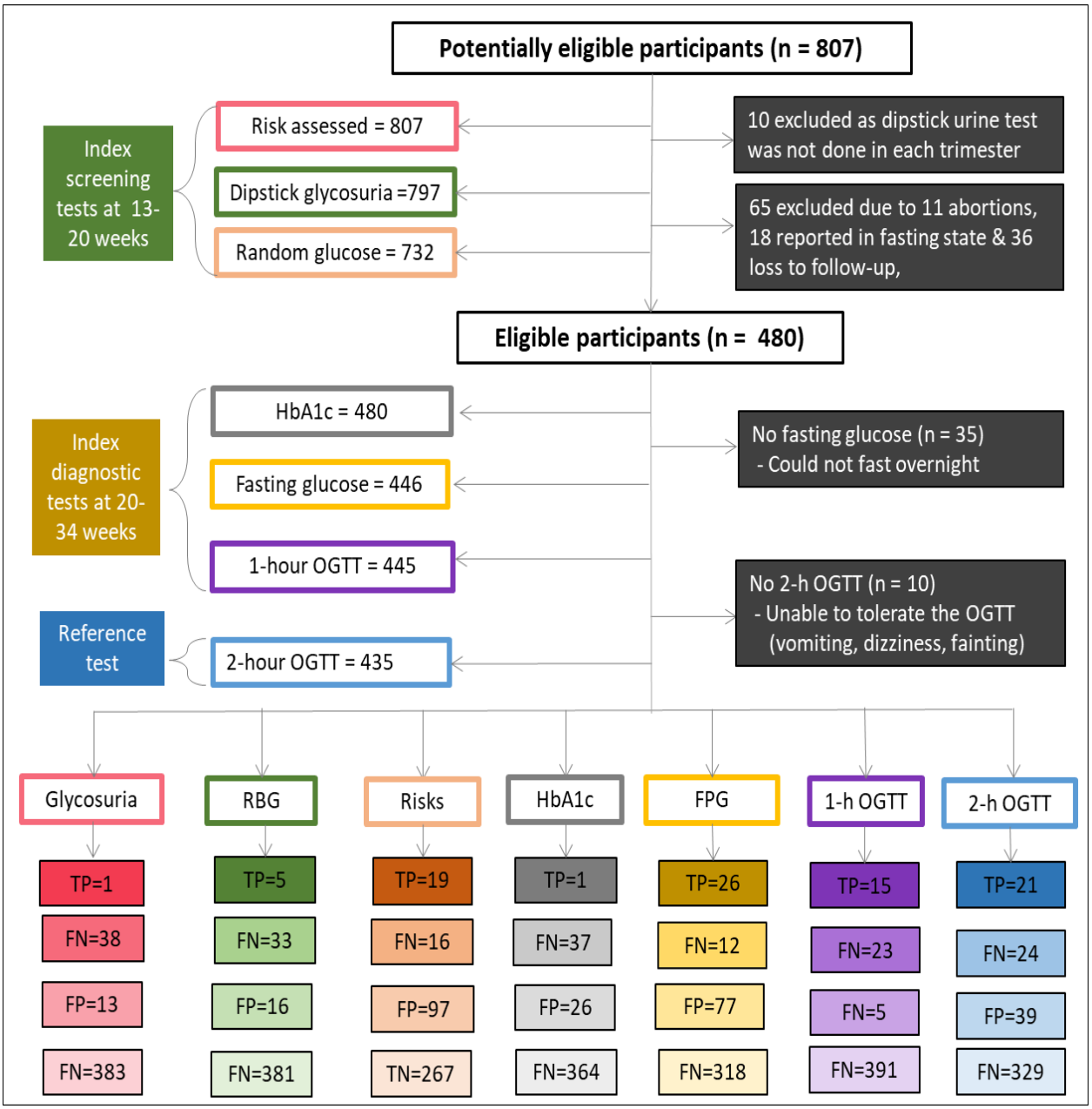

Figure 11. Flow of participants through the study and the proportions who tested positive and negative to each screening and diagnostic test

Note: TP: true positive; FN: false negative; FP: false positive; FN: false negative; RBG: random blood glucose; FPG: fasting plasma glucose: HbA1c: glycated hemoglobin; OGTT; the 'goal standard' oral glucose tolerance test

3.2.3 Validation of Test Instruments

3.2.3.1 Sensitivity, specificity, predictive and other diagnostic measures

Presented in **Table 9** and **Table 10** are the diagnostic measures of the test instruments reference to the 'gold standard' 2-h OGTT and fasting plasma glucose estimated based on WHO and NICE cut-offs. Generally, the screening tests had low sensitivity and positive predictive value whereas their specificity and negative predictive values were relatively high. Using the WHO diagnostic criteria for 2-h OGTT as reference, fasting plasma glucose ≥5.1 mmol/L had the highest sensitivity (68%) and negative predictive value (96%). However, 1-h OGTT had the highest specificity, positive predictive value (75%) and diagnostic odds ratio. Glycosuria, HbA1c and RBG were the least sensitive (<15%) and hence yielded a clinically irrelevant specificity above 95%. Although presence of at least one risk factor was 54% sensitive, its accuracy was the least among the test instruments (≈70%).

Similar pattern was observed when the NICE diagnostic criteria for 2-h OGTT (≥7.8 mmol/L) was used as the reference cut-off. But here, the test instruments had relatively lower sensitivity and DOR. Using the WHO diagnostic criteria for fasting plasma glucose (≥5.1 mmol/L) as the reference yielded generally lower diagnostic measures. Two-hour OGTT ≥7.8 mmol/L had the highest sensitivity and negative predictive value. This was followed by risk factors with a sensitivity of 32%. However, the 1-h OGTT ≥10.0 mmol/L had the highest positive predictive value and diagnostic odds ratio. When the NICE diagnostic criteria for fasting plasma glucose (using ≥5.6 mmol/L cut-off) was the reference test, sensitivity of the test instruments were slightly higher.

If selective screening based on glycosuria test result of trace and above were used, only 3.2% would have been booked to perform a diagnostic test for GDM. Out of this total, only 2.6% would be positive if the test of choice was 2-h OGTT. Should the glycosuria cut-off be changed to 1+ and above, the proportion of screen-positive cases would further have declined to less than one percent and none of the participants would have needed a diagnostic test. If selective diagnostic testing based on random blood glucose >7.0 mmol/L were used, only 4.8% would have performed a diagnostic test for GDM out of which 12.8% would have tested positive. If selective diagnostic testing based on the presence of at least one risk factor was as basis to inform diagnostic testing, 29.1% would have performed a diagnostic test out of which 53.4% would be positive.

Table 9. Diagnostic measure of test instruments using two-hour OGTT ≥8.5 mmol/L (WHO) and ≥7.8 mmol/L as (NICE) diagnostic criteria

Diagnostic measure	WHO reference cut-offs (≥8.5 mmol/L)							NICE reference cut-offs (≥7.8 mmol/L)						
	Risk factors[a]	Glycosuria[b]	RBG[c]	HbA1c[d]	FPG[e]	FPG[f]	1-h OGTT[g]	Risk factors[a]	Glycosuria[b]	RBG[c]	HbA1c[d]	FPG[e]	FPG[f]	1-h OGTT[g]
True positive	19	1	5	1	26	16	15	23	3	6	2	38	21	17
False negative	16	38	33	37	12	21	23	35	59	56	59	22	39	44
False positive	97	13	16	26	77	29	5	93	11	15	25	65	24	3
True negative	267	383	381	364	318	367	391	248	362	358	342	308	349	370
Sensitivity (%)	54.3	2·56	13·16	2·63	68·42	43·24	39·47	39.7	4·84	9·68	3·28	63·33	35·00	27·87
Specificity (%)	73.4	96·72	95·97	93·33	80·51	92·68	98·74	72.7	97·05	95·98	93·19	82·57	93·57	99·20
PPV (%)	16.4	7·14	23·81	3·70	25·24	35·56	75·00	19.8	21.43	28·57	7·41	36·89	46·67	85·00
NPV (%)	94.4	90·97	92·03	90·77	96·36	94·59	94·44	87.6	85·99	86·47	85·29	90·91	89·95	89·37
LR +	2.04	0·78	3·26	0·39	3·51	5·90	31·26	1.45	1·64	2·41	0·48	3·63	5·44	34·65
LR -	0.62	1·01	0·90	1·04	0·39	0·61	0·61	0.83	0·98	0·94	1·04	0·44	0·69	0·73
Accuracy (%)	71.1	88·28	88·74	85·28	79·45	88·45	93·55	67.9	83·91	83·68	80·37	79·91	85·45	89·17
DOR	3.3	0·78	3·61	0·38	8·95	9·64	51·00	1.8	1·67	2·56	0·46	8·18	7·83	47·65
Youden's index	0.28	-0·01	0·09	-0·04	0·49	0·36	0·38	0.12	0·02	0·06	-0·04	0·46	0·29	0·27

PPV: positive predictive value; NPV: negative predictive value; LR +: positive likelihood ratio; LR –: negative likelihood ratio; DOR: Diagnostic odds ratio; RBG: random blood glucose; HbA1c: glycated hemoglobin; FPG: fasting plasma glucose; OGTT: oral glucose tolerance test.

Indicators of increased discriminatory and predictive properties of a test are concurrently high values for test sensitivity and specificity, positive likelihood ratio, positive and negative predictive values, diagnostic odds ratio (DOR), accuracy and Youden's index. Lower negative likelihood ratio is more discriminatory. DOR values ranges from 0 to infinity whilst the Youden's index values ranges from -1 to 1 (Glas et al., 2003).

Screen-positive based on [a] presence of ≥1 risk factors, [b] reagent-strip glycosuria result of trace and above and [c] capillary random blood glucose >7·0 mmol/L. Diagnostic-positive derived from [d] HbA1c ≥6·5% (National Institute for Health and Care Excellence, 2015); fasting venous plasma glucose [e] ≥5·1 mmol/L (World Health Organization, 2013) and [f] ≥5·6 mmol/L (National Institute for Health and Care Excellence, 2015) as per WHO and NICE guidelines and one-hour postprandial OGTT [g] ≥10·0 mmol/L (World Health Organization, 2013)..

Table 10. Diagnostic measure of test instruments using fasting glucose ≥5.1 mmol/l (WHO) and ≥5.6 mmol/l as (NICE) diagnostic criteria

Diagnostic measure	WHO reference cut-offs (≥5.1 mmol/L)							NICE reference cut-offs (≥5.6 mmol/L)						
	Risk factors[a]	Glyco suria[b]	RBG[c]	HbA1c[d]	1-h OGTT[e]	2-h OGTT[f]	2-h OGTT[g]	Risk factors[a]	Glyco suria[b]	RBG[c]	HbA1c[d]	1-h OGTT[d]	2-h OGTT[f]	2-h OGTT[g]
True positive	31	5	11	10	17	27	38	18	4	8	6	13	17	21
False negative	67	101	95	93	89	76	65	27	44	40	41	35	28	24
False positive	83	9	10	18	3	12	22	98	10	13	22	7	21	39
True negative	217	330	329	317	334	318	308	265	387	384	369	388	367	349
Sensitivity (%)	31.6	4.7	10.4	9.7	16.0	26.2	36.9	40.0	8.3	16.7	12.8	27.1	37.8	46.7
Specificity (%)	72.3	97.3	97.1	94.6	99.1	96.4	93.3	73.0	97.5	96.7	94.4	98.2	94.6	89.9
PPV (%)	27.2	35.7	52.4	35.7	85.0	69.2	63.3	15.5	28.6	38.1	21.4	65.0	44.7	35.0
NPV (%)	76.4	76.6	77.6	77.3	79.0	80.7	82.6	90.8	89.8	90.6	90.0	91.7	92.9	93.6
LR +	1.14	1.74	3.59	1. 79	17.77	7.27	5.51	1.48	3.32	5.06	2.28	15.05	7.00	4.62
LR -	0.95	0.98	0.92	0.95	0.84	0.76	0.67	0.82	0.94	0.86	0.92	0.74	0.65	0.59
Accuracy (%)	62.3	75.3	72.2	70.3	75.2	79.7	79.9	69.4	87.9	88.1	85.6	90.5	88.7	85.5
DOR	1.2	1.8	3.8	1.9	21.3	9.4	8.2	1.8	3.5	5.9	2.5	20.6	10.6	7.8
Youden's index	0.04	0.02	0.08	0.04	0.15	0.23	0.30	0.13	0.06	0.13	0.07	0.25	0.32	0.37

PPV: positive predictive value; NPV: negative predictive value; LR +: positive likelihood ratio; LR –: negative likelihood ratio; DOR: Diagnostic odds ratio; RBG: random blood glucose; HbA1c: glycated hemoglobin; FPG: fasting plasma glucose; OGTT: oral glucose tolerance test.

Indicators of increased discriminatory and predictive properties of a test are concurrently high values for test sensitivity and specificity, positive likelihood ratio, positive and negative predictive values, diagnostic odds ratio (DOR), accuracy and Youden's index. Lower negative likelihood ratio is more discriminatory. DOR values ranges from 0 to infinity whilst the Youden's index values ranges from -1 to 1 (Glas et al., 2003).

Screen-positive based on [a] presence of ≥1 risk factors, [b] reagent-strip glycosuria result of trace and above and [c] capillary random blood glucose >7·0 mmol/L. Diagnostic-positive derived from [d] HbA1c ≥6·5% (National Institute for Health and Care Excellence, 2015); [e] one-hour postprandial OGTT [g] ≥10·0 mmol/L (World Health Organization, 2013) and two-hour postprandial OGTT [f] ≥8.5 mmol/L (World Health Organization, 2013) and [g] ≥7.8 mmol/L (National Institute for Health and Care Excellence, 2015) as per WHO and NICE guidelines.

3.2.3.2 Diagnostic performance based on area under the curve

In **Figure 12** is the receiver operating characteristic (ROC) curves showing the area under the curve (AUC) as indication of test performance. Interpretation of the ROC curves is presented in **Table 11**. In Figure 12 a and b, the reference test was 2-h OGTT based on the WHO (≥8.5 mmol/L) and NICE (≥7.8 mmol/L) diagnostic cut-offs. One-hour OGTT and fasting glucose were very good tests as the AUC was between 0.86-0.88. Random blood glucose was a poor test for detecting GDM (AUC≈0.6) whereas HbA1c was not a useful test because the AUC was <0.5 and the CI of the AUC was statistically insignificant (p=0.686). In Figure 12 c and d, FPG ≥5.1 mmol/L and ≥5.6 mmol/L were used as the reference cut-offs based on the WHO and NICE guidelines respectively. One-hour and 2-h OGTT were found to be 'good' test because the AUC was between 0.76-0.78. Although AUC values for random glucose and HbA1c were slightly higher compared to Figure 12 a and b, the test rating was similar as when the 2-h OGTT was used as the reference.

Table 11. Area under the curve showing test performance for 2-h OGTT and fasting glucose using WHO and NICE cut-offs as reference

Reference criteria	Test assessed	AUC[c]	95% CI	p-value[d]
2-h OGTT ≥8.5 mmol/L[a]	1-hour OGTT	0.88	0.81-0.94	<0.0001
	Fasting glucose	0.86	0.80-0.91	<0.0001
	Random glucose	0.60	0.51-0.69	0.035
	HbA1c	0.48	0.40-0.57	0.686
2-h OGTT ≥7.8 mmol/L[b]	1-hour OGTT	0.85	0.80-0.91	<0.0001
	Fasting glucose	0.83	0.78-0.88	<0.0001
	Random glucose	0.62	0.55-0.69	0.002
	HbA1c	0.48	0.40-0.55	0.567
Fasting glucose ≥5.1 mmol/L[a]	1-hour OGTT	0.77	0.71-0.82	<0.0001
	2-hour OGTT	0.78	0.72-0.83	<0.0001
	Random glucose	0.63	0.57-0.69	<0.0001
	HbA1c	0.51	0.44-0.57	0.880
Fasting glucose ≥5.6 mmol/L[b]	1-hour OGTT	0.76	0.68-0.84	<0.0001
	2-hour OGTT	0.78	0.70-0.86	<0.0001
	Random glucose	0.65	0.56-0.74	0.001
	HbA1c	0.51	0.41-0.60	0.867

[a]WHO and [b]NICE diagnostic criteria. [c]Area under the curve under the null hypothesis = 0.5. Test rated excellent for AUC 0.9-1.0; very good (0.8-0.9); good (0.70-0.80); sufficient (0.60-0.70), poor (0.50-0.60) and invaluable (AUC<0.5) if p<0.05 (Mallett et al., 2012, Raslich et al., 2007). The lower the p-value, the higher the clinical relevance of the test

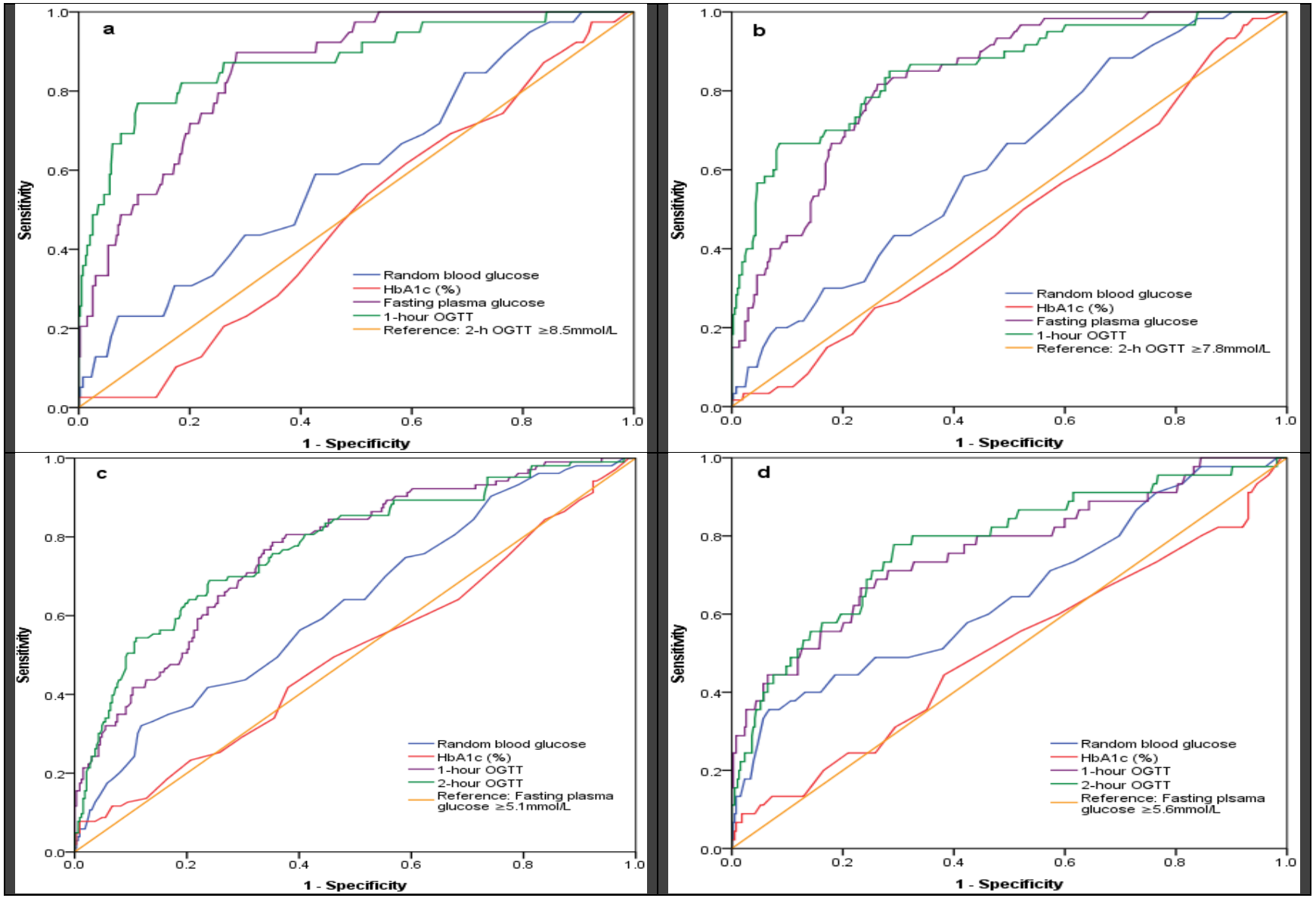

Figure 12. Receiver operating characteristic curves showing the area under the curve reference to two-hour OGTT (a/b) and fasting plasma glucose (c/d)

3.2.3.3 Cut-offs for the study population using coordinates of the curve

Using the coordinates of the ROC curve where 2-h OGTT ≥8.5 mmol/L was the reference cut-off, diagnostic thresholds for the study population that provided optimized and clinically relevant sensitivity and specificity were estimated. Random glucose value of 5.2 mmol/L corresponded to sensitivity of 60% and specificity of 54%. Similar sensitivity and specificity (62% vs. 41%) were obtained for HbA1c threshold of 5.2%. Increasing the sensitivity of both random glucose and HbA1c to 70% corresponded to threshold values of 5.0 mmol/L and 5.0% respectively but the specificity of both were not clinically relevant (38% vs. 25%). Regarding fasting glucose, 90% sensitivity and 72% specificity corresponded to 4.8 mmol/L glucose. At the same threshold, the NICE cut-off for 2-h OGTT (≥7.8 mmol/L) yielded 80% sensitivity and 74% specificity. In the case of 1-h OGTT, 7.8 mmol/L threshold corresponded to 82% sensitivity and 81% specificity.

3.3 Risk Factors for Gestational Diabetes

3.3.1 Background Characteristics of Study Participants

Table 12 shows the socio-demographic characteristics of the 445 pregnant women who did the diagnostic testing for GDM and subsequently participated in most phases of the study. Fifteen percent were each recruited from the primary and referral facilities and the remining 70% recruited from secondary facilities. A third of the study participants were residing in rural setting and the remaining were peri-urban dwellers. Half (n=223) were aged 20-29 years, 29.8% (n=131) were primiparous women whereas 12.8% (n=57) have had more than five pregnancies in their lifetime.

Two-thirds (63.8%, n=286) had little formal education compared to 41.9% (n=186) of their male partners. An equal proportion of the women (64.9%, n=286) and their partners (65.3%, n=290) were informal sector workers engaged mainly in trading, handiwork and menial jobs. Students constituted 4.5% (n=20) of the 22.0% women (n=97) who were not engaged in any economic venture at the time of the study while 5.6% of their partners were unemployed. The index pregnancy of 37.1% (n=149) of the women were unintended.

Table 12. Socio-demographic characteristic of study participants

Variable	Sub-scale	N = 445	%
Level of facility	Primary facility	69	15.4
	Secondary facility	309	69.4
	Referral facility	68	15.2
Residency	Rural dweller	133	32.8
Age groups	<20 years	32	7.2
	20-29 years	223	50.0
	30-39 years	174	39.2
	≥40 years	16	3.6
Marital status	Married	316	72.0
	Cohabitating	68	15.5
	Single	55	12.5
Woman's educational level	None/primary	62	13.8
	Junior secondary	224	50.0
	Senior secondary	92	20.5
	College/university	70	15.2
Partner's educational level	None/primary	33	7.4
	Junior secondary	153	34.5
	Senior secondary	133	30.0
	College/university	124	28.0
Woman's employment status	Unemployed	97	22.0
	Informal sector	286	64.9
	Formal sector	58	13.2
Partner's employment	Unemployed	25	5.6
	Informal sector	290	65.3
	Formal sector	129	29.1
Gravidity	1-2 pregnancies	229	51.6
	3-4 pregnancies	158	35.6
	≥5 pregnancies	57	12.8
Parity	No children	131	29.8
	1-2 children	230	52.2
	3-4 children	66	15.1
	≥5 children	13	2.9
Pregnancy intention	Unintended	149	37.1
Religious affiliation	Christian	410	91.3
	Moslem	39	8.7

Note: students constituted 4.5% (n=20) of the unemployed group

3.3.2 Health Profile of Study Participants

Reading the health, anthropometry and dietary profile of the women presented in **Table 13,** 4.0% (n=18) had pre-existing hypertension, 17.7% (n=80) had a family history of hypertension while first-degree relatives of 7.1% (n=32) had diabetes. Apart from malaria (10.3%, n=26), prevalence of infectious diseases among the study population was generally low but reflective of population rates. HIV, Hepatitis B and status syphilis were 2.1%, 4.2%

and 3.4% respectively. An equal proportion of woman were underweight (9.6%) and obese (9.4%). Half 51.7% (n=256) of the women received dietary counseling, but fewer received counseling on iron-folic acid supplementation 28.8% (n=130).

Table 13. Health, anthropometric and dietary intake profile of participants

Variable	Sub-categories	n	%
History of hypertension	Yes	18	4.0
Hypertension in family	Yes	80	17.7
Diabetes in family	Yes	32	7.1
HIV status	Positive	22	2.1
Hepatitis B	Positive	11	4.2
VDRL for syphilis	Reactive	14	3.4
Malaria	Positive	26	10.3
Infestations	Intestinal flagellates	7	4.0
Sickling	Positive	56	14.0
Blood group	A	103	19.7
	B	106	24.6
	AB	19	4.8
	O	206	50.9
Rhesus status	Negative	31	6.6
BMI category	Underweight	39	9.6
	Normal weight	232	57.1
	Overweight	97	23.9
	Obese	38	9.4
MUAC	<24 cm	24	8.2
Dietary counselling	Given	256	51.7
Advised on IFA	Yes	130	28.8
Iron-folic acid	Daily supplements	445	96.8
Has food taboos	Yes	73	17.7
Has food aversions	Yes	78	18.8
Has food cravings	Yes	99	24.0

VDRL, Venereal Disease Research Laboratory test for syphilis; BMI, body mass index; MUAC, mid-upper arm circumference; IFA, Iron-folic acid

3.3.3 Habitual Dietary Intakes of Study Participants

Figure 13 shows the habitual foods consumed and the frequency of consumption. Daily intake was largely from staple foods (90.6%), other vegetables (85.4%), fleshy foods (84.9%) and fruits and vegetable rich in vitamin A (78.8%). Detailed description of the habitual intake from each food group is found in the supplementary **Figure 16** found in the appendix. Corn (90.6%) and rice (41.2%) were the most daily consumed staple. Fish (84.9%) and poultry (21.6%) were the most consumed fleshy food. Egg and milk were consumed by 20.5% and 17.6%. Groundnut was the most daily consumed (21.6%) nuts/seeds. Pulses was the least

consumed group with black eye beans (11.0%) being the most consumed in that group. About one-fourth of the participants took dark green leafy vegetables daily. The main varieties were 'kontomire' (cocoyam/taro leaves), 'gboma' (African eggplant leaves) and ayoyo (corchorus leaves). Intake of other vitamin A-rich vegetables particularly chilli pepper (83.4%) and tomatoes (74.2%) followed the pattern as for staple foods because they are habitual accompaniments. Banana and orange which were the most consumed fruits, were eaten by about a third daily. While smoking and intake of alcohol were rare, daily intake of sweetened foods (35.7%) and beverages (21.1%) was relatively high.

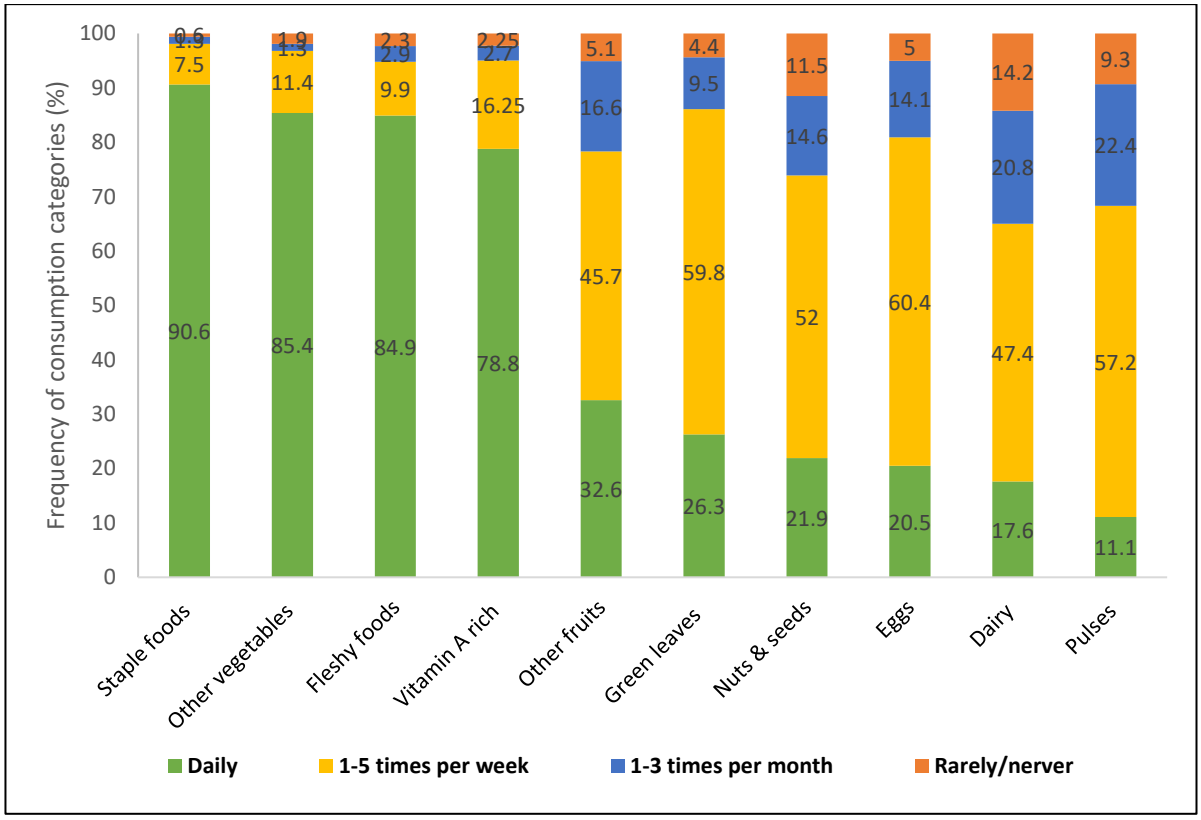

Figure 13. Frequency of consumption of the 10 main food groups

Foods tabooed were mainly fleshy foods (pork, mutton, mudfish, catfish, crab, snail, beef) and okra. Foods averted were beans, cassava flour, fermented corn products, eggs, fresh fish, oily foods (particularly groundnuts and palm nuts) and alcohol. Aside one case of white clay intake, all the foods craved for were healthy. Diets of 58.6% (n=243, 95% CI: 54.2-63.4) contained at least five of the 10 food groups and were thus rated as micronutrient adequate. Mean daily intake of high glycemic index (GI) foods was 2.6 high GI foods. The cases tended to consume more high GI foods than the controls (mean: 2.9 vs 2.6) but the difference was

not significant. Daily glycemic intake of 56.7% (n=212) was adequate (i.e. intake of high GI foods 1-2 times per day), 22.7% (n=85) was moderate (i.e. intake of high GI foods 3-4 times per day) while the remaining (20.6%, n=77) consumed excess calories (i.e. intake of high GI foods above 5 times per day). Shown in **Figure 14** is a comparison of the daily glycemic intake among the cases and controls. The cases tended to consume high GI foods in excess, but the difference was insignificant compared to the control group.

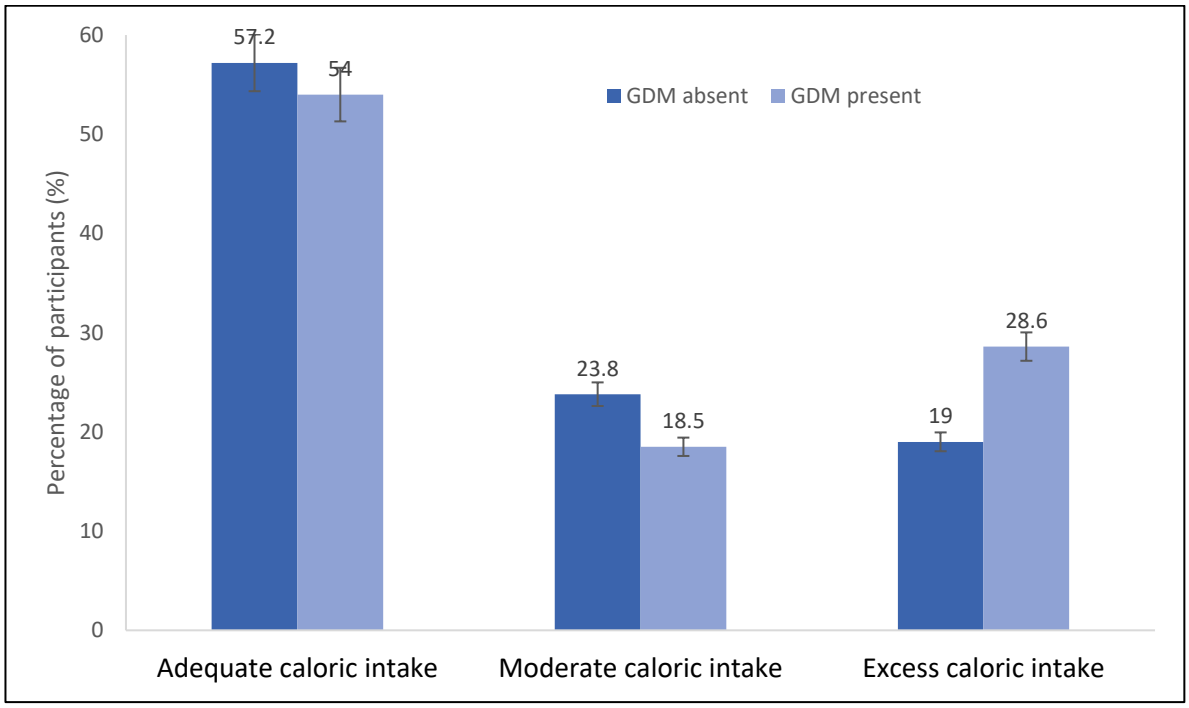

Figure 14. Comparison of daily intake of high glycemic index foods among the cases and controls

Note: The difference is not statistically significant (p=0.181). Adequate caloric intake implies (intake of high GI foods 1-2 times per day); moderate caloric intake implies (intake of high GI foods 3-4 times per day) and excess caloric intake implies (intake of high GI foods ≥5 times per day)

3.3.4 Maternal Health Profile of Cases and Controls

Seventy participants met the GDM case definition and the remaining 376 served as controls, representing one case to about approximately five controls. Mean maternal age was 28.44 years (SD=6.13); the minimum and maximum ages were 15 and 54 years respectively. Five (1.8%) participants were between 15-17 years while only one participant was above 49 years. As presented in **Table 14**, participants who were classified as cases were comparable with controls in many regards except that the cases were significantly older (29.8 vs 28.2 years), had higher gravidity (3.2 vs 2.7 pregnancies), parity (1.8 vs 1.3 children), first trimester weight (66.4 vs 62.4 kg), BMI (24.8 vs 23.2 kg/m^2) and MUAC (29.5 vs 28.1 cm).

Table 14. T-test comparing the health and anthropometric profile of the GDM cases and controls for continuous variables

Continuous variables	Mean (standard deviation)			*P-value*
	Total (N=446)	**GDM present [a] (n=70)**	**GDM absent (n=376)**	
Fasting glucose[a]	4.56 (0.99)	5.70 (0.79)	4.28 (0.69)	[d]
2-h OGTT [a]	6.33 (1.72)	7.82 (1.73)	5.90 (1.14)	[d]
Maternal age (years)	28.44 (6.13)	*29.82 (6.80)*	*28.19 (5.99)*	*0.036**
Gravida	2.73 (1.49)	*3.17 (1.57)*	*2.66 (1.47)*	*0.010**
Parity (live children)	1.35 (1.31)	*1.75 (1.45)*	*1.28 (1.27)*	*0.007**
Weight (kg)	62.98 (13.06)	*66.38 (14.32)*	*62.37 (12.75)*	*0.020**
Height (cm)	162.36 (9.33)	162.93 (7.94)	162.26 (9.54)	0.604
BMI (kg/m^2)	23.48 (4.43)	*24.77 (4.82)*	*23.21 (4.30)*	*0.026**
MUAC (cm)	28.33 (3.69)	*29.51 (4.40)*	*28.08 (3.48)*	*0.016**
Weight change[b]	11.16 (5.18)	11.67 (5.21)	11.06 (5.18)	0.445
Systolic BP (mmHg)	108.06 (11.49)	109.88 (11.91)	107.74 (11.40)	0.154
Diastolic BP (mmHg)	65.39 (9.37)	65.58 (10.23)	65.36 (9.22)	0.859
Total cholesterol (mmol/L)	5.50 (1.28)	5.32 (1.37)	5.54 (1.27)	0.189
Triglycerides (mmol/L)	3.05 (1.65)	2.88 (1.23)	3.08 (1.71)	0.331
HDL cholesterol (mmol/L)	1.47 (0.44)	1.49 (0.49)	1.47 (0.43)	0.596
LDL cholesterol (mmol/L)	2.66 (1.07)	2.51 (1.04)	2.68 (1.08)	0.201
VLDL cholesterol (mg/dl)	1.35 (0.76)	1.30 (0.60)	1.36 (0.78)	0.542
Coronary risk	4.14 (2.37)	3.80 (1.20)	4.20 (2.52)	0.180
Intake of high GI foods[c]	2.62 (1.14)	2.87 (1.24)	2.56 (1.12)	0.242

*Statistically significant at *p<0.05. BMI, body mass index; MUAC, mid-upper arm circumference; BP, blood pressure; HDL, high density lipoprotein; VLDL, very low-density lipoprotein; GI, glycemic index. Apart from the lipid profile, all other assessments were taken in the first trimester.

[a] The case definition is 2-hour OGTT ≥8.5 mmol/L and/or the fasting plasma glucose ≥5.6 mmol/L.

[b] Pregnancy weight change was estimated by subtracting weight at delivery from the weight in the first trimester.

[c] This is the number of high glycemic index foods consumed the day prior to the survey.

[d] No p-values were reported because the cases and controls were estimated from this scale variable.

3.3.5 GDM and Macrosomia

As GDM is often associated with macrosomia, secondary data on 4,262 singleton mother-newborn pairs was analyzed to assess macrosomia (defined as birth weights ≥4.0 kg). Macrosomia was 3.03% (n=120, 95% CI: 2.6-3.6). Mean birthweight was 2.98 kg (SD=0.50). Significantly higher macrosomic births were observed in infants who were born through cesarean section, who had birth order beyond second, and the maternal age was 31-40 years. **Table 15** shows the predictors for a macrosomic birth. Newborns delivered by cesarean section (14.4%) has the highest mean birth weight (3.12±0.54 kg). proportion of stillbirth among macrosomic newborns was 6.8%. Risk of macrosomia for a fifth born was 2.66 times higher compared to a second or third born. Likewise, macrosomia newborns were 2.56 times more likely for cesarean delivery.

Table 15. Risk factors for delivery a macrosomic baby (birth weigh >2.5kg)

Maternal and infant factors	Sub-categories	Prevalence [n/N (%)]	RRR	P>z	95% CI
Parity	1-2	60/1997 (3.0)	Ref.		
	3-4	37/755 (4.9)	1.53	0.068**	0.96-2.40
	>4	19/204 (9.3)	*2.66*	*0.002**	*1.43-4.95*
	Nulliparous	14/1342 (1.0)	*0.45*	*0.011**	*0.24-0.83*
Sex of baby	Male	79/2182 (3.6)	Ref.		
	Female	50/2115 (2.4)	*0.65*	*0.023**	*0.45-0.94*
HIV status	Negative	127/4235 (3.0)	Ref.		
	Positive	3/63 (4.8)	1.75	0.360	0.53-5.77
Maternal age	21-30	65/2461 (2.6)	Ref.		
	<20	2/574 (0.4)	*0.22*	*0.044**	*0.05-1.000*
	31-40	49/1097(4.5)	1.08	0.713	0.70-1.670
	>40	14/164 (8.5)	1.75	0.123	00.86-3.57
IPT taken	3 doses	70/2175 (3.2)	Ref.		
	1 dose	9/241 (3.7)	1.37	0.386	0.67-2.83
	2 doses	12/535 (2.2)	0.69	0.259	0.37-1.31
	None taken	39/1347 (2.9)	0.87	0.500	0.58-1.31
Delivery mode	SVD	81/3123 (26.0)	Ref.		
	C/S	37/614 (6.0)	*2.56*	*<0.0001**	*1.69-3.86*
	Forceps	2/70 (2.9)	1.41	0.645	0.33-6.10
	VD & episiotomy	9/468 (1.9)	1.35	0.425	0.65-2.79

Statistically significant at *p<0.05 and **p<0.10.
Data presented as % (n/N) unless otherwise indicated. Macrosomia is defined as >4.0 kg. RRR= relative risk ratio; CI= confidence interval. Estimates based on maximum-likelihood multinomial logistic regression models. IPT: intermittent preventive treatment for malaria; SVD: spontaneous vaginal delivery; C/S: cesarean section

3.3.6 Risk Factors for Gestational Diabetes

Overall, 8.3% of the participants were underweight whereas 22.9% were overweight and 8.3% obese. Comparing the cases and control, the column adjustments showed that the proportions who were underweight (6.3% vs 7.4%) and obese (8.3% vs 7.8%) groups were statistically the same but a significant proportion of those who were overweight were diagnosed with GDM (35.4% vs 20.9%). On the day prior to the survey, 28.6% of the GDM group consumed more than five high glycemic index foods while it was 18.5% in the non-GDM group (p=0.080). Comparing the lipid profile indices of cases and controls, no significant differences were noted in the mean total cholesterol (5.32 vs 5.54 mmol/L), triglycerides (2.88 vs 3.08 mmol/L), high density lipoprotein cholesterol (1.49 vs 1.47 mmol/L) and low density lipoprotein cholesterol (2.51 vs 2.68 mmol/L).

Presented in **Table 16** is the Chi-square test comparing dichotomous characteristics of cases and controls and the crude and adjusted binary logistic regressions showing the significant risk factors for GDM. It was observed that double the proportion of cases were primary facility users (case: 31.4% vs control: 15.1%, p=0.009). Significantly higher proportion were above age 35 years (23.9% vs 12.0%) and their partners had very little formal education (16.7% vs 6.7%). Also, more cases were overweight/obese (20.0% vs 10.7%), had mid-upper arm circumference (MUAC) above 30 cm and had history of spontaneous abortions (50.0% vs 32.0%) and preeclampsia (9.1% vs 1.6%). No significant differences were observed in pregnancy weight change, number of lifetime pregnancies, and other socio-demographic, anthropometric, obstetric, medical and dietary indicators assessed **(Table 16).**

In both the crude and adjusted models, spousal education below secondary level, ANC in a primary facility, adiposity (overweight/obesity, high MUAC) and intake of high glycemic index foods more than five times per day were significant risk factors for GDM. In addition, maternal age above 30 years, previous spontaneous abortion and preeclampsia in the current pregnancy were significant independent risk factors in the crude model. In the adjusted model, previous cesarean section was an additional significant risk factor **(Table 16).** For instance, women whose MUAC was above 30 cm were 199% (95% CI: 1.12-3.52) more likely to develop GDM than women with MUAC below 30 cm. Adjusting for other covariates, the risk increased to 297% (95% CI: 1.31-5.58). Also, women who consumed above 5 high glycemic index food per day had 176% risk (95% CI: 1.95-3.28) whereas in the adjusted model, the risk increased to 291% (95% CI: 1.05-8.07).

Table 16. Comparison of cases and controls and binary logistic regression showing crude and adjusted odds for GDM

Dichotomous predictor variables		GDM present (n=70)	GDM absent (n=376)	*P-value*	Unconditional binary logistic regression			
					Univariate		Multivariate	
Predictor value	**Reference value**				**Crude OR**	**95% CI**	**Adj OR**	**95% CI**
Socio-demography								
Maternal age >35 years	Maternal age ≤35 years	*16 (23.9)*	*46 (12.0)*	*0.019**	*2.29*	*1.21-4.36**	4.06	0.58-8.73
Unmarried	Married/cohabitating	13 (28.3)	65 (27.3)	0.859	1.05	0.52-2.12		
Rural residence	Urban/peri-urban residence	14 (28.6)	71 (29.1)	0.941	0.98	0.49-1.92		
Primary maternal education [a]	Higher maternal education [a]	11 (21.6)	30 (12.0)	0.077**	2.01	0.931-4.33**		
Primary partner education [a]	Higher partner education [a]	*8 (16.7)*	*16 (6.7)*	*0.039**	2.80	1.12-6.97*	*3.36*	*1.271- 8.89**
Primary facility	Secondary/referral facility	*16 (31.4)*	*38 (15.1)*	*0.009**	2.56	1.29-5.08*	*4.95*	*1.87-3.76**
Anthropometry								
Overweight/obese [b]	Normal/underweight [b]	*13 (20.0)*	*39 (10.7)*	*0.041**	*2.08*	*1.04-4.16**	*2.13*	*1.13-4.03**
1st trimester weight >90kg [b]	Weight ≤90 kg [b]	4 (6.1)	11 (3.0)	0.182	2.08	0.64-6.75		
Height <150cm[b]	Height ≥150 cm	7 (13.7)	26 (10.4)	0.466	1.37	0.56-3.35		
Weight gain >threshold [c]	Weight gain <threshold [c]	12 (24.0)	51 (20.6)	0.574	1.21	0.59-2.49		
MUAC >30cm [d]	MUAC ≤30 cm	*22 (34.9)*	*80 (21.3)*	*0.024**	*1.99*	*1.12-3.52**	*2.97*	*1.31-5.58**
Obstetric history								
Parity >3 children	Parity ≤3 children	8 (12.9)	22 (6.2)	0.066**	2.25	0.95-5.31**	2.42	0.39-14.75
Gravida >5 pregnancies	Gravida ≤5 pregnancies	5 (7.9)	19 (5.0)	0.365	1.63	0.58-4.53		
Prior macrosomia	No macrosomia history	1 (16.7)	8 (18.6)	0.909	2.87	0.09-8.56		
Prior cesarean section	No cesarean section history	10 (20.0)	43 (16.3)	0.539	1.28	0.59-2.75	*4.01*	*1.09-14.76**
Prior neonatal death	No neonatal death history	5 (10.2)	21 (8.0)	0.576	1.32	0.47-3.67	4.06	0.88-18.87**
Spontaneous abortion	No spontaneous abortion	*18 (50.0)*	*62 (32.0)*	*0.040**	*2.13*	*1.04-4.37**	1.15	0.33-4.03
Multiple pregnancies	No multiple pregnancies	2 (4.0)	7 (2.7)	0.439	1.51	0.31-7.49		
Medical examinations								
Diabetes in family	No family diabetes history	5 (7.5)	24 (6.3)	0.787	1.20	0.44-3.26	1.50	0.31-7.31
Family hypertension	No hypertension in family	7 (13.7)	22 (8.8)	0.296	1.65	0.67-4.11	1.21	0.34-4.36
Trace glycosuria & above [e]	No glycosuria [e]	4 (5.5)	11 (2.6)	0.171	2.14	0.66-6.91	3.65	0.76-17.42
Hypertensive	Non-hypertensive	9 (17.6)	47 (18.7)	0.989	1.93	0.42-2.04	3.98	0.50-31.42
Prior preeclampsia	No preeclampsia history	*6 (9.1)*	*6 (1.6)*	*0.004**	*6.23*	*1.15-19.96**		
Dyslipidemia [f]	Normolipidemia [f]	8 (15.7)	63 (25.3)	0.153	0.55	0.25-1.23	0.91	0.16-5.11
HIV positive	HIV negative	2 (5.1)	2 (0.9)	0.082**	5.84	0.797-42.74		

Nutrition								
Excess high GI foods [g]	Adequate/moderate GI foods[g]	18 (28.6)	56 (18.5)	0.080**	*1.76*	*1.95-3.28**	*2.91*	*1.05-8.07**
Mid/moderate/severe anemia [h]	Non-anemic [h]	24 (60.0)	130 (55.6)	0.365	1.20	0.61-2.37		

Statistically significant at *p<0.05 and **p<0.10.
The blank spaces are the variables that were omitted from the final regression model.
The GDM case definition was 2-hour OGTT ≥8.5 mmol /L and/or the fasting plasma glucose ≥5.6 mmol/L.
Model summary: number of observations = 358; Prob > Chi^2 = 0.0116; Log likelihood = -87.904; Pseudo R^2 = 0.2438.
BMI, body mass index; MUAC, mid-upper arm circumference.
[a] Education up to the primary level was considered low.
[b] Weight and height were measured at ANC booking in the first trimester to assess BMI. Underweight (<18.5); normal weight (18.5-24.9); overweight (25.0-29.9) and obese (≥30)
[c] Weight was measured at each antenatal care visit. Per Institute of Medicine's recommendations on pregnancy weight gain based on BMI, a high GDM risk was considered if the woman's weight gain was above the threshold for her the BMI group. Underweight: 12.5-18.0 kg; normal weight: 11.5-16.0 kg; overweight: 7.0-11.5 kg; and obese: 5.0-9.0 kg
[d] MUAC was measured once in each trimester.
and weight was measured monthly.
[e] Glycosuria includes trace 1+ to 5+ dipstick glucose at any one time point in pregnancy.
[f] Dyslipidemia refers to total cholesterol >7.73 mmol/L, high-density lipoprotein cholesterol <1.34 mmol/L, low-density lipoprotein cholesterol >4.76 mmol/L and triglycerides >4.31 mmol/L.
[g] High caloric intake defined as excess intake of high glycemic index foods ≥5 per day on the day prior to the survey.
[h] Anemia is classified as hemoglobin <11 g/dl. Anemia severity was classified as mild (10.0-10.9 g/dl), moderate (7.0-9.9 g/dl) and severe (<7.0 g/dl)

3.4 Pregnancy Outcomes Associated with GDM

3.4.1 Maternal and Newborn Outcomes Per Glycemic Status

Records of 63 GDM cases and 340 controls were traced at birth. Maternal and newborn outcomes are presented in **Table 17** for continuous variables. Mean birth weight was 3.12 kg (SD=0.46) and was 0.26 kg higher among the cases (p=0.035). Similarly, estimated blood loss was 183.93 ml (SD=103.98) and was 50 ml higher among the women diagnosed with GDM (p=0.001). No other significant differences were observed for the other variables including birth anthropometries, gestational age at birth and newborns' blood glucose.

Table 17. T-test comparing maternal and newborn birth outcomes among cases and controls for continuous variables

Continuous outcomes	GDM present (n=63)	GDM absent (n=340)	P-value [b]
	Mean ± standard deviation	Mean ± standard deviation	
Blood loss (ml)	*228.42 ± 123.48*	*178.54 ± 105.89*	*0.010**
Gestational age at birth (weeks)	38.84 ± 2.19	38.80 ± 2.18	0.906
Birth weight (kg)	*3.23 ± 0.49*	*3.06 ± 0.45*	*0.035**
Birth length (cm)	49.59 ± 2.74	48.87 ± 3.34	0.212
Head circumference (cm)	34.38 ± 1.71	33.97 ± 2.04	0.253
Ponderal index (g/cm^3)[a]	2.70 ± 0.49	2.69 ± 0.61	0.913
Newborn glucose (mmol/L)	3.924 ± 1.31	4.74 ± 0.90	0.193

[b] Statistically significant at *p<0.05. Difference estimated by unpaired t-test
[a] Ponderal Index calculated as newborn's weight (g)/ length (cm^3) x 100

Key birth outcomes among primary and secondary facility users

Interquartile ranges for birth weight, birth length, gestational age at birth and the newborn's blood glucose among primary and secondary/referral facility users is shown in **Figure 15**. Birth length of newborns delivered in the secondary facilities (49.16±3.25 cm) were lengthier than that of newborns delivered in primary facilities (47.78±3.39 cm) (p=0.028). However, among the secondary and primary facility users, significantly differences were found for birth weight (3.11±0.47 vs 3.04±0.41 kg), gestational age at birth (38.92±2.02 vs 38.63±2.64 weeks) and newborns' blood glucose (4.09±1.30 vs 4.40±0.71 mmol/L).

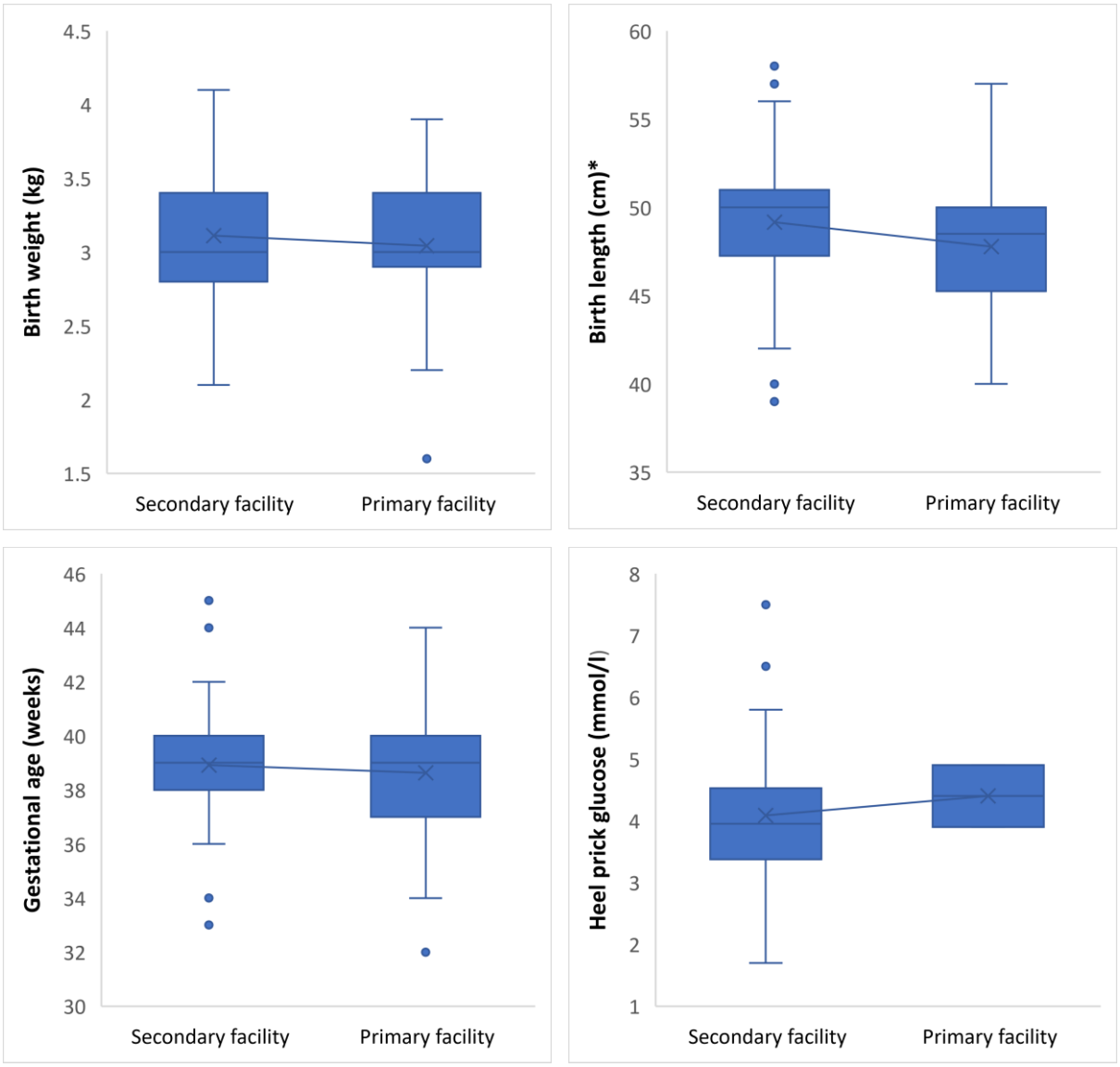

Figure 15. Comparison of birth weight, birth length, gestational age at birth and newborns blood glucose among primary and secondary facility users

*Note: *Birth length was the only variable that was statistically significantly (p=0.028)*

Categorical birth outcomes

Presented in **Table 18** are maternal and newborn outcomes for categorical variables. Deliveries of 21.5% (n=65) were by cesarean; it was 11.9% significantly higher among the cases. Although adverse outcomes tended to be higher among women diagnosed with gestational diabetes, no other significant differences were observed in the categorical variables assessed other than the cesarean section rate where the differences was very marginal (p=0.049) for the cases (31.4%) and controls (19.5%). Among the GDM group, majority (64.3%) of the cesarean section was elective.

Table 18. Chi-square test comparing maternal and newborn birth outcomes among cases and controls for categorical variables

Outcomes	Sub-categories	GDM present	GDM absent	P-value[d]
		n (%)	n (%)	
Mode of delivery	*Cesarean section*	*16 (31.4)*	*49 (19.5)*	*0.049*[*]
Type of cesarean	Emergency	5 (35.7)	25 (58.1)	0.125
	Elective	9 (64.3)	18 (41.9)	
Perineum	Intact	25 (69.4)	136 (75.2)	0.369
	Episiotomy	4 (11.2)	25 (13.8)	
	Tear	7 (19.4)	20 (11.0)	
Pre/eclampsia	Yes	7 (13.7)	22 (8.8)	0.197
Postpartum hemorrhage[a]	Yes	3 (7.9)	7 (3.3)	0.180
Prolong/obstructed labor	Yes	7 (15.6)	26 (11.1)	0.787
Sex of newborn	Male	28 (60.9)	116 (52.5)	0.332
	Female	18 (39.1)	105 (47.5)	
Birth weight	Low birth weight	2 (4.3)	17 (7.6)	0.675
	Normal	43 (91.4)	200 (89.3)	
	Macrosomia (≥4 kg)	2 (4.3)	7 (3.1)	
Gestational age at birth	Preterm <37 weeks	3 (8.1)	15 (8.7)	0.985
	Term 37-42 weeks	33 (89.2)	154 (89.0)	
	Post-term >42 weeks	1 (2.7)	4 (2.3)	
Growth for gestational age (GA)[b]	Small for GA	2 (5.4)	13 (6.2)	0.870
	Marginal	13 (35.1)	82 (38.9)	
	Large for GA	6 (16.2)	40 (19.0)	
Resuscitation	Resuscitated	15 (34.1)	60 (27.0)	0.219
Intensive care admission	Admitted	1 (2.0)	13 (5.3)	0.289
Perinatal death[c]	Died by discharge[c]	1 (2.0)	3 (1.2)	0.525

Statistically significant at *p<0.05. [a] Postpartum hemorrhage is defined as estimated blood loss >500ml. [b] Growth in relation to gestational age was estimated from Ponderal Index calculated as newborn weight (g)/ length (cm^3) expressed as a percentage and categorized as small for gestational age (<2.0), marginal (2.0-2.5), normal (2.5-3.0.) and large for gestational age (≥3.0). [c] Perinatal death includes both macerated and fresh cases

3.4.2 Adverse Pregnancy Outcomes

As observed from the simple logistic regression in **Table 19**, a unit increases in fasting plasma glucose and 2-hour OGTT were associated with a significant increase in birth weight and estimated blood loss. For every one mmol/L rise in fasting glucose, there was 0.251 kg increased in birth weight whereas for every one mmol/L rise in 2-h OGTT there was 0.562 kg increased in birth weight. Fasting glucose and 2-h OGTT values have overlap effect on birth outcome but appears to have some distinctive outcome profiles as well. For instance, for every one mmol/L rise in fasting glucose, there was an associated increase in gestational age at delivery and newborns head circumference. However, this association was observed only for fasting glucose and not 2-h OGTT.

Table 19. Simple linear regression showing the coefficients for maternal and perinatal outcomes per unit rise in fasting plasma glucose and 2-hour OGTT

Outcomes	Continuous blood glucose measurements					
	Fasting plasma glucose			2-hour OGTT values		
	Coef.	95% CI	*P- value*	Coef.	95% CI	*P- value*
Cesarean section[a]	0.185	-0.087, 0.457	0.183	0.330	-0.140, 0.801	0.168
Episiotomy[a]	-0.235	-0.601, 0.130	0.207	-0.490	-1.121, 0.140	0.127
Perineal tear[a]	0.204	-0.168, 0.575	0.281	0.143	-0.506, 0.793	0.664
Pre-eclampsia[a]	0.087	-0.193, 0.368	0.541	0.149	-0.339, 0.637	0.548
Prolong labor	0.028	-0.098, 0.155	0.660	0.077	-0.026, 0.122	0.200
Est. blood loss (ml)	*0.196*	*0.087, -0.306*	*0.001**	*0.290*	*0.010-0.482*	*0.003**
Hemoglobin (g/dl)	0.024	-0.065, 0.114	0.592	0.043	-0.105, 0.193	0.563
Gestational age (wks)	0.056	-0.004, 0.116	0.067**	0.034	-0.072, 0.140	0.529
Birth weight (kg)	*0.251*	*0.008, 0.494*	*0.043**	*0.562*	*0.141, 0.983*	*0.009**
Birth length (cm)	0.001	-0.034, 0.036	0.969	0.003	-0.059, 0.065	0.923
Head circumference	0.058	-0.001, 0.114	0.056**	0.043	-0.059, 0.147	0.405
Apgar at 5min	-0.036	-0.119, 0.064	0.558	-0.064	-0.236, 0.072	0.296
Ponderal index[b]	0.159	-0.030, 0.349	0.100	0.273	-0.060, 0.607	0.108
Newborn glucose	0.058	-0.156, 0.273	0.583	0.029	-0.420, 0.478	0.897
Resuscitation[a]	0.172	-0.081, 0.426	0.181	0.272	-0.142, 0.687	0.197
Intensive care[a]	-0.286	-.0881, 0.307	0.343	-0.734	-1.757, 0.288	0.158
Birth asphyxia[a]	0.850	-0.461, 2.163	0.203	0.457	-1.792, 2.706	0.690
Perinatal death[ac]	0.719	-0.353, 1.792	0.188	0.645	-1.193, 2.484	0.490

Statistically significant at *p<0.05 and **p<0.10. [a] These are categorical variables while the rest are continuous variables. [b]Ponderal Index derived from as fetal weight (g)/length (cm^3). [c] Perinatal death includes both macerated and fresh cases

As shown in the multivariate binary logistic regression in **Table 20** where GDM was classified as present and absent, GDM per the case definition significantly increased the likelihood for perineal tear by 2.91 times (95% CI: 1.081-5.566) whereas cesarean section was a significant outcome at the 10%-level. Regarding newborn outcomes, GDM increased the likelihood for birth asphyxia by 3.24 times (95% CI: 1.006-10.449) whereas large for gestational age (LGA) and neonatal resuscitation were associated the outcomes at the 10% significant level. Using specifically 2-h OGTT ≥8.5 mmol/L and fasting glucose ≥5.6 mmol/L as individual exposures yielded slightly varied but overlapping outcomes. For instance, 2-h OGTT ≥8.5 mmol/L was found to increase likelihood for LGA by 5.56 times (95% CI: 1.396-12.772, p=0.023) whereas cesarean section and birth asphyxia were associated outcomes at the 10% significant level. Fasting glucose ≥5.6 mmol/L increased the likelihood for perineum tear by 3.87 times (95% CI: 1.183-9.109, p=0.047) and neonatal resuscitation by 5.72 times (95% CI: 1.370-23.845, p=0.017) whereas LGA was an associated outcome at the 10% significant level (**Table 20**).

Table 20. Binary logistic regression showing the adjusted odds ratios for adverse pregnancy outcomes associated with GDM per diverse diagnostic criteria

Outcomes	Sub-categories	GDM positive per case definition [a] (n = 446)			GDM positive per NICE criteria for fasting glucose ≥5.6 mmol/L [b] (n = 446)			GDM positive per WHO criteria for 2-h OGTT ≥8.5 mmol/l [c] (n = 435)		
		RR	95% CI	P value	RR	95% CI	P value	RR	95% CI	P value
Preeclampsia	No	Ref			Ref			Ref		
	Yes	1.198	0.162-8.809	0.859	1.038	0.360-5.533	0.157	1.280	0.053-3.076	0.879
Perineum	Intact	Ref			Ref			Ref		
	Tear	*2.909*	*1.081-5.566*	*0.043**	*3.869*	*1.183-9.109*	*0.047**	1.717	0.069-7.375	0.780
Delivery mode	Vaginal	Ref			Ref			Ref		
	Cesarean	1.884	0.965-3.678	0.063**	1.244	0.007-9.058	0.445	1.490	0.829-7.227	0.098**
PPH	No	Ref			Ref			Ref		
	Yes	4.652	0.311-69.586	0.265	1.196	0.141-10.144	0.869	3.722	0.699-19.800	0.123
Birth weight	<4 kg	Ref			Ref			Ref		
	Macrosomia >4	1.914	0.489-7.484	0.350	2.175	0.432-10.941	0.346	2.809	0.552-14.290	0.213
GA at birth	37-42 weeks	Ref			Ref			Ref		
	<37 weeks	0.736	0.207-2.619	0.637	0.898	0.194-4.153	0.891	0.459	0.058-3.630	0.461
	>42 weeks	1.227	0.133-11.330	0.856	1.909	0.204-17.859	0.571	1.952	0.208-18.301	0.558
GA for growth	Normal	Ref			Ref			Ref		
	SGA[d]	0.116	0.010-1.313	0.589	0.169	0.01082.652	0.206	1.134	0.1740-7.391	0.895
	LGA[d]	2.661	0.863-5.048	0.082**	2.302	0.751-5.048	0.090**	*5.563*	*1.396-12.772*	*0.023**
Birth Asphyxia	Apgar >3	Ref			Ref			Ref		
	Apgar ≤3	*3.243*	*1.006-10.449*	*0.039**	1.618	0.321-8.131	0.495	3.192	0.792-12.868	0.062**
Resuscitation	No need	Ref			Ref			Ref		
	Resuscitated	2.906	0.937-9.011	0.065**	*5.717*	*1.370-23.845*	*0.017**	1.819	0.393-8.409	0.444
NICU admission	No need	Ref			Ref					
	Admitted	0.512	0.063-4.141	0.530	0.688	0.078-6.068	0.736	-	-	-
Perinatal death	Survived	Ref			Ref					
	Died	2.382	0.211-26.824	0.482	1.247	0.153-10.169	0.837	-	-	-

Statistically significant at *p<0.05 and **p<0.10. The blank space represents variables which were omitted from the model due to poor model fit.
GA: gestational age at birth; PPH, postpartum hemorrhage; SGA, small for gestational age; LGA, large for gestational age. Model 1 summary: N = 385; Prob > chi^2 = 0.035; Log likelihood = -51.317; Pseudo R^2 = 0.1686. Model 2 summary: N = 399; Prob > chi^2 = 0.034; Log likelihood = -28.959; Pseudo R^2 = 0.1914. Model 3 summary: N = 393; Prob > chi^2 = 0.035; Log likelihood = -23.921411; Pseudo R^2 = 0.1910. [a] GDM defined as fasting plasma glucose ≥5.6 mmol/L (National Institute for Health and Care Excellence, 2015) and/or 2-hour OGTT ≥8.5 mmol/L (World Health Organization, 2013). [b] Fasting glucose ≥5.6 mmol/L (National Institute for Health and Care Excellence, 2015) irrespective of 2-h OGTT values. [c] 2-h OGTT ≥8.5 mmol/L (World Health Organization, 2013) irrespective of fasting glucose values. [d] Small for gestational age is birth weight <10th percentile for gestational age and large for gestational age large is large birth weight >90th percentile for gestational age.

3.5 Postpartum Glycemic Status

At 12 weeks postpartum, 100 of the study participants who tested for GDM during pregnancy could be traced out of which 20 were diagnosed with GDM during pregnancy. Mean fasting plasma glucose of the GDM group in the second trimester of pregnancy was 5.70 mmol/L (SD=0.79). At 12 weeks postpartum, mean fasting plasma glucose of the GDM group had reduced by 1.3 mmol/L to 4.39 mmol/L (SD=0.83). Difference between the prenatal and postpartum fasting glucose was statistically significant (p=0.01). Out of the 20 GDM cases, 14 (70%) achieved euglycemia at 12 weeks postpartum while fasting plasma glucose of the remaining 6 (30%) of the women diagnosed with GDM was persistently above 5.6 mmol/L at 12 weeks postpartum. Presented in **Table 21** is a comparison of health indicators of woman who were euglycemic at 12 weeks postpartum and those who were persistently hyperglycemic. It was observed that the hyperglycemic women were significantly shorter in stature than the euglycemic woman while other indicators assessed were statistically similar.

Table 21. Comparison of profile of diagnosed women who had resolved and unresolved GDM at 12 weeks postpartum

Variables	**GDM unsolved 12 weeks postpartum** *(n=6)*	**GDM resolved at 12 weeks postpartum** *(n=14)*	**P-value** [a]
	Mean (SD)	Mean (SD)	
Maternal age (years)	32.67 (6.28)	32.38 (8.64)	0.944
Parity	2.50 (1.92)	1.18 (0.87)	0.082**
Gravida	4.75 (0.96)	3.45 (1.57)	0.151
Systolic blood pressure (mmHg)	129.50 (16.94)	122.69 (20.26)	0.486
Diastolic blood pressure (mmHg)	86.00 (11.88)	78.85 (14.39)	0.305
Maternal height (cm)	*153.25 (3.95)*	*159.01 (3.81)*	*0.007**
Maternal weight (kg)	73.57 (3.97)	71.09 (17.49)	0.739
MUAC[a] (cm)	33.48 (2.11)	31.40 (6.02)	0.427
Child's birthweight (kg)	3.20 (0.39)	3.20 (0.54)	>0.999

Statistically significant at *p<0.05 and **p<0.10.
[a] Difference determined by students t-test
MUAC: mid-upper arm circumference; SD: standard deviation

4 DISCUSSION

Note: The doctoral student has published some aspects of this chapter in the underlisted publications. For details, see pages 109-111.

- Prevalence of low birth weight, macrosomia and stillbirth and their relationship to associated maternal risk factors in Hohoe Municipality, Ghana http://dx.doi.org/10.1016/j.midw.2016.06.016
- Accuracy of glycosuria, random blood glucose and risk factors as selective screening tools for gestational diabetes mellitus in comparison with universal diagnosing. http://dx.doi:10.1136/bmjdrc-2017-000493
- Gestational diabetes using diverse diagnostic criteria, risk factors including dietary intakes, pregnancy outcomes and postpartum glycemic status: a nested case-control study in Ghana. https://doi.org/10.1101/582239

This study is among the few in Sub-Saharan Africa that investigated gestational diabetes, validity of screening tests and diagnostic cut-offs and used restrictive diagnostic criteria to assess prevalence, risks and pregnancy outcomes. Key findings include the following

1. Reference to 2-hour OGTT, fasting glucose had the highest diagnostic validity compared to all the screening (dipstick glycosuria, random blood glucose, glycated hemoglobin and risk factors) and diagnostic (HbA1c and 1-hour OGTT) instruments validated. Fasting glucose could be used both as a screening and diagnostic test as the screening tests were insensitive, diagnostically poor and missed majority of cases.
2. In terms of cut-off, the lower cut-off (≥5.1 mmol/L) for fasting glucose recommended by WHO had more false positives but higher discriminatory properties and is preferable for screening purposes. The higher cut-off (≥5.6 mmol/L) recommended by NICE had fewer false positives and higher disease prediction and is preferable for diagnostic purposes.
3. Depending on the diagnostic test and cut-off used, up to a quarter of participants in primary and secondary hospitals were diagnosed with GDM, similar as reported in most tertiary hospitals suggesting a rising trend in the general population.
4. The most important risk factors were excess intake of high glycemic index foods, maternal adiposity and history of perinatal death, spontaneous abortion and cesarean delivery and pre-eclampsia. This necessitates intensifying education on lifestyle modifications throughout the reproductive life cycle and improving obstetric care.
5. Key maternal outcomes were perineal trauma and postpartum hemorrhage whereas the key neonatal outcomes were fetal macrosomia, birth asphyxia and resuscitation Regarding post-delivery glycemia, a third of GDM cases remained hyperglycemic at 12 weeks postpartum calling for a structured postpartum monitoring of all GDM cases.

This chapter is organized according to the key findings and closes with a reflection on the global perspectives, limitations of the study and implications of findings for health systems in low income settings.

4.1 GDM Screening and Diagnosis and the Cut-offs

Over the years, there have been exhaustive and heated debates about whether screening of pregnant women for GDM is needed, whether only clinical risk factors should be used, whether all pregnant women be screened (universal screening) with OGTT directly and whether fasting plasma glucose and HbA1c should be considered as alternate screening methods (Agarwal, 2018). Short- and long-term adverse effects of gestational hyperglycemia are well documented (Metzger et al., 2008, Wendland et al., 2012, Damm et al., 2016). Prevention and management start with timely and accurate diagnosing. Aside clinical risk factors evaluated through history taking and physical assessment, dipstick glycosuria and random glucose are used for screening purposes particularly in resource-constraint settings and serve as basis for diagnostic testing (National Institute for Health and Care Excellence, 2015).

It is crucial that these screening tests are diagnostically valid, have clinically useful cut-offs, adequately sensitive (at least 70%) to rule out GDM and be specific enough for disease confirmation after a positive screening (Glas et al., 2003). Not only is the ideal method for screening of GDM not established or agreed upon, the evidence to make decision on the benefits and harms of screening for GDM is insufficient and therefore not justified (Agarwal, 2018, Hod et al., 2015). The IADPSG recommends using OGTT both for screening and diagnosis of GDM (IADPSG Consensus Panel, 2010). However, this would be a ‘wide goose chase’ in low resource settings.

4.1.1 Dipstick Glycosuria

Like in most low- and middle-income healthcare settings, dipstick glycosuria testing is a routine ANC practice in Ghana and diagnostic decision is made based on its outcome. The NICE recommends glycosuria of ≥1+ on more than one occasion or ≥2+ on one occasion as indication to conduct the ‘one-step’ 2-h OGTT (National Institute for Health and Care Excellence, 2015). In Ghana, glycosuria values of 1+/2+ on two occasions or 3+/4+ on one occasion are indication for OGTT (Ghana Ministry of Health, 2010). In this study, women with glycosuria of 1+ and above at any one point during pregnancy was less than one percent. Only 3% of clients had positive glycosuria and the test sensitivity was below 5%. With the prevalence of GDM based on the 2-h OGTT and fasting glucose being much higher, it is not surprising that NICE recommends a re-evaluation of use of glycosuria in pregnancy (National

Institute for Health and Care Excellence, 2015) while others have discredited its continued use (Alto, 2005, Hanna and Peters, 2002).

It is established that during pregnancy, renal glucose threshold is highly variable. Reduction in glycemic thresholds is needed for GDM diagnosis (Hanna and Peters, 2002) but there is possibility of hyperglycemia without detectable glycosuria (Cersosimo et al., 1997). Diagnostic decision for GDM should not rely on dipstick glycosuria as it is diagnostically poor. But often, glycosuria and proteinuria are checked simultaneously using a single test strip and provides vital basis for detecting pre-eclampsia as well. The test is cost-effective despite its associated limitations. Universal screening is recommended using fasting or OGTT. However, in primary healthcare settings where glycosuria testing is predominant, clients with trace results should be closely monitored and booked for diagnostic testing if trace result is obtained on more than one occasion.

4.1.2 Random Blood Glucose

Although diagnostic accuracy of random glucose was poor, it was better than glycosuria and HbA1c. Interestingly, mean random glucose was only 0.3 mmol/L-point higher than mean fasting glucose. In our study setting, care seekers typically attend healthcare facilities in fasting state in anticipation of service providers unexpectedly requesting a biochemical test that might require overnight fasting. Also, long waiting times and high clientele turn-out often compel clients to skip breakfast or eat meals typically smaller than usual in order to arrive early at the hospital and thus minimize delays. Meanwhile, the effect of pregnancy-related physiological changes altering dietary patterns and preferences cannot be ruled out (Moya et al., 2014), likewise the cultural practices which cause some pregnant women to over-indulge in food during pregnancy. No wonder the highest sensitivity and specificity for random glucose was at the 5.2 mmol/L threshold.

Random glucose using capillary finger prick checked on the spot using a glucose meter is not only cheap but can be done by low cadre health workers with minimum training in remote areas. This therefore makes it the test of choice in primary healthcare care settings where laboratory facilities are often unavailable. However, none of the health regulating bodies have established a diagnostic threshold for this test although the NICE recommends RBG >7.0 mmol/L as indication for OGTT while the WHO/IADPSG recommends >11.1 mmol/L as diagnostic criteria for pre-existing (overt) diabetes. This >11.1 mmol/L cut-off would have yielded only one positive case in this study. Due to non-consensus on diagnostic threshold

for random glucose and the fact that the test is not sufficiently sensitive to detect GDM, effectiveness of RBG needs to be further explored with emphasis on the reference threshold and optimum postprandial conditions under which the test would be most accurate. Considering difficulty faced by pregnant women in adhering to overnight fasting regulations (Hod et al., 2015), postprandial conditions like effect of the last meal time prior to testing, type and quantity of the meal on the random glycemic levels might be worth investigating.

4.1.3 Clinical Risk Factors as a Screening Tool

Even though the increasing prevalence has been attributed to increasing diabetes in the general population (Cho et al., 2018), maternal risk factors particular age, obesity, ethnicity, family history of type II diabetes and previous GDM miscarriages, stillbirths, fetal malformations, preeclampsia, and macrosomia, are increasingly becoming a significant predictor for GDM (Damm et al., 2016, Anand et al., 2017). These risk profile vary widely from one study to another. A third of the pregnant women in this study had at least one risk factor for GDM. In a similar study in South Africa, almost half (45.8%) had at least one risk factor and only 26.0% of those ‘at risk’ developed GDM compared to 54.3% in our study (Adam and Rheeder, 2017). Presence of clinical risk factors was a better screening tool for GDM compared to glycosuria and random glucose because whereas risk factors missed approximately half of the true positive rate, glycosuria and random glucose missed approximately 90%. Risk factors had higher sensitivity (54%) compared to glycosuria (5%) and random glucose (13%) but had the least (73%) specificity compared to all the other tests which had over 90% specificity.

A third (Agbozo et al., 2018) to half (Hod et al., 2015) of women diagnosed with GDM have one or more risk factors but some asymptomatic women develop GDM thus making diagnostic decision based on risk could miss half of all cases. The ideal method to screen GDM is debatable (Agarwal, 2018). Even though meta-analysis suggests that women with prior GDM have 17.92-fold adjusted risk for GDM in subsequent pregnancies (Song et al., 2018), use of risk factors do not identify women with GDM well as the high sensitivity of diverse risk factor combinations results in low specificities (Farrar et al., 2017). This supports universal screening where all pregnant women are tested using a recommended diagnostic criterion instead of selective screening via risk factors and other screening methods. However, universal screening requires health-system preparedness to screen all pregnant women and to

manage the 10-25% who might need some additional non-pharmacological and/or pharmacological support.

4.1.4 Glycated Hemoglobin

Glycated hemoglobin test had the highest number of false negative, least diagnostic odds ratio and the test performance was diagnostically invaluable. As pregnancy progresses, HbA1c levels decreases (Moya et al., 2014) as a result of factors such as increased red cell turnover, hemoglobin variations and iron deficiency anemia (Narayan and Pettitt, 1996) which is known to be a major public health problem affecting almost half of all pregnant women globally (WHO, 2015). Isolated use of HbA1c as a screening test has been shown to miss a significant number of GDM cases (Hanna et al., 2017). Nonetheless, HbA1c values provide useful information about glycemic control in the preceding three months. Like this present study were HbA1c coordinates of 5.0% was the most clinically useful sensitivity and specificity, 5.05% cut-off was found to be good to rule out women who did not have GDM (Kwon et al., 2015). Values >6.5% at first prenatal care visit are suggestive of overt diabetes (National Institute for Health and Care Excellence, 2015). However, in deprived populations where over 90% of pregnant women are unaware of their pre-pregnancy glycemic status and half make their first ANC visit after the first trimester, it is difficult to delineate pre-existing hyperglycemia from pregnancy-induced diabetes. Considering the limited availability of HbA1c testing in many primary and secondary facilities, the high cost of the test (approximately 15 Dollar equivalent in Ghana), the lack of correlation between HbA1c and average blood glucose due to gestational metabolic alterations (Berggren et al., 2017) and the risk of missing GDM patients and wrongly labeling women as having GDM (Ye et al., 2016), use of HbA1c as a routine GDM detection tool in resource-constraint settings is non-beneficial at the population level.

4.1.5 Oral Glucose Tolerance Test

Ironically, there is no contention on the fact that the OGTT remains the cornerstone for diagnosis of GDM and one abnormal plasma glucose value is sufficient to make a diagnosis (Hod et al., 2015, National Institute for Health and Care Excellence, 2015, IADPSG Consensus Panel, 2010, World Health Organization, 2013). However, use of 2-h OGTT as the ‘gold standard’ test is supported by some health regulatory bodies (National Institute for

Health and Care Excellence, 2015) while others focuse on prognostic accuracy rather than diagnostic accuracy and do not endorse any gold standard test per se (World Health Organization, 2013). Meanwhile, there are wide variations in cut-off values needed in making a diagnosis of GDM ranging from 7.8 mmol/L (National Institute for Health and Care Excellence, 2015), 8.5 mmol/L (World Health Organization, 2013, IADPSG Consensus Panel, 2010, American Diabetes Association, 2013), 8.6 mmol/L (ACOG Practice Bulletin, 2018) to 9.0 mmol/L (Diabetes Canada Clinical Practice Guidelines Expert Committee, 2018b). Also, there are disagreements regarding the diagnostic approach, that is, whether one-step screening using 75-g glucose (IADPSG Consensus Panel, 2010, World Health Organization, 2013, National Institute for Health and Care Excellence, 2015) or two-step screening using 50-g glucose challenge test, followed, if abnormal, with a 75-g OGTT (Diabetes Canada Clinical Practice Guidelines Expert Committee, 2018b). Regarding when postprandial glucose should be measured, although many advisory bodies recommend 2-hour OGTT, a few recommend 3-h OGTT (ACOG Practice Bulletin, 2018). Most guidelines recommend the timing for testing to be restricted to early pregnancy (24–28 weeks). Although the WHO recommends this timing, the guideline is flexible on the timing of the test during pregnancy (World Health Organization, 2013). More recently, there are considerations to perform OGTT in a non-fasting state (Hod et al., 2015).

Interesting some regulatory bodies have lower thresholds for fasting glucose and higher thresholds for 2-h OGTT and vice versa. For instance, the NICE cut-off for fasting glucose is 5.6 mmol/L but that for 2-h OGTT is 7.8 mmol/L whereas the WHO cut-off for fasting glucose is 5.1 mmol/L but that for 2-h OGTT is 8.5 mmol/L. Amid the controversies and chaos surrounding aspects of GDM screening despite five decades of research on GDM, what is clear for health systems in low income settings is the need for simplicity and flexibility in GDM testing. Ghana for example is battling with budgetary constraints to the health sector and lack of political will to invest into healthcare; inequities in the human resource, infrastructure and equipment allocation across different levels of healthcare delivery in rural and urban areas; and socio-cultural practices, economic and geographic constraints that affect health seeking behaviors, thus the need for a simple and flexible test cannot be overemphasized. Simple, flexible and less expensive GDM test approaches will facilitate compliance by clients and motivate health insurances providers to make payments.

The OGTT is poorly reproducible, expensive, requires preparation, not physiologic, ethnicity-dependent, given without consideration to body weight, unpleasant, causes nausea and

vomiting in pregnant women and compliance with follow-up appointments for testing is poor (Cundy et al., 2014, Agarwal, 2018, Utz et al., 2018, Njete et al., 2018). Besides, making a GDM diagnosis without providing management alternatives is unethical and as good as no diagnostic testing at all. Hence, as used in this present study for GDM case definition, higher restrictive cut-off for OGTT is recommended to be used to make GDM diagnosis and most importantly, to commence pharmacological management in low income settings. This study demonstrates that higher cut-offs limit false positives, better predicts GDM and classifies fewer women with the condition which can be managed by weaker health systems thereby addressing the concern of GDM been touted as one of the diseases discovered due to medicalization of obstetric care (Agarwal, 2018, Cundy et al., 2014, Twohig et al., 2018, Naaktgeboren et al., 2018). Going forward, studies are needed in low income resource settings to identify cut-offs that are based on mean glucose values at which odds of adverse pregnancy outcomes reach 1.75 times (IADPSG Consensus Panel, 2010) and that can form the basis to diagnose GDM.

4.1.6 Fasting Plasma Glucose

Unlike OGTT, use of fasting plasma glucose as a diagnostic test for GDM is not touted with so much controversies and chaos by advisory bodies. The test preparations are much simpler to accomplish by clients and can be done in many more health settings worldwide. However, there are varied diagnostic cut-offs needed to make a diagnosis of GDM ranging from 5.1 mmol/L (World Health Organization, 2013, IADPSG Consensus Panel, 2010, American Diabetes Association, 2013), 5.3 mmol/L (Diabetes Canada Clinical Practice Guidelines Expert Committee, 2018b), 5.6 mmol/L (National Institute for Health and Care Excellence, 2015) to 5.8 mmol/L (ACOG Practice Bulletin, 2018). Fasting glucose is not a first-line diagnostic test for GDM although an abnormal value can be used to make a diagnosis irrespective of OGTT outcomes (World Health Organization, 2013, IADPSG Consensus Panel, 2010, American Diabetes Association, 2013). In recent times, there are suggestions to consider fasting plasma glucose as alternate screening method (Agarwal, 2018). In this present study, fasting plasma glucose was found to have the highest true positive rate and the test performance was very good thereby making it a useful test for ruling out GDM and minimizing missed cases. The test has an added advantage of being readily available, easy to perform, relatively inexpensive and requiring minimal client preparation. It has a better diagnostic property thereby making it applicable for use as both a GDM screening and a diagnostic test.

When assessing diagnostic accuracy, tests with high discriminatory measures are helpful for screening and making health policy decisions whereas tests with highly predictive measures are useful for predicting probability of disease progression at the individual level in order to facilitate client-centered case management (Raslich et al., 2007). In the US, fasting glucose reduced 7% missed cases when used as a screening tool (Herrera et al., 2015). Similarly, in South Africa, use of lower cut-off for fasting glucose (≥5.1 mmol/L) mis-diagnosed 54% of pregnant women but was reduced to 31% when the NICE cut-off was used (≥5.6 mmol/L) (Adam and Rheeder, 2017).

In was noted in this present study that the higher cut-off (≥5.6 mmol/L) recommended by NICE had fewer false positives and higher predictive properties making it the test and cut-off option for predicting the probability of an individual developing GDM and making a GDM diagnosis. As advocacy increases to adhere to the universal screening approach of testing all pregnant women for GDM, screening tests will become obsolete. However, in situations where selective screening is preferred or the only feasible alternative, the lower cut-off (≥5.1 mmol/L) recommended by the WHO which was found to be the most sensitive and had higher discriminatory properties could be used even though this cut-off over-diagnosed due to the high number of false positives detected. This lower cut-off is preferred if prevention of missed cases is the focus; screen-positive cases detected can then proceed to do OGTT.

4.2 What are the Key Drivers of GDM in Low-Income Settings?

4.2.1 Obesity Associated with Excess Caloric Intake

Despite the diverse risk profiles observed in this study, adiposity and excess intake of high glycemic index (GI) foods are striking. Changes in lifestyle have contributed to the increasing risk of obesity. Maternal diets were monotonous and energy-dense resulting in over one-third neither meeting the minimum dietary diversity indicator or eating healthily. Excess energy that is not expended is stored as fat leading to adiposity. Obesity is associated with an increased likelihood of GDM and a meta-analysis shows an increasing cumulative incidence of type II diabetes from 2.1% to 35.7% within 5.5 months to 15 years of follow-up after the index pregnancy complicated by GDM (Zhu and Zhang, 2016). High carbohydrate intake has been associated with GDM in South Africa where pregnant women believe that controlling for sugar and sweetener cravings during pregnancy is difficult to achieve (Krige et al., 2018). Concentrating efforts at addressing modifiable risk factors is central to the prevention and management of GDM (Utz et al., 2018). Intensifying education on lifestyle modifications

focusing on reduced intake of high GI foods, lower pregnancy weight gain in obese women and monitoring and intervening to ensure optimum glycemic control are crucial (Hod et al., 2015). Midwives at the forefront of ANC care need training on approaches to engage pregnant women in order to give family-centered nutrition counseling that is acceptable and fits the socio-cultural context. Also, capacity of other frontier health workers needs to be enhanced to provide tailored dietary counselling considering socioeconomic status, food security including availability, food preferences, processing, cooking and storage methods. Owing to obesity being associated with higher risk for GDM, it is crucial not to fuel the obesity epidemic by promoting healthy diversified intakes while limiting excess energy intake during pregnancy. Further studies are needed to identify locally available carbohydrate-based food sources that have low glycemic index.

4.2.2 Poor Access to Healthcare Leading to Bad Obstetric History

Most studies on GDM in Africa are conducted in urban tertiary hospitals where prevalence is expectedly high. Interestingly, similar prevalence was noticed among secondary and primary facility users in this study who are peri-urban and rural dwellers. This could be explained in the context of rural dwellers having more children compared to urban dwellers (Ghana Statistical Service, 2013) culminating in longer childbearing years and advance age at childbirth. In settings where fertility and abortion rates are high, reducing childbearing especially in older women is crucial. Also, primary healthcare users often have lower education and are more unlikely to afford healthcare. Adhering to treatment regimen and making healthy dietary choices could also be problematic. Besides, primary facilities are limited to receiving basic Emergency Obstetric and Newborn Care (EmONC) services that often excludes emergency services like removal of retained products, neonatal resuscitation, blood transfusion and cesarean section. Traveling longer distances for emergency EmONC increases risks for complications and bad obstetric outcomes. But undoubtfully, the nutrition transition poses risk for urban dwellers (Cho et al., 2018, Mwanri et al., 2014, Hod et al., 2015) who are significantly more obese (4.3% vs 13.5%), have higher triglycerides (35.0% vs 64.4%) (Agbozo et al., 2018) and double odds for obesity (Oppong et al., 2015, Njete et al., 2018). Bridging access to healthcare and improving equity at all levels could be central to reducing the GDM surge.

4.3 What are the Effects of GDM?

4.3.1 Compromised Perinatal Survival

Despite the diverse factors that are associated with increased risk for GDM, its effects on maternal and fetal outcomes are inconsistent (Metzger et al., 2008, Wendland et al., 2012). It was observed that a unit rise in glucose significantly increased birth weight and blood loss whereas hyperglycemia in pregnancy was associated with perineal tear, large-for-gestational age and birth asphyxia. In many low-resource settings postpartum hemorrhage and birth asphyxia are common causes of maternal and neonatal deaths respectively. With 85% of annual global deliveries occurring in low- and middle-income countries coupled with the surge in GDM, efforts at reducing near-miss events and maternal mortality especially in weak health systems could be derailed if GDM detection, management and follow-up efforts are not intensified. Few studies in Africa have assessed the effect of GDM on pregnancy outcomes. In Morocco for instance, larger birth weight was the only significant effect (Utz et al., 2018). Macrosomic babies have two-fold odds for cesarean birth and stillbirth in Ghana (Agbozo et al., 2016). Women who deliver macrosomic babies per vaginal have higher risk for prolonged labour, perineal tear and shoulder dystocia (Wendland et al., 2012, O'Sullivan et al., 2011, Metzger et al., 2008). The newborns whose lungs are not fully developed, are often hypoxic and require resuscitation and admission to NICU to establish extra-uterine breathing (Agbozo et al., 2016). In primary facilities where emergency obstetric and neonatal services are unavailable, perinatal death becomes inevitable.

4.3.2 Fetal Macrosomia Leading to Labour Complications

Fetal adiposity particularly macrosomia and large for gestational age are pregnancy outcomes associated with increased risk of adverse maternal and perinatal outcomes (Wendland et al., 2012). Vaginal delivery of macrosomic babies increases risk for prolong/obstructed labour, perineal trauma and postpartum hemorrhage. Yet, unlike low birth weight, little attention is paid to macrosomic births in most developing countries. Prevalence of macrosomia in developed countries is between 5% and 20% although an increase of 15%-25% has been reported in the past decades. This is driven by an increase of maternal obesity and diabetes (Henriksen T., 2008). In developing countries however, data on the changing prevalence of macrosomia are rare. Macrosomia could lead to complicated delivery and is linked to obesity in later life. This can pose additional threat to mother-newborn pairs especially in resource-

limited settings such as Ghana because of the challenges associated with emergency obstetric and other essential care. Until recently, there was no data on the overall prevalence of macrosomia in Ghana. A cross-sectional survey on macrosomic births in Northern Ghana identified a prevalence of 10.5% (Abubakari et al., 2015). The prevalence of macrosomia in the secondary data analyzed was low (3.03%) (Agbozo et al., 2016), similar as the 3.3% macrosomic births recorded in among the pregnant cohort empathizing the low rates of macrosomia in the study area. Considering that 16% GDM prevalence was found in this study, if macrosomia was to be used as a proxy for GDM, GDM would have been underestimated by over 10%.

4.3.3 Progression to Type II Diabetes

Significant associations have been found between fasting and post-prandial glucose levels during pregnancy and future risk of diabetes. Uncontrolled GDM is known to increase short- and long-term cardio-metabolic risk especially for type 2 diabetes (Eades et al., 2015, Kampmann et al., 2015, Hod et al., 2015). A third of the GDM cases in this study were persistently hyperglycemic at 12 weeks postpartum. If lower cut-off criteria, say fasting glucose ≥5.1 mmol/L was used, over half of the women would still be hyperglycemic at 12 weeks postpartum. In Morocco where nutritional counselling and pharmacology intervention were given, 93.2% attained glycemic control (Utz et al., 2018) but at 8 weeks postpartum, 50% of the intervention group had fasting glucose values indicative of type 2 diabetes (Utz et al., 2018). A 2.6-70% cumulative incidence of diabetes has been observed after following-up on diagnosed with GDM women from 6 weeks to 28 years post-gravidity (Kim et al., 2002). In a Scottish study, quarter of GDM women progressed to diabetes from 4 months to 16 years after GDM diagnosis (Eades et al., 2015).

Evidence shows an increasing risk for type II diabetes with increasing post-gravidity follow-up period. Risk of developing diabetes among women diagnosed with GDM was 6.9% at 5 years and increased to 21.1% at 10 years following the initial GDM diagnosis (Sivaraman et al., 2013). This implies that the 30% of women who were hyperglycemic at 12 weeks postpartum in this present study could increase if the no control measures are provided. This situation is worrying and necessitates proper transition of the continuum of care from obstetricians and midwives to cadres of health professional who are versatile with diabetes care after the routine postpartum phase ends. By so doing, mother-offspring pairs who experience diabetogenic conditions during pregnancy would be handed over to an appropriate

care provider to be monitored and supported to avert long-term complications. Risk of diabetes following GDM is not found to be associated with maternal age, gestational age at diagnosis, and numbers of previous and subsequent pregnancies (Sivaraman et al., 2013). Other than maternal height, no significant associated risks were found in this present study. However, this is a novel finding worth further research to determine the effect of low maternal stature on risk for diabetes following diagnosis of GDM.

4.4 How Does Findings Relate to the Burden of GDM Globally?

It was observed in this cohort study that prevalence of GDM according to 2-h OGTT was 9.0%, and was similar to the 9.3% recorded in a tertiary facility in Ghana in 2015 (Oppong et al., 2015). However, overall, findings show a GDM prevalence of 15.9% when test results from 2-h OGTT and fasting glucose were combined using restrictive higher diagnostic cut-offs for both tests. Generally, glycemic values of primary healthcare users tended to be higher, which could be an indication of poor access to healthcare and non-adherence to test preparations like overnight fasting. Evidence shows an increasing burden of GDM globally with majority of cases occurring in low- and middle-income countries (Cho et al., 2018). GDM prevalence in Africa is relatively lower (9.5%), but investments into diabetes healthcare is not commensurate with the current rising trends (Cho et al., 2018).

Lower prevalence has been reported in African countries including South African (9.1%) (Macaulay et al., 2018) and Nigeria (8.6%) (Olagbuji et al., 2015) compared with developed regions like North America (12%) and Europe (14%) (Cho et al., 2018). But Africa is catching-up fast as pockets of high cases have recently been reported in Tanzania (19.5%) (Njete et al., 2018), South Africa (25.8%) (Adam and Rheeder, 2017) and Morocco (23.7%) (Utz et al., 2018). However, diverse algorithms for testing and diagnosing pose challenges in comparing prevalence, risks, treatment effects, pregnancy outcomes, and harmonizing clinical practice (Agarwal, 2018).

Comparing a study conducted in South Africa to this present GDM, prevalence based on the fasting glucose per WHO guideline ≥5.1 mmol/L was similar (26% vs 24%), prevalence per the NICE guideline ≥5.6 mmol/L was slightly different (17% vs 11%) whereas using the 1999 WHO guideline (fasting glucose ≥7.0 mmol/L) yielded much lower prevalence (7% vs 3%) (Adam and Rheeder, 2017). In Tanzania, large variation was found between GDM prevalence per fasting glucose (18.3%) and 2-h OGTT (4.3%) (Njete et al., 2018). Whether this is a

situation of over or underdiagnosing is uncertain but certainly calls for harmonization of diagnostic tests and cut-offs globally. Irrespective of the test modalities, there is an obvious trend of a rising prevalence of GDM in line with the epidemiological and nutrition transition. The implications might be detrimental for primary health systems in rural communities and low-income settings if such facilities are not resourced with health professionals and equipment to enhance screening, testing and management of cases or clear algorithms instituted for referral.

4.5 Limitations and Strengths of the Study

There are some limitations with this study worth highlighting. Although HbA1c was performed in the fasting state (n=445), few non-fasting pregnant women (n=35) were included. Nonetheless prandial state has been shown not to affect HbA1c levels. Whereas random blood glucose was checked using capillary finger prick before 20 gestational weeks, fasting plasma glucose was checked from venous blood from 20-34 weeks. Variability in sampling collection procedures and testing times poses a challenge when equating these two glucose values. Because pregnant women also receive antenatal care in primary facilities where laboratory services could be unavailable, accuracy of point-of-care testing using fasting whole blood glucose obtained from a capillary finger prick should have been investigated as well.

In determining BMI, first trimester weight was used instead of pre-pregnancy weight as that was the only possibility. But in the first trimester, substantial weight changes are not expected (Institute of Medicine, 2009). MUAC was useful in assessing maternal adiposity as a GDM risk and could be used when pregnancy is advanced, and BMI is no longer useful. As a result of the global non-consensus on diagnostic thresholds for GDM, (Agarwal, 2018, Hod et al., 2015), the study team restricted to using higher thresholds for 2-h OGTT (IADPSG/WHO: ≥8.5 mmol/L) and fasting glucose (NICE: ≥5.6 mmol/L (Metzger et al., 2010a, World Health Organization, 2013) as the case definition. Higher diagnostic cut-offs are known to have higher sensitivity, better disease prediction (Agbozo et al., 2018) better within-patient correlation (Metzger et al., 2008) and less likelihood for overdiagnosis (Cundy et al., 2014). Slightly different estimates could have been obtained if other diagnostic thresholds were used. The call for countries to develop national guidelines for screening and diagnosis considering resource availability (Hod et al., 2015) could facilitate context-specific diagnoses and care.

A key challenge in GDM testing is the 'no show' syndrome. While 23% of the pregnant women booked for GDM testing in Tanzania failed to attend their appointments (Njete et al., 2018), 45% was observed in this present study. However, this did not affect the estimates as 50% attribution was accounted for in the design. Establishing postpartum contact with participants was difficult due to poor house addresses and relocations out of the study area. Out of the 70 GDM cases, only 20 (representing 28.6%) could be traced at 12 weeks postpartum. Hence the postpartum hyperglycemic estimates need to be interpreted in the context of the study population and cautiously generalized.

Having observed elevated fasting glucose among participants less than 20 years, and the underweight group, poor adherence to fasting requirements cannot be rule-out. The Indian strategy of performing 2-h OGTT irrespective of fasting state (Hod et al., 2015) could be considered in settings where adherence to overnight fasting and antenatal schedules are problematic. Encouraging partner support could improve diagnostic outcomes as higher partner education was found to reduce GDM risk significantly.

Routine delivery data recorded by health professionals was used for the initial secondary data analysis. Therefore, measurements errors including inappropriate measurements, readings or recordings of parameters such as birth weight and other indices were likely to occur. However, the effect of these errors was random and unlikely to affect the results due to the large sample size used (n=4,262). Also, association of gestational age at birth on pregnancy outcomes could not be assessed because this information was unavailable in the secondary records reviewed.

Despite these limitations, unlike in most diagnostic accuracy studies where retrospective data sources were used, our study was conducted prospectively using the blind comparison to a gold standard design, a type of randomized controlled trial design that compares accuracy of diagnostic procedures in the same individual. This design increases probability of the test outcomes being close to the true values. In low- and middle-income countries, studies of this nature are mostly concentrated in tertiary hospitals. Our study shows higher glycemic values among primary healthcare users. This provides evidence of obstetric transition even in rural communities and highlights the need to enhance access to quality maternal healthcare at primary healthcare levels. A key strength is the follow-up to assess short-term birth outcomes and glycemic status. As previous obstetric outcomes of the multiparous women were extracted from the ANC booklet, recall biases were minimized.

Dietary data was collected using the food frequency questionnaire which was validated against the 24-hour recall method generating information on both current and habitual food habits. Assessing anthropometry by BMI, mid-upper arm circumference and pregnancy weight change provided alternatives of monitoring adiposity and nutritional status as pregnancy progressed. Study participants were recruited from primary, secondary and referral facilitates providing overview of the disease burden in peri-urban and rural populations. Unlike in similar epidemiological studies where retrospective data are used, data was collected prospectively allowing the ease to explore the role of diverse and interesting risk factors. The main strength of the secondary data analysis was the large sample size of over 4,200 delivery records used.

4.6 Clinical, Public Health and Policy Implications of Findings

Fasting glucose had the highest diagnostic validity. None of the screening tests was clinically useful thus making selective screening diagnostically non-beneficial. In settings where screening is the first step to diagnostic testing, fasting plasma glucose should be used both as a screening and a diagnostic test. Lower diagnostic cut-offs should be used to detect screen-positive cases whereas higher cut-off should be used to make a GDM diagnosis. Prevalence of GDM ranged from 5-27% depending on the diagnostic test and cut-off used. Main adverse birth outcomes were perineal tear and birth asphyxia. A third of the sample were unable to achieve euglycemia at 12 weeks postpartum. Findings highlight the need for timely universal testing, integration of diagnostic testing into routine antenatal care at all levels of healthcare and monitoring of blood glucose after routine postpartum care ends.

4.6.1 Commence Pharmacological Treatment if Fasting Glucose ≥5.6 mmol/L

Even though the WHO (World Health Organization, 2013), IADPSG (Metzger et al., 2010a), and NICE (National Institute for Health and Care Excellence, 2015) have recommended fasting glucose as a diagnostic test for GDM, the preferred test is the ‘gold standard’ 2-h OGTT. Criteria for diagnosing diabetes in pregnancy based on the 1-h post-load value have not been fully established (World Health Organization, 2013) and this study has shown that this test has a low sensitivity (<50%). Therefore, in settings where 2-h postprandial glucose-load testing is unavailable or difficult to obtain for confirmation of diagnosis, GDM diagnosis and decision to commence pharmacological treatment should be established based on pre-

prandial glucose values ≥5.6 mmol/L as substitute for an OGTT due to the high predictive properties of this cut-off. This could be complemented with presence of maternal risk factors which, although has least specificity, has a higher sensitivity than most of the tests assessed and collectively, serve as basis to commence treatment. The lower cut-off (≥5.1 mmol/L) for fasting glucose has high discriminatory properties and is therefore useful for screening purposes. This cut-off could be used as basis to initiate non-pharmacological management such as dietary counseling, exercise programmes and pregnancy weight control.

4.6.2 Integrate Fasting Glucose Monitoring into All GDM Screening Procedures

Because fasting plasma glucose was the most sensitive test with minimal false negatives diagnoses, its integration into all GDM detection procedures through universal testing of all pregnant women is recommended as the test is much more readily available, less expensive, the procedure is less cumbersome and therefore easier to accomplish for many women compared to OGTT. At the population level, the WHO diagnostic criteria ≥5.1 mmol/L could be useful for screening purposes because of its discriminatory properties, which is key for making health policy decisions. At the individual level, the NICE diagnostic criteria ≥5.6 mmol/L which has higher GDM prediction properties could be useful for making diagnostic and therapeutic decision.

4.6.3 Apply Universal Screening – Test All Pregnant Women

In the wake of updated guidelines for detecting hyperglycemia in pregnancy whereby diagnostic thresholds have reduced (World Health Organization, 2013, National Institute for Health and Care Excellence, 2015, Metzger et al., 2010a, American Diabetes Association, 2015), there are widespread concerns about over-diagnosing and the associated implications particularly for fragile health systems. In as much as over-diagnoses (false positive) will increase costs, under-diagnoses (false negative) have adverse public health implications. Selective screening using risk factors is better when compared with glycosuria and random blood glucose because these tests missed majority of cases thereby decreasing opportunities for diagnostic testing. However, selective screening using risk factors also missed over half of all GDM positive women who could otherwise have missed the chance to be tested and subsequently managed. Universal screening is the only strategy by which majority of women with GDM will be diagnosed. Hence all pregnant women should be tested for GDM irrespective of the risk profile or obstetric history. GDM prevalence in Ghana might increase

substantially by virtue of using the universal screening approach. To minimize the impact that the surge in prevalence could have on the health system in Ghana, there is need to develop screening algorithms specific to the Ghanaian context and to establish diagnostic cut-offs that would balance obstetric and long-term health risks and benefits unique to socioeconomic and clinical context.

4.6.4 Strengthen Primary Healthcare Systems to Screen and Diagnose GDM

Gestational diabetes is common in the study population. Prevalence ranged from 5-27% depending on the test and diagnostic criteria. But prevalence based on 2-h OGTT was 9.0%, same as the 9.3% observed in the largest tertiary hospital in Ghana indicating an increase even in peri-urban and rural communities. Prevalence was high among primary healthcare users who often have poor access to healthcare. Evidence of increasing prevalence of pregnancy-triggered diabetes from negligible rates to almost 30% in certain settings in African (Macaulay et al., 2014, Hall et al., 2011, Adam and Rheeder, 2017) necessitate a critical review of diagnostic strategies by health systems if adverse outcomes such as newborn macrosomia, hypoglycemia, hyperinsulinemia, respiratory distress, perinatal mortality, maternal pre-eclampsia, caesarean delivery (Metzger et al., 2008) and risk for long-term metabolic conditions (Damm et al., 2016) are to be reduced. This highlights the need to tackle rural-urban inequities in access to healthcare by equipping primary facilities with basic amenities to test, provide non-pharmacological management and refer non-responsive cases. While this study supports testing all pregnant women using fasting plasma followed by 2-hour OGTT if available, consensus is needed on the diagnostic criteria which could be applicable for health systems in low resource settings who are the least prepared to handle implications of the surge in GDM prevalence.

4.6.5 Tackle Modifiable Risks and Monitor GDM Women beyond Postpartum

The manifold risk factors identified necessitate a wide range of holistic and integrated facility and community-based interventions. Concentrating on the modifiable risks through interventions that focus on lifestyle modification is crucial. Nutrition education tailored towards moderate intake of high glycemic index foods and dietary diversification, glycemic control and weight management in overweight/obese women is crucial. Owing to multiple

micronutrients derived from diversified diets, investing efforts into dietary diversification might be more sustainable at improving dietary intakes across the pregnancy continuum.

4.6.6 Monitor all GDM Women After Routine Postpartum Care Ends

Access to adequate and comprehensive Emergency Obstetric and Newborn Care and prompt referral is important to reduce adverse maternal and fetal complications during birth. To avert long-term metabolic effects, there should be transition of care when the routine postpartum phase ends to ensure follow-up and monitoring of glycemic control among women who experience gestational diabetes. Referral to community health nurses and general practitioners is recommended. Where possible, GDM-affected women can be educated to do self-glycemic monitoring at home. Where possible, mother-to-mother peer support, community-based and telemedicine monitoring strategies could be explored.

4.6.7 Areas for Further Research

Physiologic interactions between fasting plasma glucose and 2-h postprandial glucose during pregnancy needs further research because even though some overlap effect was seen for birth outcomes associated with high fasting glucose and high 2-h OGTT, there seems to be some distinctive outcome profiles as well. To facilitate management for women diagnosed with GDM, glucose cut-off values for African populations and health systems in low resource settings that would balance the risks and benefits of adverse pregnancy outcomes and long-term complications that are applicable to the health systems context is needed. To improve access to GDM diagnosing in primary facilities, correlation profile of venous versus capillary blood glucose and the correlation of point-of-care device versus laboratory analysis needs to be researched to assess the extent to which findings from the Ghanaian population would compare with current global evidence. Finally, effective monitoring strategies for GDM women is needed.

5 SUMMARY

Background: Gestational diabetes is increasing globally. Studies from Sub-Saharan Africa have investigated the risk factors but reported prevalence is often based on one diagnostic test while short-term outcomes have scarcely been explored. In primary settings, gestational diabetes is tested after screen-positive glycosuria and/or presence of clinical risk factors. There is suspicion of missing cases due to likelihood of active hyperglycemia without detectable glycosuria and the wide profile of risk facts associated with gestational diabetes. Despite recent updates of diagnostic guidelines with lowered diagnostic cut-off in most cases, opinions are divided on the screening methods diagnostic cut-offs to apply, and whether to do selective screening followed by diagnostic testing of screen-positive cases vis-à-vis universal testing of all pregnant women.

Objective: This study was conducted to address three overarching objectives:

(1) validate the diagnostic validity of screening tests for gestational diabetes and estimate the proportion of cases that could be missed if selective screening is applied;
(2) estimate the prevalence of gestational diabetes and assess the risk factors; and
(3) assess the pregnancy outcomes including the extent of attainment of euglycemia at 12 weeks postpartum.

Materials and methods: This study employed blind-comparison-to-the-gold-standard and case-control designs embedded in a prospective cohort study. Singleton non-diabetic singleton pregnant women (n=807) were recruited in the first trimester from five state-owned hospitals serving rural and peri-urban communities in Ghana. They were all screened for gestational diabetes from 13-20 weeks using dipstick glycosuria, random glucose and clinical risk factor assessment. Between 20-34 weeks, 491 pregnant women were tested for gestational diabetes using glycated hemoglobin, fasting glucose, 1-hour and the ‘gold standard’ 2-hour oral glucose tolerance test following the universal ‘one-step’ approach. Dietary and obstetric history were assessed retrospectively while physiologic measurements were repeated throughout pregnancy. Case definition was fasting ≥5.6 mmol/L and/or 2-hour postprandial glucose ≥8.5 mmol/L. Short-term outcomes of 403 and 100 women were traced at delivery and 12 weeks postpartum respectively. Validity of test instruments were estimated using standard disease measures. Adjusted odds ratio for gestational diabetes and relative risk for adverse birth outcomes were estimated by logistic regressions.

Results: Fasting plasma glucose had the highest diagnostic validity among all the screening and diagnostic tests evaluated. Fasting glucose cut-off ≥5.1 mmol/L threshold had the highest clinically relevant sensitivity and specificity but the ≥5.6 mmol/L threshold had higher disease prediction. Selective screening using glycosuria, random glucose and risk factors missed 97.4%, 87.2% and 45.7% of cases respectively. Using the area under the curve to determine the diagnostic accuracy and test performance, fasting and 1-hour postprandial glucose tests were found to be very good, random glucose was poor whereas glycated hemoglobin was not diagnostically useful. Depending on the diagnostic test and cut-off used, 5-27% of participants were diagnosed with gestational diabetes. Overall 15.9% met the case definition; prevalence per 2-hour postprandial glucose ≥8.5 mmol/L was 9.0% and per fasting glucose ≥5.6 mmol/L was 10.8%; 3.9% were positive in both tests. Adjusted risk factors for gestational diabetes included high glycemic intake, obesity, previous Cesarean section and antenatal care in a primary facility. In terms of outcomes, a unit rise in blood glucose significantly increased maternal blood loss and fetal birthweight. Associated adverse birth outcomes were perineal tear and birth asphyxia. At 12 weeks postpartum, 30% of the diagnosed women did not achieve euglycemia.

Conclusions and recommendations: Findings show rising gestational diabetes in the general population. Selective screening using glycosuria, random glucose and clinical risk factors are unnecessary due to their low diagnostic validity. Fasting glucose monitoring need to be integrated into all gestational diabetes detection protocols. Cut-off ≥5.1 mmol/L could be applicable for screening at the population level but to make therapeutic decision, cut-off ≥5.6 mmol/L is recommended where 2-hour oral glucose tolerance test is unavailable. Primary facilities need strengthening to test and refer cases. Diet and adiposity are key risk factors that necessitate lifestyle modifications with focus on nutrition education and weight control. Fetuses exposed to hyperglycemia uterine environment require quality obstetric care as birth asphyxia which is a key outcome is likely to compromise their survival. Follow-up on women diagnosed with gestational diabetes is crucial to avert transition into active diabetes. Cut-off values that would balance risks and benefits of adverse pregnancy and long-term outcomes is needed for the Ghanaian population. Physiologic interactions between fasting and oral glucose tolerance tests need further research.

5 ZUSAMMENFASSUNG

Hintergrund: Gestationsdiabetes steigt weltweit an. Studien aus Subsahara-Afrika untersuchen die Risikofaktoren; es gibt aber wenig Studien zur Prävalenz und diese basieren oft nur auf einem einzigen diagnostischen Test. Es gibt auch kaum Studien zur Nachverfolgung post partum. In primären Gesundheitseinrichtungen in Ghana beruht die Diagnose Gestationsdiabetes auf einem positiven Glykosurie-Test oder dem Vorhandensein klinischer Risikofaktoren. Vermutlich werden aber viele Fälle übersehen, bei denen eine aktive Hyperglykämie ohne feststellbare Glykosurie besteht. Trotz kürzlich angepasster internationaler Richtlinien für das Screening und die Diagnostik, mit in den meisten Fällen gesenkten Grenzwerten, sind die Meinungen bezüglich der Screening-Möglichkeiten nach wie vor gespalten zwischen einem universellen Screening aller schwangeren Frauen und einem selektiven Screening nach Risikobelastung. Darüber hinaus gibt es unterschiedliche Vorschläge für diagnostische Tests und deren Grenzwerte.

Zielsetzung: Diese Studie wurde durchgeführt, um die folgenden drei Ziele zu erreichen:

(1) die Validität von Tests zum Screening und zur Diagnose von Gestationsdiabetes in Ghana zu ermitteln, sowie den Anteil von Fällen einzuschätzen, die bei selektivem Screening übersehen werden;

(2) (2) die Prävalenz von Gestationsdiabetes in Ghana zu ermitteln, sowie Risikofaktoren zu identifizieren und

(3) (3) die kindlichen und mütterlichen Schwangerschaftsergebnisse, einschließlich der mütterlichen glykämischen Situation 12 Wochen postpartum zu untersuchen.

Material und Methoden: Die vorliegende Studie ist eine Kohortenstudie mit eingebetteter Fall-Kontroll-Studie die Schwangere während der Schwangerschaft und bis zu 12 Wochen post partum einschließt. Nicht-diabetische Frauen mit einer Einlings-Schwangerschaft (n=807) wurden in ihrem ersten Trimester in fünf staatlichen Krankenhäusern, welche ländliche und halb-städtische Gemeinden in Ghana versorgen, rekrutiert. Sie wurden alle zwischen der 13. und 20. Schwangerschaftswoche auf Gestationsdiabetes untersucht, und zwar mittels Tests auf Glucosurie und Blutzucker. Ebenso wurde ein klinisches Risikoassessment gemacht. Zwischen der 20. und 34. Schwangerschaftswoche, wurden 491 schwangere Frauen nach dem „single-step“ Verfahren untersucht. Dabei wurden glykosyliertes Hämoglobin, Nüchtern-Blutzucker, oraler Glukosebelastungstest 1-Stunden-

Wert und als „Goldstandard“ der 2-Stunden-Wert erhoben. Ernährungs- und geburtshilfliche Anamnesen wurden retrospektiv erhoben und bewertet. Die Falldefinition für Gestationsdiabetes lautete: Nüchtern-Blutzucker ≥ 5,6 mmol/L und/ oder 2-Stunden Wert nach oralem Glukosebelastungstest ≥ 8,5 mmol/L. Von 403 Frauen wurden die Geburtsergebnisse erfasst; 100 Frauen aus dieser Gruppe wurden zusätzlich nach 12 Wochen postpartum untersucht. Die adjustierten Odds Ratios für Gestationsdiabetes und für weitere Schwangerschaftskomplikationen wurden mittels logistischen Regression ermittelt.

Ergebnisse: Nüchtern-Blutzucker im Plasma hatte die höchste diagnostische Validität von allen getesteten Screening- und Diagnostik-Tests. Nüchtern-Blutzucker-Grenzwerte von ≥5,1 mmol/L hatte die höchste klinisch relevante Spezifität, aber der Schwellenwert ≥5,6 mmol/L hatte einen höheren Krankheitsvorhersagewert. Selektive Screenings, welche mit Testen von Glykosurie, spontanen Blutzuckermessungen und Risikoprofilen durchgeführt wurden, verfehlten 97,4%, 87,2% beziehungsweise 45,7% der Fälle. Benutzt man die „area under the curve“, um die diagnostische Genauigkeit und die Leistung eines Tests zu bestimmen, ergaben der Nüchtern-Blutzucker und der 1-Stunde-Wert des Glukosebelastungstests die besten Ergebnisse. Spontane Blutzuckermessungen hingegen schnitten schlecht ab, während das glykolisierte Hämoglobin diagnostisch nicht brauchbar war. Abhängig davon, welcher diagnostische Test und welcher Grenzwert verwendet wurde, ergaben sich Prävalenzen von 5-27%. Unter Verwendung des eingangs genannten Goldstandards für diese Studie (Nüchtern-Blutzucker ≥ 5,6 mmol/L und/ oder 2-Stunden Wert nach oralem Glukosebelastungstest ≥ 8,5 mmol/L) ergab sich eine Prävalenz für Gestationsdiabetes von 15,9%: Die Prävalenz für den 2-Stundenwert des Glukosebelastungstests von ≥8,5 mmol/L war 9,0% und für den Nüchtern-Blutzucker ≥5,6 mmol/L war 10,8%; bei 3,9 % waren beide Tests positive. Die Risikofaktoren für Gestationsdiabetes beinhalteten großen Zuckerkonsum, Adipositas und vorhergehenden Sectio caesarea. Ein Anstieg der Glukose im Blut um eine Einheit hatte einen signifikanten Anstieg des mütterlichen Blutverlusts sowie des Geburtsgewichts des Neugeborenen zur Folge. Assoziierte ungünstige Geburtenergebnisse beinhalteten perineale Geburtsverletzungen und kindliche Asphyxie. Zwölf Wochen post partum hatten 30% der Frauen mit Gestationsdiabetes noch keine Euglykämie erreicht.

Schlussfolgerung und Empfehlungen: Die Ergebnisse zeigen, dass die Prävalenz des Gestationsdiabetes in der Ghana zunimmt. Selektive Screening-Verfahren wie Glykosurie und spontane Blutzuckermessung sind wenig valide und unnötig. Die Nüchtern-Blutzucker-Überwachung sollte jedoch routinemäßig in die Schwangerenvorsorge integriert werden. Die

Nüchtern-Blutzucker-Obergrenze von ≥5,1 mmol/L sollte in Ghana für Screenings der aller Schwangeren benutzt werden, um jedoch therapeutische Entscheidungen zu treffen, soll ein diagnostischer Grenzwert von ≥5,6 mmol/L gelten, falls kein oraler Glukosetoleranztest durchführbar ist. Primäre Gesundheitseinrichtungen sollten beim Screening und in der Überweisung von Gestationsdiabetes-Fällen unterstützt werden. Diabetogene Ernährung und Adipositas sind Hauptrisiken, welche eine Änderung des Lebensstils benötigen. Der Fokus der Beratung sollte in der Ernährung und der Gewichtskontrolle liegen. Feten welche intrauterinen Hyperglykämien ausgesetzt waren, brauchen eine spezialisierte Geburtshilfe, da Geburts-Asphyxien eine häufige Folge von Gestationsdiabetes sind und diese das Sterberisiko erhöhen. Es ist wichtig, Frauen mit Gestationsdiabetes nachzubetreuen, um zu verhindern bzw. zu erkennen, ob ein Gestationsdiabetes in einen manifesten Diabetes mellitus übergeht. Die spezifische klinische Wertigkeit von erhöhtem Nüchternblutzucker und pathologischem oralem Glukosetoleranztest im Kontext der Situation in Ghana sollte weiter untersucht werden.

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7 OWN PUBLICATIONS

7.1 Publications from the Doctoral Research

7.1.1 Published Peer-Reviewed Papers

1. **Agbozo** F, Abubakari A, Narh C, and Jahn A (2018). Accuracy of glycosuria, random blood glucose and risk factors as selective screening tools for gestational diabetes mellitus in comparison with universal diagnosing. *BMJ Open Diabetes Research and Care*; **6:**e000493. http://dx.doi.org/10.1136/bmjdrc-2017-000493
2. **Agbozo** F, Abubakari A, Der J and Jahn A (2016). Prevalence of low birth weight, macrosomia, stillbirths and related maternal factors in Hohoe Municipality, Ghana. Journal of Midwifery 40:200–206, http://dx.doi.org/10.1016/j.midw.2016.06.016
3. **Agbozo** F, Colecraft E, Jahn A and Guetterman T (2018). Understanding why child welfare clinic attendance and growth of children in the nutrition surveillance programme is below target: lessons learnt from a mixed methods study in Ghana. BMC Nursing 17:25. https://doi.org/10.1186/s12912-018-0294-y
4. **Agbozo** F, Atito P, Jahn A and Abubakari A (2018). Energy and nutrient composition of on-site lunch meals, dietary diversity and anthropometry of beneficiary pupils in private and public basic schools in Ghana. Nutrition and Health, 1-9. http://dx.doi.org/10.1177/0260106018793048
5. Agbozo F, Ocansey D, Atito P and Jahn A (2019). Compliance of a Baby-Friendly Designated Hospital in Ghana to the WHO/UNICEF Baby and Mother-Friendly Care Practices. Journal of Human Lactation, p1-12 https://doi.org/10.1177/0890334419848728

7.1.2 Pre-Print Publication

6. **Agbozo** F, Abubakari A, Zotor F and Jahn A (2019). Gestational diabetes using diverse diagnostic criteria, risk factors including dietary intakes, pregnancy outcomes and postpartum glycemic status: a nested case-control study in Ghana. BioRxiv 582239 https://doi.org/10.1101/582239 (under review with *Plos One; manuscript ID: PONE-D-19-07774*)

7.1.3 Manuscripts Under Peer Review

7. **Agbozo** F, Abubakari A, Der J and Jahn A. Adequacy of maternal intakes according to FAO minimum dietary diversity indicator, red blood cell indices and anaemia in pregnancy in Ghana. Maternal & Child Nutrition. (MCN-10-18-OA-3508)

7.2 Further Publications During the Doctoral Study Period

7.2.1 Peer Review Publications

8. Schuler C, Ntow G and **Agbozo F** (2019). A retrospective qualitative study to explore the neonatal care practises of mothers with low birth weight infants in the Hohoe municipality, Ghana. Journal of Pediatric Nursing https://doi.org/10.1016/j.pedn.2018.12.017
9. Nazmun N, Sarker M, Ahmed H, Hossain M, Dureab F, **Agbozo F**, Jahn A (2019). Overall Care-Seeking Pattern and Gender Disparity at a Specialized Mental Hospital in Bangladesh. Mater Sociomed. 2019 Mar; 31(1): 35-39
10. **Agbozo** F, Amardi J, Dwase H and Ellahi B (2018). Nutrition Knowledge, Dietary Patterns and Nutritional Status of Older Persons in Ga West Municipality, Ghana. African Health Sciences, 18(3): 743-755. https://dx.doi.org/10.4314/ahs.v18i3.33
11. Abubakari A, **Agbozo** F and Abiiro G (2017) Factors associated with optimal antenatal care use in Northern region, Ghana, Women & Health, DOI: http://dx.doi.org/10.1080/03630242.2017.1372842
12. **Agbozo** F, Atitto P and Abubakari A (2017). Nutritional status of pupils attending public schools with and without school feeding programme in Hohoe Municipality, Ghana. Journal of Food & Nutrition Research, 5(7):467-474. DOI: http://dx.doi.org/10.12691/jfnr-5-7-3
13. **Agbozo** F, Der J, Glover N and Ellahi B (2016). Household and market survey on availability of adequately iodized salt in the Volta region, Ghana. International Journal of Health Promotion and Education, 54(6). http://dx.doi.org/10.1080/14635240.2016.1250658
14. **Agbozo** F (2016). Qualitative assessment of counselling on infant and young child feeding provided by community health workers to caregivers at child welfare clinics in Ghana. International Journal of Communication & Health. 9:97-108 (ISSSN 2359-8220)
15. **Agbozo** F, Atito P and Abubakari, A (2016). Malnutrition and associated factors in children: a comparative study between public and private schools in Hohoe Municipality, Ghana BMC Nutrition, 2(32), 1-10. http://dx.doi.org/10.1186/s40795-016-0073-7
16. **Agbozo** F, Colecraft E and Ellahi B (2016). Impact of type of child growth intervention program on caregivers' child feeding knowledge and practices: a comparative study in Ga West Municipality, Ghana. Food Science & Nutrition, 4(4):562–572. http://dx.doi.org/10.1002/fsn3.318

7.2.2 Further Manuscripts Currently Under Peer Review

17. Amobaa N, **Agbozo F**, Runge-Ranzinger S & Grys P. Mental health challenges and coping strategies among senior high School students - a mixed method study in Techiman municipality. BMC Psychiatry (BPSY-D-18-00954)
18. Abubakari A, Tahiru R, **Agbozo F** and Garti H. Exclusive Breastfeeding and Associated Factors Among Mothers with Twins In The Tamale Metropolis. International Breastfeeding Journal (IBFJ-D-19-00007)

7.1.3 Published Peer-Reviewed Conference Abstracts During the Doctoral Study Period

1. **Agbozo F**, Abubakari A and Jahn A (2019). Risk factors for gestational diabetes and comparison of associated pregnancy outcomes by diagnostic criteria. Trans R Soc Trop Med Hyg 2019; 113: S1–S98 https://doi:10.1093/trstmh/trz094
2. Bannerman E, Klomegah S, Zotor F, **Agbozo F** (2019). Dietary intakes, perceived quality of life and risk factors for metabolic syndrome among middle aged adults in Ghana: a case-control study. Trans R Soc Trop Med Hyg 2019; 113: S199–S245 https://doi:10.1093/trstmh/trz090
3. **Agbozo** F, Abubakari A, Jahn A (2019). Indication and predictors for caesarean sections in Ghana and the birth outcomes. European Journal of Obstetrics & Gynecology and Reproductive Biology Volume 234, Page e5. https://doi.org/10.1016/j.ejogrb.2018.08.159
4. **Agbozo** F, Abubakari A and Jahn A (2018). Maternal morbidities in Ghana: risk factors and effect on newborn health outcomes. International Journal of Gynecology & Obstetrics. Volume 143, Supplement 3, p190. ISSN 0020-7292
5. **Agbozo F**, Abubakari A, Narh C, Jahn A (2017). Are we missing pregnant women with gestational diabetes? Evidence from a diagnostic accuracy study comparing glycosuria, glycated haemoglobin, random and fasting glucose to oral glucose tolerance test. Tropical Medicine and International Health. Volume 22, Issue S1 pp 351-352. https://doi.org/10.1111/tmi.12984
6. **Agbozo F**, Abubakari A, Jahn A (2017). Does gestational intake of adequate diets using the FAO women's dietary diversity indicator affect haemoglobin levels at delivery and newborn health outcomes? Tropical Medicine and International Health, 22(S1), 331-332. https://doi.org/10.1111/tmi.12979
7. Ocansey D and **Agbozo** F (2017). Reassessment of a designated baby-friendly health facility in Greater Accra Region, Ghana. Pan African Medical Journal - Conference Proceedings. 3(3):114. http://dx.doi:10.11604/pamj.cp.2017.3.114.265
8. Schuler C, Ntow G and **Agbozo F** (2017). Caring practices of mothers with low birth weight infants in the neonatal period; A retrospective qualitative study in the Hohoe municipality, Ghana. Tropical Medicine and International Health, 22(S1), 306. https://doi.org/10.1111/tmi.12979
9. **Agbozo F**, Colecraft E and Guetterman T (2017). A mixed methods study providing insights on why targets on child welfare clinic attendance and growth patterns of participating children are unmet in Ghana. Annals of Nutrition &Metabolism 71, 645-646 https://doi.org/10.1159/000480486
10. Ellahi B, **Agbozo F**, Dikmen D, Darrah S, and Zotor F (2017). Prevalence of metabolic syndrome in a Ghanaian population. Annals of Nutrition and Metabolism, 71, 755-756
11. Arthur E, McDonald M, **Agbozo F**, Ellahi B, Mutoro A, Wright C, Garcia A (2017). Feeding behaviours as risk factors for undernutrition in infants living in semi-urban communities of the Volta region, Ghana Annals of Nutrition and Metabolism 71, 528-529
12. Zotor F, Egbi G, Gbogbo S, Ofosu W, **Agbozo F**, and Harrison E (2017). Mixed green leafy vegetables powder consumption improves anaemia status of Ghanaian school children. Annals of Nutrition and Metabolism 71, 1048-1049

8 ANNEX

8.1 Data Collection Tools and Questionnaires

8.1.1 Form 1. Prenatal Data Collection Form

Interviewer's name:	
Name of facility:	
Date of Interview:	

Section A: Participant Identification

Client's study ID no:	
Client's hospital registration no.	
Name of client:	
Primary phone no:	
Secondary phone no.	
Exact Home address:	
Common name by which client is known in her neighborhood:	
After delivery, exactly where do you intend to attend postnatal clinic?	
After delivery, exactly where do you intend to attend child welfare clinic (weighing)?	

Section B: Socio-Demographic Information *(Please tick where appropriate)*

Client's completed age (years):			**Date of birth:**	
Marital status	(1) Married		(2) Cohabitating	
	(3) Single		(4) Other (specify):	
Client's highest educational level	(0) None		(1) Primary	
	(2) Junior high school		(3) Middle school	
	(4) Senior high school		(5) Technical/vocational school	
	(6) College/Polytechnic		(7) University	
Client's occupation	Unemployed		Student	
	Housewife		Teacher	
	Petty trader		Sales attendant	
	Business woman		Micro-finance staff	
	Farmer		Banker	
	Fisher folk		Civil/public servant	
	Hairdresser		Health worker (specify)	
	Seamstress			
	Others (specify)		Others (specify)	
Partner's highest	(0) None		(1) Primary	
	(2) Junior high school		(3) Middle school	
	(4) Senior high school		(5) Technical/vocational school	

educational level	(6) College/Polytechnic		(7) University	
Partner's occupation	Unemployed		Student	
	Farmer		Teacher	
	Fisher man		Health worker	
	Driver		Micro-finance staff	
	Mechanic		Banker	
	Carpenter		Civil/public servant	
	Mason		Sales attendant	
	Tailor		Security man	
	Trader			
	Others (specify)		Others (specify)	
Clients hometown:	Name of town: _____		District: _____ Region: _____	
Ethnicity	(1) Ewe		(2) Akan	
	(3) Ga/Ga Ademgbe		(4) Guan	
	(5) Northern tribe (Specify) _____		(6) Others (Specify) _____	
Religious affiliation	(1) Christian		(2) Moslem	
	(3) Other (specify) _____			
Total household size				
Did you plan for this pregnancy	No		Yes	
Are you happy being pregnant?	No		Yes	

Section C: Obstetric History

Gestational age at first ANC registration			
Gestational age at first contact with field worker			
Date of Last menstrual period			
Expected date of delivery (from Last Menstrual Period):		Expected date of delivery (from ultrasound scan):	
Gravida (number of pregnancies):		Parity (number of live births):	
Abortions:_____	Spontaneous:_____	Induced:_____	

Past Six Pregnancies (including miscarriages and abortions)

	Child 1	Child 2	Child 3	Child 4	Child 5	Child 6
Date						
Sex						
Home or hospital delivery						
If hospital, specify name						
Problems during pregnancy						
Mode of delivery						
Live or dead						
Singleton or multiple birth						
Preterm, term or post-term						
Birth weight						
Labour complications						
Postpartum complications						
Condition of child under 5y						

Section D: Medical & Surgical History *(Please tick where appropriate)*

Does the client have any of the following?			Does client's family have any of the following?			If yes, who?
	No	Yes		No	Yes	
Hypertension			Hypertension			
Heart disease			Heart disease			
Diabetes			Diabetes			
Prior gestational diabetes						
Sickle cell disease			Sickle cell disease			
Asthma			Asthma			
Tuberculosis			Tuberculosis			
Jaundice			Multiple pregnancies			
Epilepsy			Birth defects			
Mental illness			Mental illness			
STIs (specify) _____			Renal disease			
Previous operations (specify) _____			Others (specify) _____			

Section E: Anthropometric Data

Type	Measurement	Date	Gest. Age (weeks)
Pre-pregnancy weight (if known) (kg)			
Body weight at at first ANC registration (kg)			
Height at first ANC registration (cm)			
MUAC (cm)			
Pregnancy body weight at 2nd ANC visit			
Pregnancy body weight at 3rd ANC visit			
Pregnancy body weight at 4th ANC visit			
Pregnancy body weight at 5th ANC visit			
Pregnancy body weight at 6th ANC visit			
Pregnancy body weight at 7th ANC visit			
Pregnancy body weight at 8th ANC visit			
Pregnancy body weight at 9th ANC visit			

Section F: Laboratory Investigations

Test	Result	Date	Gest. Age (wks)
Haemoglobin 1			
Haemoglobin 2			
Haemoglobin 3			
Haemoglobin 4			
Hb-Electrophoresis			
G6PD			
Blood group			
Rhesus factor			
Antibody screen			
VDRL/PRP			
HBsAg			
Stool RE			
Urine RE			
HIV status			
For malaria test, indicate whether Rapid Diagnostic Test or Blood Film for Malaria Parasites			
Malaria test 1			
Malaria test 2			
Malaria test 3			

Lipid profile

Measurement	Result	Date	Gest. Age (wks)
Total cholesterol			
Triglycerides			
High density lipoprotein			
Low density lipoprotein			

Screening & diagnosis tests for gestational diabetes & diabetes in pregnancy

Test	Result	Date	Gest. Age (wks) when tested
At first contact with client			
Urine dipstick test			
Random capillary blood glucose			
At the 2nd contact with client, that is between 24 to 32 weeks			
Urine dipstick test			
Fasting *capillary blood* glucose			
Fasting *venous plasma* glucose			
Oral glucose tolerance at *1 hour*			
Oral glucose tolerance at *2 hours*			
Glycosylated haemoglobin			

Ultra sound scan

	Scan 1	Scan 2	Scan 3
Date of scan			
Gestational age when scan was taken			
Expected date of delivery (EDD)			
Estimated fetal weight (EFW)			
Crown rump length (CRL)			
Fetal heart rate (FHR)			
Biparietal diameter (BPD)			
Femur length (FL)			
Head circumference (HC)			
Abdominal circumference (AC)			
Occipitofrontal diameter (OFD)			
Humerus length (HL)			
Liquor volume			
Presentation			

Section G: Food Frequency Questionnaire

Food Groups	Food Items	Frequency of consumption categories *Please tick the appropriate response category*													
				Monthly			Weekly			Daily					
		Never	Rarely	1 per mth	2 per mth	3 per mth	1 per wk	2 per wk	3 per wk	4 per wk	5 per wk	6 per wk	1 daily	2 daily	3+ daily
		0	1	2	3	4	5	6	7	8	9	10	11	12	13
Cereals & grains	Maize products														
	Rice products														
	Wheat products														
	Millet														
	Sorghum														
	Oats														
Others															
Roots, tubers & plantain	Yam														
	Cassava														
	Plantain														
	Cocoyam														
	Potatoes														
	Water yam														
Others															
Legumes, nuts & oily seeds	White beans														
	Red beans														
	Black beans														
	Bambara beans														
	Soya beans														
	Groundnuts														
	Neri														
	Agushie														
	Dawadawa														
	Soy milk														
	Tiger nuts														
	Cashew nuts														
	Palm fruits														
	Coconut														
Others															
Animal source foods	Fish														
	Poultry														
	Beef														
	Goat														
	Sheep														
	Pork														
	grasscutter														
	Shellfish														

Food Groups	Food Items	Frequency of consumption categories													
				Monthly			Weekly						Daily		
		Never	Rarely	1 per mth	2 per mth	3 per mth	1 per wk	2 per wk	3 per wk	4 per wk	5 per wk	6 per wk	1 daily	2 daily	3+ daily
		0	1	2	3	4	5	6	7	8	9	10	11	12	13
Animal source foods	Snail														
	Eggs														
	Sausage														
	Milk														
	Yoghurt														
Others															
Green leafy vegetables	Kontomire														
	Gboma														
	Ademe (ayoyo)														
	Fotete (aleefu)														
	Moringa leaves														
	Cassava leaves														
	Dandelion leave														
	Spinach														
	Lettuce														
Others															
Other vegetables	Tomatoes														
	Okra														
	Garden eggs														
	Onion														
	Garlic														
	Pepper														
	Abedru														
	Mushroom														
	Green pepper														
	Cabbage														
	Carrots														
	Lettuce														
	Green peas														
	Cauliflower														
	Cucumber														
Others															
Fruits	Pawpaw														
	Orange														
	Banana														
	Pineapple														
	Mango														

Food Groups	Food Items	Frequency of consumption categories													
				Monthly			Weekly						Daily		
		Never	Rarely	1 per mth	2 per mth	3 per mth	1 per wk	2 per wk	3 per wk	4 per wk	5 per wk	6 per wk	daily	2 daily	3+ daily
		0	1	2	3	4	5	6	7	8	9	10	11	12	13
Fruits	Water melon														
	Apple														
	Guava														
	Grapes														
	Pear														
Others															
Fats & oils	Palm oil														
	Coconut oil														
	Palm kernel oil														
	Groundnut oil														
	Shea-butter														
	Refined vegetable oil														
	Olive oil														
	Margarine														
	Butter														
Miscellaneous	Sweets, sugary foods/drinks Specific _____														
	Alcohol														
	Cigarette smoking														
Others															

Food taboos, avoidances and cravings	Please tick the appropriate response			
Is there any food that is forbidden for you to eat?	[0] No		[1] Yes	
If yes, what food(s) is forbidden for you to eat?				
Is there any food you avoid eating as a result of your current pregnancy?	[0] No		[1] Yes	
If yes, what food do you avoid eating as a result of this current pregnancy?				
Is there any food you eat uncontrollably as a result of this pregnancy?	[0] No		[1] Yes	
If yes, what food(s) do you eat uncontrollably as a result of this pregnancy?				

Section H: Health Education Topics at Antenatal Clinics				
Has client ever been educated on any of the under-listed topics at the ANC during this current pregnancy?				
Topic	**N**	**Y**	**If yes, how many times**	**Ask client to mention any issues discussed under each topic**
Danger signs in pregnancy				
Diet, nutrition, anaemia, deworming				
Hygiene				
Rest / exercise				
Husband / support person involvement				
Medications or immunizations				
Birth preparedness & complication readiness				
STI prevention / condom use / safer sex				
Voluntary counselling & testing				
Mother-to-child transmission of HIV				
Labour and delivery				
Baby care				
Breastfeeding & breast care				
Family planning motivation				

Promote use of insecticide treated materials				_____ _____ _____ _____
Iron folate supplementation				_____ _____ _____ _____
Others				_____ _____ _____ _____ _____

Assessment of intake of folic acid

Are you taking folic acid, multivitamin or mineral supplements during this pregnancy?	
Yes	**No**
If yes, what are the benefits of taking these drugs? _____ _____ _____ _____ _____ _____	If no, why are you not taking these drugs? _____ _____ _____ _____ _____ _____

Section I: Screening for antepartum depression

As you are pregnant, we would like to know how you are feeling. Please tick the answer that comes closest to how you have felt **in the past 7 days**, not just how you feel today

No	In the past 7 days:				
1.	I have been able to laugh and see the funny side of things	(a) As much as I always could		(b) Not quite so much now	
		(c) Definitely not so much now		(d) Not at all	
2.	I have looked forward with enjoyment to things	(a) As much as I ever did		(b) Rather less than I used to	
		(c) Definitely less than I used to		(d) Hardly at all	
3.	I have blamed myself unnecessarily when things went wrong	(a) Yes, most of the time		(b) Yes, some of the time	
		(c) Not very often		(d) No, never	
4.	I have been anxious or worried for no good reason	(a) No, not at all		(b) Hardly ever	
		(c) Yes, sometimes		(d) Yes, very often	
5.	I have felt scared or panicky for no very good reason	(a) Yes, quite a lot		(b) Yes, sometimes	
		(c) No, not much		(d) No, not at all	
6.	Things have been overwhelming me	(a) Yes, most of the time I haven't been able to cope at all		(b) Yes, sometimes I haven't been coping as well as usual	
		(c) No, most of the time I have coped quite well		(d) No, I have been coping as well as ever	
7.	I have been so unhappy that I have had difficulty sleeping	(a) Yes, most of the time		(b) Yes, sometimes	
		(c) Not very often		(d) No, not at all	
8.	I have felt sad or miserable	(a) Yes, most of the time		(b) Yes, quite often	
		(c) Not very often		(d) No, not at all	
9.	I have been so unhappy that I have been crying	(a) Yes, most of the time		(b) Yes, quite often	
		(c) Only occasionally		(d) No, never	
10.	The thought of harming myself has occurred to me	(a) Yes, quite often		(b) Sometimes	
		(c) Hardly ever		(d) Never	

Section J: Referral to Specialist

Extract this information from referral records

Has client been referred to see a specialist?	No		Yes	
What type of specialist was she referred to? (tick)	Obstetrical/gynaecologist		Physician specialist	
	General doctor/medical assistant		Dietician/nutritionist	
	Psychiatrist/mental health worker		Social worker	
	Others (specify)			
If yes, date of referral				
To which facility was she referred?				
What is the reason for the referral?	_____ _____ _____ _____ _____			
Was client offered any treatment?	No		Yes	
If offered treatment, specify treatment given?	_____ _____ _____ _____ _____ _____			
Any other comments				

Section K: Participant's Antenatal Progress Record

No.	Date	body weight kg	BP mmHg	Urine		Gest. Age (weeks)	Fundal height (cm)	Presen-tation	Descent	Foetal Heart	No. of IFA given	Intake of intermittent preventive treatment for malaria prevention		
				Protein	Sugar							Dose 1	Dose 2	Dose 3
1														
2														
3														
4														
5														
6														
7														
8														
9														
10														
11														
12														
13														
15														
16														
17														

Take pictures of this page or make copies

8.1.2 Form 2. Intrapartum Perinatal Data Collection Form

Name of Midwife:	
Name of hospital:	
Date:	

Section A: Participant Identification

Name of client:	
Primary phone no:	
Home address:	
Date for 6 weeks postnatal clinic appointment:	

Section B: Maternal Pregnancy Outcomes

Tick where appropriate Otherwise, please complete the sections

Date & time of delivery	Date: _____		Time: _____	
Cord blood sample?	**Laboratory test**	**Results**		
	Cord blood sample for malaria parasite microscopy			
	Cord blood sample for plasma glucose concentrations			
	Cord blood sample C-peptide test			
Placental weight (kg)				
Body weight after delivery (kg)				
Mode of delivery	Spontaneous vaginal delivery		Forceps delivery	
	Vaginal delivery with episiotomy		Caesarean section	
	Others (specify) _____ _____		Others (specify) _____ _____	
If caesarean delivery, what was the reason?				
Labour complications	***Was there any labour complications?***			
	No		Yes	
	If yes, what was the complication?			
	Prolong labour		Obstructed labour	
	Pre-eclampsia		Eclampsia	
Labour complications	Antepartum haemorrhage		Volume of blood loss	_____ ____ml
	Postpartum haemorrhage		Volume of blood loss	_____ ____ml
	Others (specify)		Others (specify)	

	_____		_____
Referral	***Was mother referred to another level facility?***		
	No		Yes
If referred, what was the reason for the referral?			
Maternal death	***Was there a case of maternal death?***		
	No		Yes
If yes, what was the cause of death?			
Referral status:	1. Self-referral 2. Refereed for delivery 3. Emergency referral		

Section C: Newborn Assessment

Tick where appropriate Otherwise, please complete the sections

Sex	Male:		Female:	
Gestational age at delivery (weeks)				
Newborn measurements	Birth weight	_____ Kg	Birth length	_____ cm
	Head circumference	_____ cm	Chest circumference	_____cm
	Mid-upper arm circumference		_____ mm	
Birth outcome	Live		Still	
	If still, indicate whether fresh or lacerated			
	Fresh		Lacerated	
APGAR score	At 1 minute:		At 5 minute:	
Newborn blood sugar analysis (to be done between 1-2 hours hour after birth)				
Heel prick for blood random plasma glucose	Result: ---------- mmol/L			

Birth injury	*Does newborn have any injury as a result of the delivery process?*			
	No		Yes	
	If yes, specify the exact type of birth injury?			
	Should dystocia		Bone fracture Specify:	
	Nerve palsy			
	Others (specify)		Others (specify)	
Congenital malformation	*Was neonate born with any congenital malformation?*			
	No		Yes	
	Spinal bifida		Cleft lip	

	Down syndrome		Cleft palate	
	Heart defect (specify)		Others (specify)	
Infant feeding	How long after delivery was breastfeeding initiated?			
	Less than 30 minutes		30 minutes to 1 hour	
	1 hour to 12 hours		Above 12 hours	
	Could newborn breastfeed well?			
	No		Yes	
	If no, what was the reason?			
	In the absence of breastfeeding, how was newborn fed?			
	Intravenous feeding		Formula feeding	
	Sugar solution		Glucose solution	
	Others (specify)			
	If formula feeding, what type of formula was given?			
	NAN		SMA	
	Lactogen		Other (specify)	
Health problems	*Does newborn have any other health problems?*			
	No		Yes	
	If yes, specify the exact type of health problem:			
	Has newborn admitted for intensive care?			
	No		**Yes**	
If yes, what is the reason for admission into intensive care?				

8.1.3 Form 3. Laboratory Form

Name of lab personnel taking the blood sample:			
Name of client:			
Date:		Time:	
Client's study ID no:		Study lab no.	

	Test	*Checklist*	*Time of specimen collection*		*Test*	*Checklist*
1.	**Fasting plasma glucose**	☐	_____	5.	**Blood film for malaria parasite**	☐
2.	**Oral glucose tolerance at 1 hour**	☐	_____	6.	**Full blood count**	☐
3.	**Oral glucose tolerance at 2 hours**	☐	_____	7.	**Lipid profile**	☐
4.	**Glycosylated haemoglobin**	☐	_____	8.	**Ferritin**	☐

8.1.4 Form 4. Postpartum/Postnatal Data Collection Form

Data can be collected at <u>postnatal clinic</u>, <u>child welfare clinic</u>, or in the <u>client's home</u> at 12 Weeks after delivery

Interviewer's name:	
Date of interview:	

Section A: Participant Identification

Client's study ID no:	
Client's hospital registration no.	
Name of client:	
Primary phone no:	
Secondary phone no.	
Home address:	

Section B: Maternal Information

Resting blood pressure	Measurement 1	_____mmHg	Take 2nd measurement after 5 minutes	_____ mmHg
Body measurements	Weight (kg)		Height (cm)	
	Triceps skinfold (mm)		MUAC (cm)	
Blood glucose	Fasting plasma glucose		Glycosylated haemoglobin	
	If she has already eaten, then perform		Random plasma glucose	

Screening for postpartum depression

As you have recently had a baby, we would like to know how you are feeling. Please tick the answer that comes closest to how you have felt **in the past 7 days**, not just how you feel today

No	In the past 7 days:			
1.	I have been able to laugh and see the funny side of things	(a) As much as I always could		(b) Not quite so much now
		(c) Definitely not so much now		(d) Not at all
2.	I have looked forward with enjoyment to things	(a) As much as I ever did		(b) Rather less than I used to
		(c) Definitely less than I used to		(d) Hardly at all
3.	I have blamed myself unnecessarily when things went wrong	(a) Yes, most of the time		(b) Yes, some of the time
		(c) Not very often		(d) No, never
4.	I have been anxious or worried for no good reason	(a) No, not at all		(b) Hardly ever
		(c) Yes, sometimes		(d) Yes, very often
5.	I have felt scared or panicky for no very good reason	(a) Yes, quite a lot		(b) Yes, sometimes
		(c) No, not much		(d) No, not at all

6.	Things have been overwhelming me	(a) Yes, most of the time I haven't been able to cope at all		(b) Yes, sometimes I haven't been coping as well as usual
		(c) No, most of the time I have coped quite well		(d) No, I have been coping as well as ever
7.	I have been so unhappy that I have had difficulty sleeping	(a) Yes, most of the time		(b) Yes, sometimes
		(c) Not very often		(d) No, not at all
8.	I have felt sad or miserable	(a) Yes, most of the time		(b) Yes, quite often
		(c) Not very often		(d) No, not at all
9.	I have been so unhappy that I have been crying	(a) Yes, most of the time		(b) Yes, quite often
		(c) Only occasionally		(d) No, never
10.	The thought of harming myself has occurred to me	(a) Yes, quite often		(b) Sometimes
		(c) Hardly ever		(d) Never

Section C: Neonatal Information

Age of neonate (weeks)				
Neonatal death	Is infant alive (*ask mother to bring baby for you to see*)			
	No		Yes	
	If neonate is dead, what date did the infant die?			
	What was the cause of death?			
	End the interview there if infant is dead			
Anthropometry	Body weight	Kg	Baby's length	cm
	Head circumference	cm	Chest circumference	Cm
	Mid-upper arm circumference		_____mm	
Blood glucose	Random blood glucose	_____ __	Fasting plasma glucose	_____ _____
Neonatal conditions	*According to the mother or from the child health records, did infant suffer from any illness?*			
	No		Yes	
	If yes, what was the health problem?			
	Sepsis		Pneumonia	
	Diarrhoea		Malaria	
	Jaundice		Other (specify) _____ _____ _____ _____	
	In case of jaundice, how many days old was baby when the jaundice occurred?			
Physical assessment	**Is the infant looking *visibly* healthy?**			
	No		Yes	
	If no, what is the problem?:			

<table>
<tr><td rowspan="2">Mothers opinion of child's health status</td><td colspan="4">Ask mother if she happy with the baby's health status</td></tr>
<tr><td>No</td><td></td><td>Yes</td><td></td></tr>
<tr><td colspan="5">If yes, what is the problem?:</td></tr>
<tr><td rowspan="5">Breastfeeding assessment</td><td colspan="5">Is baby breastfeeding?</td></tr>
<tr><td>No</td><td></td><td>Yes</td><td></td></tr>
<tr><td colspan="5">If not breastfeeding, what is the reason?:</td></tr>
<tr><td colspan="5">Is baby <u>exclusively</u> breastfeeding?</td></tr>
<tr><td>No</td><td></td><td>Yes</td><td></td></tr>
<tr><td colspan="5">If not exclusively breastfeeding, why?:</td></tr>
<tr><td rowspan="4">Immunizations</td><td colspan="5">Tick the immunizations that the baby has completed</td></tr>
<tr><td>BCG</td><td></td><td>OPV 0</td><td></td></tr>
<tr><td>Puemo 1</td><td></td><td>OPV 1</td><td></td></tr>
<tr><td>Penta 1</td><td></td><td></td><td></td></tr>
</table>

8.2 Participant Information and Consent

Title: Gestational Diabetes Mellitus in Volta Region Ghana: Prevalence, Risk Factors and Pregnancy Outcomes

Principal Investigator: Faith Agbozo; MPhil Nutrition, RN, cPHNs
Principal supervisor: Prof. Albrecht Jahn; PhD, MD (Obstetrician & Gynaecology specialist)

Address: Institute of Public Health, University of Heidelberg in Germany.
Mobile: +233 262 156005 ; +49 152 11054 5392
E-mail: faith.agbozo@uni-heidelberg.de / faagbozo@uhas.edu.gh

Introduction

My name is Faith Agbozo, a lecturer at the University of Health and Allied Sciences. I am a registered nurse and a certified public health nutritionist and currently a doctoral student at the Institute of Public Health, University of Heidelberg in Germany under the supervision of Prof. Albrecht Jahn, a public health specialist and a medical doctor with specialization in obstetrics and gynaecology. I am conducting a research for my doctoral thesis on effect of diabetes in pregnancy and maternal nutrition on the health of mother-newborn pair at delivery. I want to use this opportunity to enlighten you on the research after which you will decide whether or not to participate.

General information about the research

Globally, evidence shows that just as the number of people suffering from chronic non-communicable diseases such as hypertension, diabetes, stroke and cancer is rising, so are more cases of diabetes in pregnancy also on the ascendency. Babies born to mothers with diabetes in pregnancy receive more sugar from the mother than they ideally need. The primary effect is that, the baby may be too large for the age yet the vital organs such as the lungs may be immature. Consequently, the baby is likely to have several problems at birth such as difficulty breathing, low blood sugar due to detachment of supply from the mother at birth and need for intensive care. The mother may experience obstructed or prolonged labour and hence may require caesarean delivery. Apart from the risk of maternal and newborn death, the mother-child pair may develop diabetes in later years. Proper management has been shown to reduce the adverse pregnancy outcomes. But this is possible only when the mother is checked for diabetes in pregnancy during antenatal visits using accurate tests. Also, when factors that put a mother at risk of diabetes in pregnancy known, then interventions may be implemented to prevent or reduce the adverse effects in at risk mothers.

Purpose of the study

This research is being conducted in the entire Volta region and involves 840 pregnant women (and later, their babies) of whom you will potentially be one of them. Findings from this study might help in strengthening existing policies to improve maternal and child health in Ghana. It will also help policy makers and implementers such as the Ghana Health Service and the Ministry of Health to come out with interventions and strategies to prevent and manage diabetes in pregnancy which will lead to improvement in maternal and newborn health and

invariably reduction in maternal and child mortality not only in the Volta region but Ghana at large.

Type of research intervention and expenditure of time

This research will be conducted in three stages, that is, during your antenatal visits, at delivery and six weeks after delivery. If you agree to be part of the study, you will be requested to participate in all these three stages. For today, I will take information recorded in your ANC booklet and measure your blood glucose levels. During your next ANC visit, you will be informed not to eat before coming to ANC because your fasting blood sugar levels will be measured. Also, you will be required to do a lab test that will take two hours to complete. You will be given some glucose solution to drink. Then your blood sugar levels measured to assess how your body will tolerate the glucose drank.

Although you wouldn't have eaten overnight to the next morning, you wouldn't feel too hungry because the glucose solution will give your needed energy. During the 2-hour test period, we will use the opportunity to enquire about you previous pregnancies (if any) and ask you some few questions such as what you usually you eat. By so doing, the time will be judiciously used. But as a study participant, you are free to decide whether or not you want your left-over blood sample to be stored or discarded after analysis. Instead of using your name, a number would be assigned to your blood sample that would be drawn and used for lab analysis such that it would be impossible for anyone to identify you with the test results. After the stipulated period, the specimen (stored blood sample) would be destroyed by incinerator (a burning type of waste disposal used in hospitals).

During delivery, the midwives, nurses and doctors will keep an eye on the health status of you and your baby. Before discharge from the hospital after delivery, you will be informed on when to come back to the hospital for the six weeks postnatal visit. There the research team will meet you again and assess how you and your baby are doing. In case you are diagnosed with diabetes in pregnancy, you and your baby will be visited by the research team at the child welfare clinic (weighing) once every three months for 12 month (1 year) to monitor the blood sugar levels of you and your baby. You will be eligible to participate if only your pregnancy is 24 to 28 weeks old (6-7 months), you intend to deliver in this hospital and stay in this study area after delivery. If this is the case, you will be asked to indicate your willingness to participate in this study by signing the consent form.

Discomforts/risks

You would have to do without food 8 to 12 hours after meal the previous night before the lab test can be done in the morning. We appreciate how difficult it is for a pregnant woman to go without food sometimes. Therefore, the test will be conducted timely. The process of drawing blood samples also come with some pain and discomfort. But this is part of routine antenatal care and we will try and minimize the discomfort as much as possible. There is a slight risk that you may share some personal or confidential information by choice or chance. If at any point during the study you feel uncomfortable talking about or answering any question posed by the researcher, you may decline to answer.

Benefits

This study will confer both direct and indirect befits to you. Should you be diagnosed with diabetes in pregnancy or any other disease, you will be referred to the appropriate specialist for treatment. You will be strictly monitored throughout the study period and given special attention at all the stages of the projects. On a wider scale, your participation is likely to help save lives of many children pregnant women and babies by using the knowledge given in the development of strategies that will improve maternal and new-born health.

Voluntary participation and right to leave the research

Your participation in this research is entirely voluntary. You may choose not to participate or leave the study at any time during any of the stages without any penalty, harassment or intimidation from the researchers, midwives, nurses or doctors. The choice that you make will have no bearing on the medical care that you will receive in this hospital. You can withdraw your consent at any time during the study, without specification of reasons and without any detriment to your medical care.

Use of data collected after withdrawal

When you withdraw from the study, the data collected on you will be destroyed if you make that intention known to us. Otherwise, we may continue to use your data but only for the intended research purpose.

Confidentiality and privacy policy

Any information you give us will be protected to the best of our ability. We will record your name during the interview process. This is to help us address you by your name should we contact you or follow-up up on you at the postnatal clinic or in your community if need be. However, you will not be named in any reports or documents regarding this study and any information about you will be anonymous. Your information will be collected and written down for our analysis purposes. It will be stored in a file that will not have your name written on it, but a number assigned to it instead. The information that we collect from your will be kept private. Your data will be secure from unauthorized access.

Sharing the Results

As the findings of this research can be useful to provide knowledge on accurate diagnosis of diabetes in pregnancy and improve maternal and child health delivery both locally and internationally, findings from this study will be disseminated in an aggregated data form with clinical staff and policy makers in Ghana. Results will be published in international journals and presented at scientific conferences.

Compensation

There will be no payments, either monetary or non-monetary as result of participation in this study. Women coming for the 2-hour laboratory test will be served with breakfast afterwards.

The breakfast will consist of hot milo or tea beverage with either meat pie or rock buns and boiled eggs.

Conflict of interest

We the researchers hereby declare that we do not have any conflict of interest whatsoever relating to the study.

Contacts for additional information

In case of any pertinent questions about the research, please ask them now for further clarification. If later, some issues arise that enquire explanation, feel free to contact Faith Agbozo on 0262 165005 or via email on faagbozo@uhas.edu.gh

Your rights as a Participant

This research has been reviewed and approved by the Ghana Health Service Ethics Committee. If you have any questions about your rights as a research participant you can contact the Administrator of the Ghana Health Service Ethics Committee, Madam Hannah Frimpong on any of the following telephone numbers 0302681109; 0244712919; 0243235225 or 0507041223. You can also contact her through her email address at Hannah.Frimpong@ghsmail.org

Informed Consent Form

Evidence of willingness of volunteer to participate on the study

"I have read the foregoing information, or it has been read to me. I have had the opportunity to ask questions about it and any question I have asked has been answered to my satisfaction. I consent voluntarily to participate as a subject in this study. I understand that I have the right to withdraw from the study at any time without it affecting my further medical care in any way. I have not waived any of my rights by signing this consent form. Upon signing this consent form, I will receive a copy for my personal records".

Name of participant: _____

Signature of participant: _____

Date (Day/month/year): _____

If unable to sign, thumb-print in the space above

If participant is unable to read, the witness to the consent process should complete this section

I have witnessed the accurate reading of the consent form to the potential participant, and the individual has had the opportunity to ask questions. I confirm that the individual has given consent freely.

A literate witness must sign (if possible, this person should be selected by the woman and should have no connection to the research team). Participants who are illiterate should include their thumb print as well.

Name of witness: _____

Signature of witness: _____

Date (Day/month/year): _____

If unable to sign, thumb-print in the space

Name of field worker: _____

Signature of field worker: _____

Date (Day/month/year): _____

Name of investigator: _____

Signature of investigator: _____

Date (Day/month/year): _____

8.3 Referral and Feedback form

_____/_____/20_____

Referral Letter

Dear Specialist,

Madam _____ is a participant on our study which is primarily aimed to validate the screening and diagnostic tools for GDM, estimate prevalence of hyperglycaemia and malnutrition in pregnancy, assess risk factors, determine maternal and neonatal pregnancy outcomes associated with the condition and evaluate early postpartum glycemic changes and health status of mother-infant pairs.

In the course of the study, the research team has made the following observations:

_____

_____

_____

_____

_____

_____

_____

_____

_____

_____

_____

As a result, we are referring our client to you for advice and management. We kindly request that you provide us feedback on treatment provided to her.

Thank you for your kind cooperation

_____

Ms Faith Agbozo *(Principal Investigator - PhD Student in Public Health with specialization in Epidemiology/Biostatistics, and Reproductive/Child Health)*

On behalf of **Prof Dr Albrecht Jahn** *(Academic Supervisor - PhD Public Health; MD, Specialist in Obstetrics and Gynaecology; MSc. in Community Health & Health Management; MSc. Biology, Dipl. Biol.)*

Feedback from Specialist

Name of Client: _____

Folder Number: _____

Name of Facility: _____

_____

Date: _____

Primary diagnosis: _____

_____

Secondary diagnosis: _____

_____

Treatment given: _____

_____

_____

_____

_____

_____

_____

Next Appointment Date (if any): _____

Any Other Information or Comments: _____

_____

_____

_____

_____

Signed

_____

Name of Physician

8.4 Supplementary Results

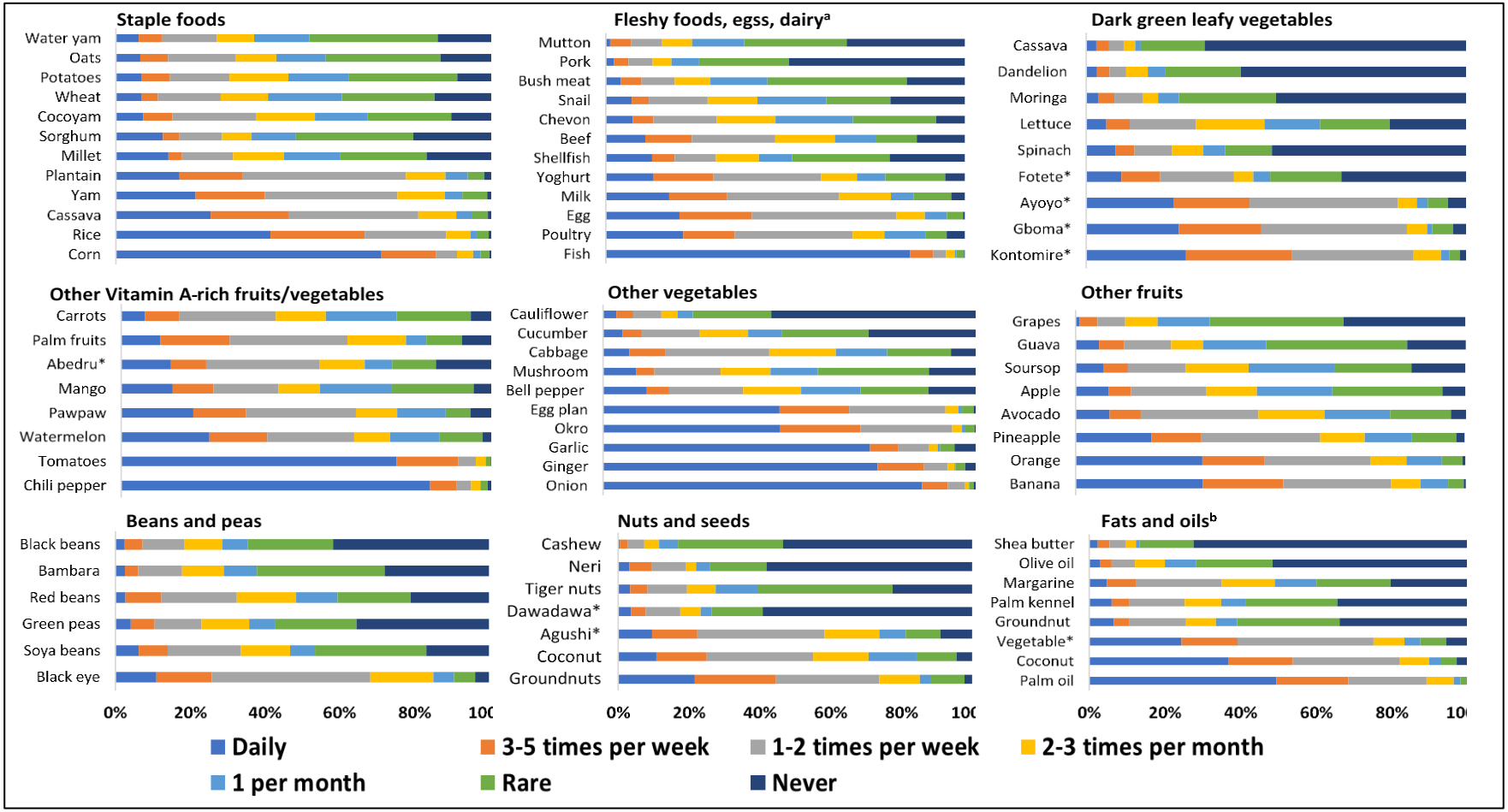

Figure 16. Habitual dietary intakes according to the FAO minimum dietary diversity indicator for women and the frequency of consumption

[a]Eggs and dairy products are two separate groups but added to the fleshy food group due to similarity in nutrient content. [b]Fats/oils is not part of the FAO food list for assessing dietary diversity. Dawadawa (African locust bean), agushi (melon seeds), 'kontomire' (cocoyam leaves), 'gboma' (African eggplant leaves), ayoyo (corchorus leaves), fotete (Amaranthus leaves), abedru (Turkey berries) and vegetable oil (includes all types commercially produced).

9 CURRICULUM VITAE

FAITH YESUTOR AGBOZO

Nationality: *Ghanaian* Date of Birth: *September 12, 1984*
Sex: *Female* Marital status*: Married (with 3 children)*

Education

Oct 2015- Sept 2019	***PhD Candidate*** (Public Health), Heidelberg Institute of Global Health, Medical Faculty, Heidelberg University, Germany
Aug 2010- Dec 2012	***MPhil Nutrition,*** University of Ghana, Legon, Accra Ghana.
Aug 2005- May 2009	***BSc Home Science***, (First Class Honours). University of Ghana
Jan – Dec 2008	***Diploma*** *in* ***Nursing***, University of Ghana, Legon, Accra Ghana
Sept 2003- Aug 2006	***Diploma*** *in* ***Registered General Nursing***, Nurses Training College, Korle-Bu, Accra, Ghana

Work Experience

2013 to date	**Lecturer;** Department of Family and Community Health, School of Public Health, University of Health and Allied Sciences, Ho Ghana
2010-2013	**Nutrition Officer**; Ghana Health Service, Ga West Municipal Hospital. Amasaman, Accra, Ghana
2007-2010	**Staff and Senior Staff Nurse**; Ghana Health Service, Ga West Municipal Hospital. Amasaman

Voluntary Services

2017 to date	**Steering Committee Member,** Technology for Maternal and Child Health project by Savana Signatures, an NGO based in northern Ghana.
2017 to date	**Consultant** on livelihood support and female empowerment in the northern parts of Volta region, World Vision Ghana
2015 to date	**External Assessor** for certification of health facilities as baby and mother friendly, Ghana Health Service/UNICEF
2014 to date	**Counsellor** on adolescent sexual/reproductive health, Ghana Education Service
2003-2013	**Volunteer**; World Vision Ghana on girl education and adolescent sexual & reproductive health and Pathfinder Ghana on post abortion care

Professional Qualifications

2016	Certified Public Health Nutritionist (cPHN); *Reg. no. 2016/002, June 2016)*
2007	Registered General Nurse (RGN). *Registration no. 3339; December 17, 2007*

Professional Memberships

Global: International Epidemiological Association *(Life time member ID: 00007571)*
The Nutrition Society *(Member ID: 51004)*
World Public Health Nutrition Association *(Member ID: 27762661)*
Organization for Women in Science for the Developing World *(ID: 6623)*
International Lactation Consultant Association *(member ID: 163013)*
International Society for Development and Sustainability (*ID: M171107*)
Regional: Africa Nutrition Society *(Membership ID: ANS-12-177)*

West African Network of Emerging Leaders *(WANEL)*
National: Ghana Registered Nurses Association *(life time member ID: 3339)*
Ghana Nutrition Association; Ghana Biomedical Convention
University Teachers Association of Ghana

Research Grants

Co-IP Project title "Leave no child behind: Improved service and home-based newborn care" funded by German society for International Cooperation (GIZ) Clinic Partnerships Program for a project in Tamale Teaching Hospital. Amount: **49,950 Euro**. Grant ID: 1804047 (2019)

Travel Grants, Fellowships and Scholarships

2019 Fellowship for the 30th International Summer School of Epidemiology organized by the Institute of Epidemiology and Medical Biometry at Ulm University and School of Public Health, University of North Carolina at Chapel Hill. July 29 – August 02, 2019
2018 New Voice in Global Health by the World Health Summit to give a presentation at the 10th World Health Summit in Berlin Germany, October 14–16, 2018
2018 Travel grant from the Heidelberg University Graduate Academy to present at the International Federation of Gynecology and Obstetrics (FIGO) conference in Rio de Janeiro, Brazil, from October 14-19 October 2018
2017 Travel grant from the scientific committee to present at the 10th European Congress on Tropical Medicine and International Health in Antwerp, Belgium, 16-20, October 2017.
2016 Nutrition Society ANEC (NS-ANEC) Travel Fellowship Award for the 7th Africa Nutritional Epidemiology Conference in Marrakesh, Morocco
2015-2019 DAAD scholarship for doctoral training
2015-2016 Fellowship; African Women in Agriculture Research and Development
2012 Nevin Scrimshaw International Nutrition Foundation Short-Term Fellowship

Service to the Scientific Community

- *Member of the Steering Committee:* Savana Signatures (an NGO in northern Ghana working on sexual and reproductive health and rights)
- *Structured Female Career Advancement Mentorship:* Through the African Women in Agriculture Research and Development (AWARD) Fellowship Programme
- *Course Contributor* on the Reproductive Health model of the MSc International Health programme at the Institute of Public Health, University of Heidelberg, Germany
- *Journal Reviewer:*
  - Plos One
  - BMC Nursing
  - Nutrition & Health
  - Tropical Medicine & Health
  - International Journal of Nutrition & Metabolism
  - Journal of Pediatric Endocrinology & Metabolism
  - Journal of Health, Population and Nutrition
  - International Breastfeeding Journal
  - Maternal and Child Health

Supervision of Student Dissertations during the Doctoral Study Period

Postgraduate

1. 2019; Joshua Akuu, Co-supervisor. *Quality, effectiveness and satisfaction with the community –based management of acute malnutrition in Builsa North District,*

Ghana. Masters in International Health; Institute of Global Health, Heidelberg University

2. 2016/2017; Christina Schuler; Main Supervisor. *A retrospective qualitative study to explore the neonatal care practices of mothers with low birth weight infants in Hohoe Municipality*. Masters in International Health; Swiss Tropical & Public Health Institute, University of Basel, Switzerland
3. 2016; Matthew McDonald and Eunice Arthur; *Local Supervisor*; MSc Human Nutrition; *Caring practices as risk factors for undernutrition in infants living in communities of the Volta Region, Ghana*; College of Medical, Veterinary and Life Sciences, University of Glasgow, UK

Undergraduate

1. 2017/2018; Bannerman Edith; *Risk factors for metabolic syndrome: a case-control study among middle aged adults in the Kpando municipality;* Bachelor of Public Health Nutrition; School of Public Health, University of Health & Allied Sciences, Ghana
2. 2017/2018; Elsie Amegbe; G*rowth and feeding practices of twins to singleton births in the first thousand days of life: a cross sectional comparative study in the Hohoe municipality*; Bachelor of Public Health Nutrition; University of Health & Allied Sciences, Ghana

Short Courses Attended during the Doctoral Study Period

- Reproductive Epidemiology & Principles of Epidemiology; Institute of Epidemiology & Medical Biometry, Ulm University & School of Public Health, University of North Carolina, July 29-Aug 2, 2019
- Me and my Supervisor organized by Heidelberg Graduate Academy, July 2019
- Project Management organized by the Heidelberg Graduate Academy, June 2019
- Advanced Epidemiology and Biostatistics for Doctoral Students by Heidelberg Institute of Global Health. Dec 2018 - March 2019
- Effective Visual communication of science, Heidelberg University Graduate Academy, Nov 2018
- Maternal and offspring health and non-communicable disease – connecting maternal fetal medicine to the future generations – pregnancy complications and NCD by FIGO Pregnancy and NCD Committee & FIGO CBET Committee, October 2018
- Designing Effective Academic Posters by Heidelberg University, September 2018
- Introduction to emergency contraceptive by University of East Anglia, August 2018
- Research Data Management by Heidelberg University Graduate Academy, July 2018
- Global Health & Disability, London School of Hygiene & Tropical Medicine, Apr 2018
- Writing & publishing a scientific paper by Heidelberg Graduate Academy, March 2018
- Improving the Health of Women, Children and Adolescents: from Evidence to Action by the London School of Hygiene and Tropical Medicine, March 2018
- The Lancet Maternal Health Series: Global Research and Evidence by the London School of Hygiene and Tropical Medicine, December 2017
- Principles of Teaching at University by Heidelberg Graduate Academy, Sept 2017
- Midwifery in the Context Public Health by the University of Newcastle, Sept 2017
- Food and Agricultural Organization/African Network of Food Data workshop on Food Composition organized by FAO in Marrakesh Morocco on October 14, 2016
- Statistics for Nutrition Research by Nutrition Society in Marrakesh Morocco, Oct 2016
- Mixed methods research by African Doctoral Academy (ADA), Stellenbosch University, South Africa from July 04-08, 2016

- Introduction to qualitative data analysis using ATLAS.ti. at ADA, Stellenbosch University from June 27 to July 01, 2016
- Leadership and change management course by the African Women in Agriculture Research and Development (AWARD) in Kampala Uganda from May 22-28, 2016
- Women Advancement Forum: International Exchanges, Research and Academia by German Academic Exchange Service, in Accra, Ghana from April 11-13, 2016.
- Introduction to Development Politics organized by STUBE Baden Württemberg in Weil de Stadt, Germany from 11-13 December 2015

Conference Presentations during the Doctoral Study Period

1. Oral Presentation titled "Risk factors for gestational diabetes and comparison of associated pregnancy outcomes by diagnostic criteria" at the 11th European Congress on Tropical Medicine & International Health, 16-20 September 2019 in Liverpool, UK
2. Poster presentation titled "Maternal dietary intakes and anaemia in the first, second and third trimesters of pregnancy and at pre-delivery" at the 4th International Congress Hidden Hunger from February 27 - March 1, 2019 in Stuttgart, Germany
3. Poster presentation titled *"Is there need to reconsider screening procedures for gestational diabetes mellitus at lower level facilities? Evidence from a diagnostic accuracy study"* at the World Health Summit, 14-16 October 2018, Berlin, Germany
4. Oral presentation titled *"Maternal morbidities in Ghana: Risk Factors and Effect on Newborn Health Outcomes"* at the world conference of obstetrics and gynaecology from 14-19 October 2019 at Rio de Janeiro, Brazil
5. Oral poster presentation titled *"Indication and predictors for caesarean sections in Ghana and the birth outcomes"* at the 26th European Congress of Obstetrics and Gynaecology, 8-10 March 2018, Paris, France
6. Oral presentation titled *"Are we missing pregnant women with gestational diabetes? Evidence from a diagnostic accuracy study comparing glycosuria, glycated haemoglobin, random and fasting glucose to oral glucose tolerance test"*, 10th European Congress on Tropical Medicine & International Health, 16-20 Oct 2017, Antwerp, Belgium
7. Poster presentation titled *"Does gestational intake of adequate diets using the FAO women's dietary diversity indicator affects haemoglobin levels at delivery and newborn health outcomes? Preliminary findings from a prospective cohort study in Volta region, Ghana"* presented at the 10th European Congress on Tropical Medicine and International Health, 16-20 October 2017, Antwerp, Belgium
8. 7th African Nutrition Epidemiology Conference, 9-14 Oct 2016, Marrakech, Morocco
9. Ghana Biomedical Convention Conference. 2-5 August 2016, Ho, Ghana
10. 3rd International Conference on Nutrition & Growth, 17-19 March 2016, Vienna
11. 12th Federation of European Nutrition Societies conference, 20-23 Oct 2015, Berlin

Signature: **Date:**

10 ACKNOWLEDGEMENTS

Right from the word go, I knew that this journey towards acquiring a PHD was not going to be a walk over. Even though I had braced myself up mentally for the journey ahead, looking back in retrospect, I recognize that ample preparation without the support and encouragement of people within and outside the academic circles will make the process daunting if not impossible.

After virtual search from the length and breadth of Germany, I finally managed to secure an academic supervisor, Prof Dr Albrecht Jahn. He trusted my ability to accomplish the proposed study that many thought was difficult considering the time, logistics and skills needed. Prof Jahn was not only a supervisor but a mentor, research colleague and father. He imbibed in me other crucial skills like grant-writing, team building and negotiations skills that will shape my career path for life. Mein Doktorvater, ich bedanke mich ganz herzlich bei Ihnen.

And to the entire 'Bergheimer' group – Prof. Dr. med. Olaf Müller, Dr Florian Neuhann, Mrs. Gold-Feuchtmüller, Dr Claudia Beiersmann, and to my colleagues Sandra, Margarida, Nuri, Joy, Fekri, Babak, Veronica, Lena, Caroline, Shahrzad, Frederick, Elvis .....…., I thank you all for providing serene environment within the 'Global Health Policies and Systems' and 'Disease Control in Disadvantaged Populations' research groups and for making it an 'academic family' worth living and working with.

Heartfelt gratitude to the Deutscher Akademischer Austauschdienst (DAAD) and the Government of Ghana for providing financial support towards my doctoral training. Also, I gratefully acknowledge my home institution and employer, the University of Health and Allied Sciences for granting me permission to be away on further studies.

With nostalgia I remember the stress and challenges of tracing pregnant women from their first antenatal care to 12 weeks after delivery; the bumpy journeys that began before dawn, the sad news about the loss of pregnancies; the breakfast package for participants that took forever to be ready; the many times we got lost trying to locate study participants in their homes; and the list goes on! These women kept faith with me and believed that the process was for the good of them and their unborn babies for which I say thank you for your cooperation for 10 months and still counting. For those whose birth outcomes were eventful, I believe lessons learnt from this study will improve birth experiences for you and for your future generations.

A bundle of gratitude to the focal persons who coordinated the project at the Volta Regional Hospital (Cynthia), Ho Municipal Hospital (Rebecca, Florence), Hohoe Municipal Hospital (Samuel, Philip, Cynthia, Perfect), Margret Marquart Catholic Hospital (Patience, Senyo), Jasikan District Hospital (Hope, Lydia) and Royal Clinic Ho (Judith and Mary). Many thanks for being my third and fourth eyes in the study facilities. My gratitude to the management and staff of the Ghana Health Service based in the study hospitals for their support during the fieldwork. Kudos to the laboratory team (Rukiya, Shelter, Joshua, Nicoline) at the Research Lab of the University of Health and Allied Sciences, School of Public Health in Hohoe headed

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To all who pushed me directly and indirectly towards this path, it turned out to be a worthwhile push and I owe it also to you.

Above all, you the Almighty God deserve all praise for how far you have brought me!

EIDESSTATTLICHE VERSICHERUNG

1. Bei der eingereichten Dissertation zu dem Thema

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