GHANA COLLEGE OF PHYSICIANS AND SURGEONS

FACULTY OF OBSTETRICS AND GYNAECOLOGY

SONOGRAPHIC MEASUREMENT OF THE FETAL ADRENAL GLAND AS A MARKER OF ADVERSE PERINATAL OUTCOME IN PREECLAMPSIA.

OPEI KWAFO ADARKWA

(BSc., MB ChB, MGCS, MPH)

SEPTEMBER 2023

GHANA COLLEGE OF PHYSICIANS AND SURGEONS

FACULTY OF OBSTETRICS AND GYNAECOLOGY

SONOGRAPHIC MEASUREMENT OF THE FETAL ADRENAL GLAND AS A MARKER OF ADVERSE PERINATAL OUTCOME IN PREECLAMPSIA.

FACULTY OF OBSTETRICS AND GYNECOLOGY

THESIS SUBMITTED TO THE FACULTY OF OBSTETRICS AND GYNAECOLOGY, IN PARTIAL FULFILMENT OF THE REQUIREMENTS FOR THE CONFERMENT OF A FELLOW OF THE GHANA COLLEGE OF SURGEONS (FGCS) IN MATERNAL FETAL MEDICINE.

FINAL SUBMISSION

AUTHOR (FULL NAME) OPEI KWAFO ADARKWA

RESIDENT NUMBER: OG/07/19/013/F

WORD COUNT 19.980

SEPTEMBER, 2023

Final version 1.0 6/2023

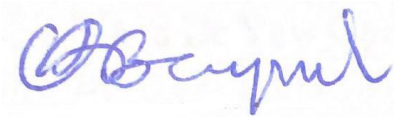
DECLARATION

I hereby declare that I have duly acknowledged the intellectual property of others in this work. The contents of this dissertation are mine and I have not submitted it to any other institution for the award of a degree or published it in any other journals.

SIGNATURE…  …… DATE 13/11/23

DR. OPEI KWAFO ADARKWA

(CANDIDATE)



DR. ATTA OWUSU BEMPAH DATE 13/11/23

(ACADEMIC SUPERVISOR)

DR. MICHAEL YEBOAH DATE 13/11/23

(HEAD OF DEPARTMENT)

ACKNOWLEDGEMENT

I am immensely grateful to the Almighty God for giving me life, strength, and the resources to conduct this study.

I would like to express my sincere gratitude to my supervisor, Dr. Atta Owusu Bempah, for his unwavering support, guidance, and expertise throughout the entire duration of this thesis. His dedication, constructive feedback, and encouragement have been priceless in moulding this research project to this stage.

I am also grateful to Dr. Michael Yeboah, the Head of the Directorate (HOD) for his availability and immense support throughout this study.

I also acknowledge the consultants, senior specialists, and esteemed professors who supported me to ensure the successful completion of this study. They are Dr. Amponsah Peprah, Dr. Roderick Larsen-Reindorf, Dr. Eric Lartey Quarshie, Dr. Yaw Opare Larbi, Dr. Frank Ankobea, Dr. John Jude Annan, Dr. Thomas O. Konney, Dr. Kwabena Amo- Antwi, Dr. Augustine Tawiah, Professor Baafuor Opoku, Professor Henry Sakyi Opare-Addo, and Professor Alexander Tawiah Odoi.

I also want to express my gratitude to Theophilus Adu- Bredu and Mr. Bernard Arhin, who brought their technical expertise to bear during the ultrasound examination of study participants, as well as during the analysis stage.

I extend my heartfelt appreciation to the participants of this study, whose voluntary involvement and cooperation have provided the necessary data for this research. Their willingness to share their information and allow for ultrasound examination has enriched the findings and implications of this study.

Lastly, I want to express my deepest appreciation to my family for their unwavering love, encouragement, and belief in my abilities. Their constant support, understanding, and sacrifices have been the bedrock of my academic journey.

ABSTRACT

Background

Preeclampsia is a leading cause of maternal and neonatal morbidity and mortality worldwide. The situation is alarming in Lower- and Middle-Income Countries like Ghana. Data from the two leading tertiary referral centres in Ghana corroborate these statistics. Perinatal morbidity and mortality rates remain high despite several advances. This has been the situation in the two leading Tertiary Health facilities in Ghana. Tools are needed to better predict perinatal outcomes, improve clinical decision-making, and facilitate parental counselling. The fetal adrenal gland plays a crucial role in the survival of the fetus in utero, ex-utero and later in life especially under stressful conditions like preeclampsia. Few studies have investigated the role of the ultrasound measurement of the fetal adrenal gland among growth-restricted fetuses. This is a major fetal complication of preeclampsia and further studies are needed to better elucidate the role of gestational-age-specific fetal adrenal gland size as a marker of adverse perinatal outcomes.

Objective

The main objective of the study was to evaluate the ultrasound measurement of the fetal adrenal gland dimensions and their relationship with adverse perinatal outcomes in preeclampsia.

Methods

This was a cross-sectional study conducted in a tertiary referral facility in Ghana, which explored the sonographic measurement of the human fetal adrenal gland and its relationship with adverse perinatal outcomes. The study involved 120 pregnant women aged at least 18 years and above with Preeclampsia, carrying singleton non-anomalous fetuses, with Estimated Gestational Ages above 28 weeks. Sonographic measurements of the Fetal Adrenal gland and key clinical data such as physical examination findings and important laboratory results were taken. Perinatal outcome data were extracted from patients' records on the 7th day after delivery.

Data captured was cleaned and transported into STATA 17.0 and analysed.

The main outcome of the study was a composite of adverse perinatal outcome including low APGAR scores (<7) at the 5th minute, neonatal death, NICU admission, stillbirth, seizures, and

intubation, oxygen therapy. These were compared to the measured fetal adrenal gland dimensions.

Results

In all 80.00% were classified as having adverse perinatal outcomes and 20.00% had good perinatal outcomes**.** There was a statistically significant difference between the means of the fetuses that had an adverse perinatal outcome and a good perinatal outcome. The means of fetuses who eventually had an adverse outcome were smaller compared to those who had a good outcome. The Total Adrenal gland length and the Total Adrenal Gland Volume remained statistically significant even after adjusting for gestational age. P value <0.05 was used as the level of significance. The two dimensions obtained an Area Under the Receiver Operating Curve of 0.8268 and 0.8303.

Conclusion

There was a statistically significant relationship between the Total Adrenal Gland Length, Total Adrenal Gland Volume and perinatal outcomes of fetuses of mothers with preeclampsia with relatively good predictive ability. Further research is needed to calibrate its use.

Keywords: preeclampsia, adverse perinatal outcome, fetal adrenal gland, ultrasound measurements of the fetal adrenal gland size.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

ACTH	Adrenocorticotropic Hormone
ALT	Alanine Transaminase
AST	Aspartate Transaminase
BMI	Body Mass Index
cFZV	corrected Fetal Zone Volume
cTGV	corrected Total Gland Volume
DZ	Definitive Zone
FGR	Fetal Growth Restriction
FZ	Fetal zone
FZV	Fetal Zone Volume
HDP	Hypertensive Disease of Pregnancy
HELLP	Haemolysis Elevated Live Enzymes Low Platelet
HFA	Human Fetal Adrenal glands
HPA-axis	Hypothalamic Pituitary-Adrenal axis
KATH	Komfo Anokye Teaching Hospital
KBTH	Korle-Bu Teaching Hospital
MC2R	Melanocortin receptor
NICU	Neonatal Intensive Care Unit
StAR	Steroidogenic acute regulatory protein
SVD	Spontaneous Vaginal Delivery
TGV	Total Gland Volume

CHAPTER ONE
INTRODUCTION

1.0 Background

Preeclampsia can be described as a progressive multisystem disease of pregnancy characterized by new onset hypertension and proteinuria or hypertension with signs and symptoms of end-organ dysfunction with or without proteinuria in the second half of pregnancy. The exact cause is unknown, but some authors believe it is caused by placental and maternal vascular dysfunction(1). The condition is responsible for significant maternal and perinatal morbidity and mortality. It usually resolves in the postpartum period but may have long-term medical consequences including cardiovascular and renal diseases(2).

Preeclampsia belongs to a group of conditions called Placenta Mediated Pregnancy complications. It has both maternal and fetal effects. They are associated with significant maternal morbidity, iatrogenic premature delivery, adverse pregnancy outcomes and fetal death. (3)

Hypertensive Disorders in Pregnancy complicate about 2-8% of pregnancies worldwide(4). In the United States, it represents about 5% of all pregnancies(5). At the Komfo Anokye Teaching Hospital, preeclampsia contributes about 48.8% of all cases of Hypertensive Disease in Pregnancy (HDPs)(6). HDPs alone account for about 10-15% of maternal mortalities almost all of which are experienced in Lower- and Middle-Income Countries (4). A review of delivery and mortality records at KATH revealed that HDPs were the leading cause of maternal mortality over the last decade(7).

Globally, pre-eclampsia and eclampsia are responsible for about 10-15% of direct causes of maternal deaths(4). At the Korle-Bu Teaching Hospital, out of 199 maternal deaths recorded between 2010-2011, 63 (31.7%) were as a result of Hypertensive disease of pregnancy with a case fatality rate of 3.9%(8).

In terms of perinatal outcomes, a study done at the Korle-Bu Teaching Hospital; among 368 pregnant women with preeclampsia found the following adverse outcomes: Neonatal Intensive Care Unit admissions 91 (24.7%), respiratory distress syndrome 56 (15.2%), asphyxia 14 (3.8%) which needed ventilator support and preterm delivery 80 (21.7%). Stillbirth, early neonatal death, fetal growth restriction and low birth weight were present in 25 (6.8%), 14

(3.8%), 23 (6.1%) and 91 (24.7%) respectively. These complications were more common with preeclampsia than with other Hypertensive Disorders in Pregnancy. The overall perinatal mortality rate was 106 per 1000 births(9).

The timely diagnosis, management, and appropriate timing of delivery of the at-risk fetus, as well as at-risk mother, in HDPs is key to improving perinatal outcomes and achieving a successful pregnancy outcome. Despite several advances in the field of fetal surveillance, perinatal morbidity and mortality remain high. More needs to be done in terms of finding other reliable prognostic markers to appropriately diagnose, manage and time delivery to optimize feto-maternal outcomes. Under stressful in-utero conditions like preeclampsia where there is hypoxia, synthesis of cortisol from the fetal adrenals is also increased and this plays a major role in the cardiovascular adaptation of the fetus to the stress. There is also redistribution of fetal blood to the brain, the heart, and adrenals consequently there is an increase in fetal adrenal gland size and weight. Fewer studies have assessed the role of the ultrasound measurement of the fetal adrenal gland as a marker of adverse perinatal outcomes.

1.1 Study rationale

Several markers and tools for assessing fetal well-being are under investigation and have modest sensitivities in the early gestational ages. In the late gestational ages, data still shows increased morbidity among fetuses with a normal umbilical artery doppler(10). To improve clinical decision-making(11), accurately predict perinatal outcomes and facilitate parental counselling, other tools which correlate well with outcomes will have to be investigated. This study sought to investigate one possible reliable tool which may improve the accurate prediction of feto-neonatal outcomes. Again, there is paucity of normative data concerning variations in adrenal size in pregnancy and how it is affected by adverse in-utero conditions.

The fetal stress system, which is made up of the adrenal glands, the Hypothalamic Pituitary Adrenal axis, and the sympathetic-adrenal medullary system, is activated by the fetus in response to prolonged intrauterine stress. Fetal blood flow is redistributed to the brain, heart, and adrenals as part of the process of adaptation to chronic intrauterine stress.

Some authors assert that fetuses with Fetal Growth Restriction that develop larger fetal adrenal glands have better neonatal outcomes than those with smaller adrenal glands in the event of

FGR (9, 19). Physiologic autoregulation severe enough will result in FGR, but poorer outcomes or perhaps adrenal insufficiency may be seen in fetuses without this compensation (17).

The fetal adrenal gland measurement in ultrasonography has been proposed as a predictor of preterm birth (21). A few studies have assessed the role of fetal adrenal ultrasound in the prediction of pre-term labour, with far fewer assessing the relationship between fetal adrenal gland size and perinatal outcome (12). In Ghana, there is no data on the ultrasound measurement of the fetal adrenal gland and its role in the outcomes of preeclampsia. This study sought to add to the information regarding the human fetal adrenal gland and adverse perinatal outcomes. This information can inform policy change and form the basis for further research into the role of the human fetal adrenal gland in the management of preeclampsia.

1.2 Problem statement

In Ghana, preeclampsia in pregnancy is linked with high rates of maternal and neonatal morbidity and mortality. Hypertensive disorders were identified as the primary cause of maternal mortality (37.3%) in a five-year assessment of maternal deaths at the Korle-Bu Teaching Hospital (8,13). Preeclampsia is also responsible for a huge portion of perinatal death and morbidity (9). At the Komfo Anokye Teaching Hospital, the narrative is the same (6,14).

More often, it occurs in the late 2nd and 3rd trimesters where delivery may be delayed for a while to improve the chances of fetal survival if maternal and fetal conditions remain stable. Prediction of feto-maternal outcomes can be very difficult, especially in earlier gestations where fetal surveillance modalities for monitoring fetal wellbeing have comparably modest sensitivities and specificities(15). There is paucity of research data on the role of the fetal adrenal gland in preeclampsia outcomes in Ghana and Sub-Saharan Africa. Despite several advances. Preeclampsia-related perinatal morbidity and mortality remain high. Other tools which correlate well with outcomes and may support clinical decision-making and improve parental counselling are needed.

1.3 Research questions

Is there any relationship between fetal adrenal gland size and adverse perinatal outcomes?

1. What are the adrenal gland sizes of fetuses of women with preeclampsia?

2. What is the relationship between adrenal gland sizes of fetuses of women with preeclampsia and its relationship with gestational age?
3. What is the proportion of women with preeclampsia who have adverse perinatal outcomes?
4. Is there a relationship between fetal adrenal gland sizes and perinatal outcomes?

1.4 Research hypotheses

The following are the research hypotheses to be evaluated in this study:

1. Gestational age has a positive relationship with the adrenal gland size of fetuses of mothers with preeclampsia.
2. The proportion of women with adverse perinatal outcomes in preeclampsia is likely to be higher than the hypothesized value of 50%.
3. Fetuses with **s**maller fetal adrenal gland sizes are likely to have adverse perinatal outcomes in preeclampsia.

1.5 General objective

1. To assess ultrasound measurement of human fetal adrenal gland size and adverse perinatal outcomes in pregnancies complicated with pre-eclampsia.

1.6 Specific objectives

The study's primary goal is to evaluate the size of the human fetal adrenal gland as measured by ultrasound and the adverse perinatal outcomes in pregnancies complicated by pre-eclampsia with specific emphasis on the following:

1. To determine the adrenal gland sizes of fetuses of women with preeclampsia.
2. To determine the relationship between fetal adrenal gland dimensions of fetuses of mothers with preeclampsia and its relationship with gestational age.

Null hypothesis: Gestational age does not influence the adrenal gland size of fetuses

of mothers with preeclampsia.

Alternative hypothesis: Gestational age has a positive relationship with the adrenal gland size of fetuses of mothers with preeclampsia.

3. To determine the proportion of pregnant women with adverse perinatal outcomes in preeclampsia.

Null Hypothesis: The proportion of women with adverse perinatal outcomes in preeclampsia is comparable to the hypothesized value of 50%.

Alternate Hypothesis: The proportion of women with adverse perinatal outcomes in preeclampsia is likely to be higher than the hypothesized value of 50%.

4. To determine the relationship between the fetal adrenal gland dimensions and adverse perinatal outcomes in preeclampsia.

Null hypothesis: There is no relationship between fetal adrenal gland size and adverse perinatal outcome in preeclampsia.

Alternative hypothesis: Fetuses with **s**maller fetal adrenal gland sizes are likely to have adverse perinatal outcomes in preeclampsia.

Definition of terms

- **Asphyxia**- "Reduction of oxygen supply to below critical physiological levels in the tissues of neonates(16).

    - **Hypothalamic Pituitary Adrenal** (HPA-AXIS)- "A link between the central nervous system and the endocrine. It works in concert to coordinate the release of the right amount of hormones in the human body. It is key in neuropsychiatric function, homeostasis, and energy metabolism(17)

    - **Human fetal adrenal gland** – "Also called suprarenal glands because of their location right on top of the kidney. They are small, triangular-shaped glands. Their main function is to produce hormones that help regulate your metabolism, immune system, blood pressure, response to stress and other essential functions(18).

    - **Hypertensive Disease of Pregnancy**- "A spectrum of high blood pressure disorders that occur in pregnancy comprising preeclampsia, preeclampsia superimposed on chronic hypertension, gestational hypertension, and chronic hypertension(19)
    - **Neonatal Intensive Care Unit**- A specialized intensive care unit for sick babies and caring for premature infants.
    - **Perinatal period**- "The perinatal period is defined as the period from the 28th week of pregnancy to the end of the 1st week of life"(20).
    - **Pre-eclampsia**- "New onset of systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg on at least 2 occasions, at least 4 hours apart after 20 weeks of gestation in a previously normotensive individual **or** systolic blood pressure ≥160 mmHg or diastolic blood pressure ≥110 mmHg confirmed within a short interval (minutes) to facilitate timely antihypertensive therapy"(21).

      And:

    - "Proteinuria (≥300 mg per 24-hour urine collection [or this amount extrapolated from a timed collection], or protein: creatinine ratio ≥0.3, or urine dipstick reading ≥+ [if other quantitative methods are not available])"(21)

"Or with or without proteinuria, new-onset hypertension with the new onset of any of the following:

- "Thrombocytopenia (platelet count <100,000/microL)"
- "Renal insufficiency (serum creatinine of >1.1 mg/dL [97 micromol/L] or a doubling of the serum creatinine concentration in the absence of other renal disease)"(21)
- "Impaired liver function as indicated by liver transaminase levels at least twice the normal concentration".
- "Pulmonary oedema"
- "Persistent cerebral or visual symptoms"

- **"Pre-eclampsia with severe features- Any of these findings in a patient with preeclampsia:"**

- "Systolic blood pressure ≥160 mmHg or diastolic blood pressure ≥110 mmHg on 2 occasions at least 4 hours apart (unless antihypertensive therapy is initiated before this time)"
- "Thrombocytopenia (platelet count <100,000/microL)
- "Impaired liver function as indicated by liver transaminase levels at least twice the normal concentration or severe persistent right upper quadrant or epigastric pain unresponsive to medication and not accounted for by alternative diagnoses or both".
- "Progressive renal insufficiency (serum creatinine concentration >1.1 mg/dL [97 micromol/L] or a doubling of the serum creatinine concentration in the absence of other renal disease)"
- "Pulmonary oedema"
- "Persistent cerebral or visual disturbances" (21)

- **"Chronic hypertension superimposed by pre-eclampsia with severe features."**

- "A sudden increase in blood pressure that was previously well controlled or an escalation of antihypertensive therapy to control blood pressure. In addition, new onset of proteinuria or sudden increase in proteinuria in a patient with known proteinuria before or early in pregnancy" (21).

- **HELLP**
  - "Presence of Haemolysis, Elevated Liver enzymes, low platelet, hypertension may be present" (21).

- **Adverse perinatal outcome-** For this study adverse perinatal outcome has been defined as **"**Any perinatal outcome, including intrauterine fetal demise, stillbirth, early preterm birth, low birth weight, low 5-minute APGAR scores (<7), neonatal death, seizures, intubation, will be regarded as poor or adverse perinatal outcome".
- **Respiratory Distress Syndrome**- "A condition of the newborn marked by dyspnea with cyanosis, most frequently occurring in premature infants, children of diabetic mothers and infants delivered by Caesarean Section, and sometimes with no predisposing cause". (16)
- **Sympathetic-adrenal medullary system**- "A physiological link between the sympathetic nervous system and the adrenal medulla and which plays an active role in the fetus' response to stressful stimuli" (22)

CHAPTER TWO
REVIEW OF RELEVANT LITERATURE

2.0 The burden of preeclampsia and adverse outcome

Preeclampsia is known to affect about 2-8% of all pregnancies worldwide. It is said to be progressive, unpredictable, and serious(23)". Yearly, about 46,000 maternal deaths and over 500,000 fetal and newborn deaths can be attributed to preeclampsia. The burden of the disease is disproportionately high in Lower- and Middle-Income countries. Factors accounting for the high rates of neonatal morbidity and mortality in the developing world include the lack of quality Neonatal Intensive Care services(24). In Sub-Saharan Africa, every 1in 10 pregnancies suffers from Hypertension in Pregnancy. In a meta-analysis involving 854,304 women, 9.2% (95% CI: 4.2-16.0) had superimposed preeclampsia, 44% (95% CI: 36.7-52.0) had preeclampsia and 22.1% (95% CI: 14.8-30.8) had severe preeclampsia(25). Preeclampsia makes up a large fraction of the hypertensive conditions experienced during pregnancy in Ghana, affecting about 7.6% of all pregnancies(8). Over the last decade, these have overtaken haemorrhage as the leading cause of maternal mortality in two main tertiary hospitals in Ghana(8,14).

In terms of the age distribution, the majority of patients with preeclampsia are between 20 – 34 years(6,9). Increasing maternal age in part due to increasing levels of education and older age at marriage and increasing use of Artificial Reproductive Technologies is a recognised risk factor. This was demonstrated by Bartsch et al in their study where they found the relative risk of preeclampsia to be increasing with increasing maternal age (age ≥35: RR 1.2, 95% CI 1.1-1.3; age ≥40: RR 1.5, 95% CI 1.2-2.0)(26). One large systematic review found the prevalence of preeclampsia among 291,247 adolescents to be 6.7% (27). There are also other studies which have found an association between adolescence with preeclampsia(28). Lower socioeconomic status has been linked to preeclampsia in some. In a study in Sweden, it conferred about five times the risk. This study was done among 3547 pregnancies. (29,30). Other studies have not supported the association of lower socioeconomic status with preeclampsia(30–35).

Pregnancies complicated by preeclampsia have a higher risk of poor neonatal outcomes owing to prematurity and poor uteroplacental perfusion. In a study done at the Korle-Bu Teaching Hospital, a composite of poor neonatal outcomes of 58.2% was obtained for both preeclampsia and eclampsia(36). A similar study done in Kumasi, found adverse maternal or perinatal

outcomes in hypertensive disease to be 87%. Preterm delivery at or under 34 weeks was more likely in patients with preeclampsia or eclampsia (adjusted RR, 2.74; 95% CI, 1.40–5.36) and caesarean section (adjusted RR, 1.37; 95% CI, 1.01–1.87)(6). In another study done in Accra among 798 women with Hypertensive disease in Pregnancy, clients with pre-eclampsia had a higher rate of emergency Caesarean section (88.9% vs. 50%, P = 0.04), accompanied by an adjusted Relative Risk of low birth weight (adjusted RR 7.95, 95% CI 1.41–44.80) and perinatal death (adjusted RR 18.41, 95% CI 1.20–283.22)(37).

Other short-term morbidities associated with Preeclampsia include cerebrovascular bleeding, retinal detachment, kidney injury and HELLP syndrome. Aside from these, Preeclampsia continues to demonstrate significant perinatal morbidity and mortality. The consequences of it are known to outlast delivery. It has future consequences that affect both the mother and the child. Research is still ongoing in the field, but currently, hypertension and chronic kidney disease have been implicated even up to about 15 years post-delivery(2). The evidence has further debunked the age-old theory that delivery of the placenta is the cure for preeclampsia." Women who have had preeclampsia develop hypertension at an earlier stage in life allowing the disease to have a much longer time to have lasting effects on their bodies. About half of women who are diagnosed with preeclampsia in pregnancy also develop hypertension in 10 years(38). The risk of cardiovascular accidents including thrombosis, ischemic and haemorrhagic strokes also increases significantly(39,40) with a previous history of preeclampsia. A similar increase in relative risk is also present with end-stage kidney disease. The progression to end-stage kidney disease could be proportional to the time of occurrence and the severity of preeclampsia. It worsens with every pregnancy saddled with preeclampsia(41).

2.1 Fetal adrenal gland physiology and steroidogenesis

The Human Fetal Adrenals (HFA) are different from adult adrenals in terms of structure. Around week seven of gestation, when the adrenal cortex has differentiated into an outer Definitive Zone (DZ) and an inner Fetal Zone (FZ), which together make up 80–90% of the adrenal tissue, morphology is defined already at this stage. At the intersection of the DZ and FZ, a Transitional Zone forms during the second trimester and maintains its appearance up until birth.

Activation of the Hypothalamic-Pituitary-Adrenal (HPA) axis is critical to adrenal steroidogenesis. Pituitary-produced Adrenocorticotropic Hormone binds to the adrenal melanocortin receptor (MC2R) which activates the endocrine capabilities of the HFA(42). The Fetal Zone and subsequently, the Transitional Zone are described as the most active in steroidogenesis, expressing Steroidogenic acute regulatory protein (StAR). If there is a stressful stimulus, the HPA axis is triggered. "Corticotropin-releasing hormone (CRH) is released from the Hypothalamus at a higher rate, which in turn stimulates the Anterior Pituitary to produce the Adrenocorticotropic Hormone (ACTH). ACTH stimulates the adrenal gland cortex to produce glucocorticoids. Glucocorticoids negatively feedback on the HPA axis" (43).

Some authors propose that placental dysfunction as occurs in Hypertensive Disease in pregnancy will lead to a chronic hypoxic state, which will act as a stressor, thus activating the HPA axis. Subsequently, there will be hypertrophy of the HFA gland cortex(12).

2.2 Ultrasound appearance

The fetal adrenal gland is oval or pyramidal in the longitudinal plane. They appear discoid or lentiform in the transverse plane. Sonographically, the fetal adrenal cortex appears echolucent and is surrounded by a more echogenic medulla. It can be visualized in the first trimester but reliably imaged after 20 weeks. There is a linear increase in the size of the fetal adrenal glands from 12-17 weeks of gestation(44). Adrenal glands lie superior and medial to the ipsilateral kidney. The medial border of the left adrenal gland is adjacent to the aorta while the medial border of the right fetal gland is adjacent to the inferior vena cava. The Echogenic central strip is formed by congested sinusoids in the inner portion of the gland. The peripheral hypoechogenic area represents the less congested adrenal or definitive cortex. The echogenic area increases in echogenicity as gestational age increases especially in the last 5 weeks of pregnancy. The length increases with gestational age and maintains a constant relationship with kidney length (48-66% of renal length)(45).

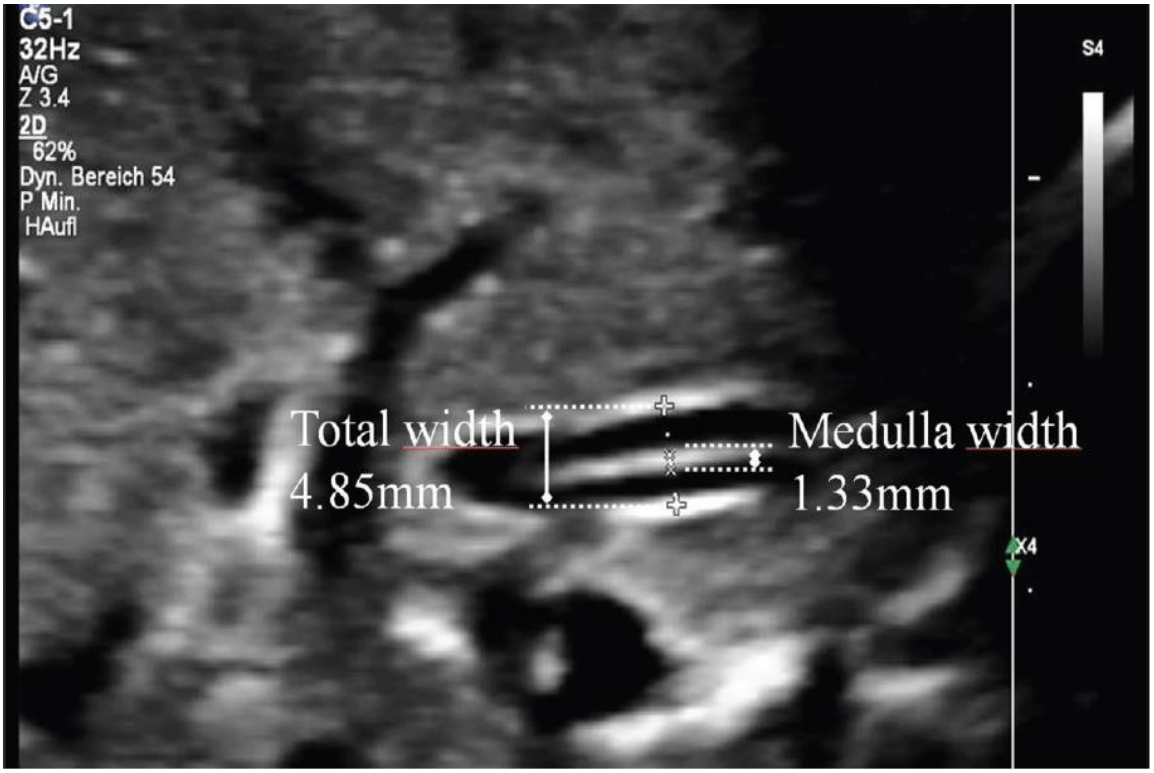


Figure 2.2 1 Fetal Adrenal in a Zoomed Transversal Plane

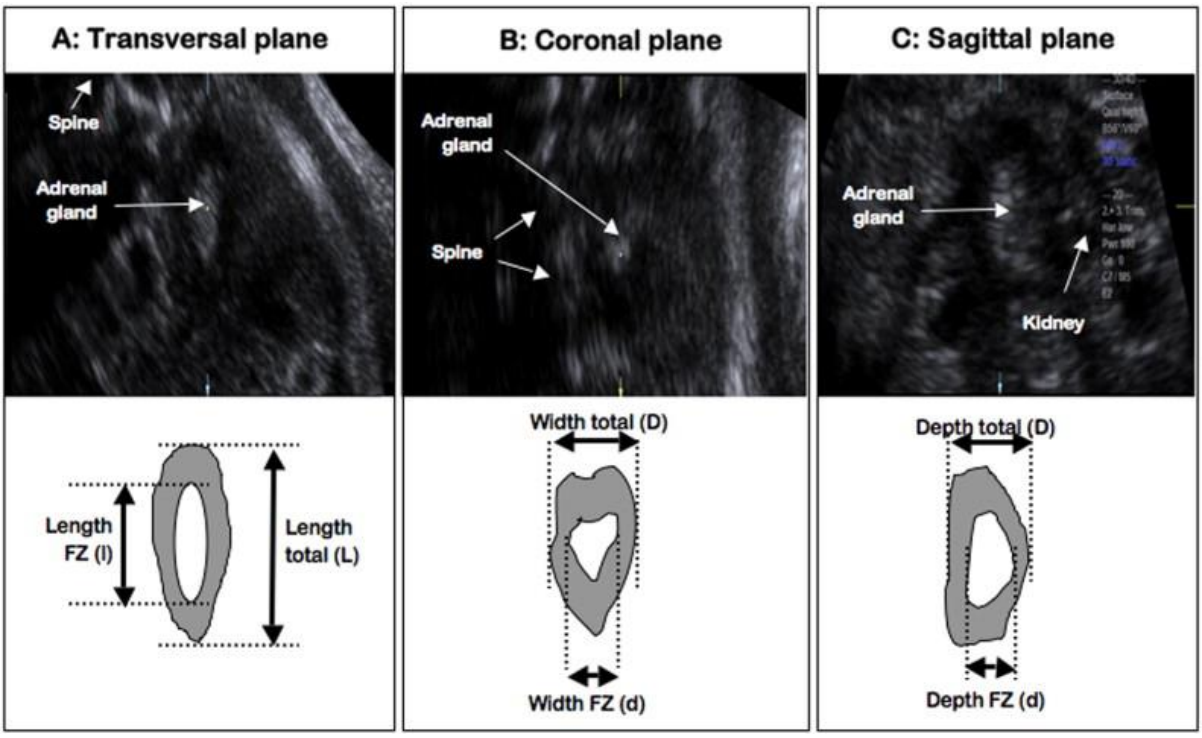


Figure 2.2 2 A, "Ultrasonograph of transverse, B, coronal, and C, sagittal planes of the Human Fetal Adrenal gland(46).

2.3 Role of ultrasonographic measurements of the fetal adrenal gland

In one study, the volume of the fetal adrenal gland was imaged in 3D ultrasonography as a marker for the prognosis of preterm labour. It found fetal adrenal gland volume measurement as a reproducible, accurate, non-invasive, and novel marker for the prediction of preterm birth(47–49).

Furthermore, some researchers have been able to apply the use of fetal adrenal Doppler velocimetry in the prediction of spontaneous pre-term labour. Carvalho et al found out in their limited study involving 51 pregnant women between 24 and 36 weeks that fetal adrenal doppler velocimetry is predictive of preterm labour within 7 days like cervical length measurement (50)

Hoffman et al conducted a multicentre observational nested cohort research et al. on asymptomatic nulliparous women bearing singletons between the ages of 22 and 36 weeks. In this study, 1627 pregnancies' results were examined They concluded that in asymptomatic nulliparous women, the size of the fetal adrenal glands was not a reliable indicator of spontaneous preterm birth (51)

Ultrasound measurement of the fetal adrenal gland has also been applied in the prediction of the success of induction of labour. Ozdemir et al found that 2D ultrasound assessment of the fetal adrenal gland can be included in the protocol for assessment of clients for success of induction labour based on corrected fetal adrenal gland volume measurements(52). Mosbeh et al also compared modified Bishop's score, cervical length assessment and fetal adrenal gland changes in the prediction of success of induction of labour(53).

Several studies have also been done to assess the role of ultrasound in the prediction of preterm labour (54). A few studies have also assessed its role in fetal growth restriction(12,55,56).

A smaller study among 98 primigravida conducted by Assaad et al found a relationship between mode delivery and adrenal gland size. They found that fetuses who delivered via Caesarean Section had a smaller Fetal Adrenal gland size. Cut-offs based on receiver operating characteristics were D1(fetal zone length) = 0.16 cm, D2 (fetal zone width) = 0.7 cm, and D3(fetal zone depth) = 2.37 cm (57). It is important to assess other confounding factors among the primigravida studied in this study. Primigravida who had Caesarean delivery may have had other maternal and fetal factors including medical conditions in pregnancy and fetal growth Restriction which will in turn stressfully influence their fetal adrenal gland size as well as make them more prone to having operative delivery. Again, a larger study could have also made more reliable and generalizable conclusions.

Saowapak et al did a study to examine the relationship between 2D and 3D measurement of the fetal adrenal gland volume and fructosamine levels as well as Glycated Haemoglobin levels among 80 women with gestational Diabetes Mellitus.” The relationship between estimated fetal weight as well as neonatal birth weight was also determined. The total adrenal gland length and fetal zone volume were statistically significant with Estimated Fetal Weight ($r = 0.69$, $p = 0.02$ and $r = 0.84$, $p = 0.01$, respectively). After adjusting for Estimated Fetal Weight, the fetal zone volume (FZV) was significantly correlated with fructosamine levels (adjusted-OR = 2.4, 95% CI: 1.5, 3.9, $p = 0.01$) and HbA1c levels (adjusted-OR = 2.5, 95% CI: 1.6, 4.3, $p = 0.01$)”(58). They deduced from the results that Fetal Zone Volume might serve as an indiscriminate metric for glucose monitoring. The results of this study partially demonstrated the wide range of uses for fetal zone volume measurement(58). Other studies have also

examined the fetal adrenal gland and gestational diabetes mellitus and have significant changes in the size of the gland (59,60)

Researchers have also accepted the fetal adrenal gland volume as a marker to depict increased intrauterine fetal stress, this they demonstrated in their study where they found a larger fetal adrenal gland volume and a lower cortisol to DHEAS ratio for fetuses with exposure to intraamniotic infection (61). Studies have also focused on the possibility of using fetal adrenal gland changes as a potential marker for compromised fetuses. The corrected Total adrenal gland volume was larger and the corrected fetal zone volume was smaller for compromised fetuses(56). Oelmeier's study involving 445 singletons showed that the adrenal gland ratio did not correlate with outcome. However, in logistic regression, both umbilical artery Pulsatility index and adrenal gland ratio showed a significant relationship with fetal growth restriction(62).

Esser et al also published a case report which suggests that a grossly enlarged fetal adrenal gland may be a prenatal indicator of prenatal Congenital Adrenal Hyperplasia (CAH). They published two case reports which all had enlarged fetal adrenal glands, and they all also had CAH. Both pregnancies were from the same parents who were found to be heterozygous for nucleotide 656 of the CYP21B gene. CAH was confirmed by autopsy and Chorionic Villous Sampling in the first and second pregnancies respectively(63).

2.4 Composite parameters showing significant results.

Heese et al 2018 used the width of the cortex (the half of total width minus medulla width) and the adrenal gland ratio (ratio of total width and medulla width). The mean of the cortex width and the adrenal gland ratio in growth-restricted fetuses were higher in comparison to the controls ($P < 0.001$; $P = 0.036$, respectively). (12).

In growth-restricted fetuses, Kaya et al 2019 found that the Z-scores for the gland total length, total width, cortex width and ratio of the total width to medulla width were significantly higher in the study group ($p<0.001$). The medulla length showed no difference(55).

Mohajeri et al 2017 also found a significant correlation between Adrenal Gland Volume, Gestational Age, and fetal Zone Volume. FGR fetuses in their study had a larger corrected adrenal gland volume [Volume= (π/6) x Length x width x depth)/ Estimated Gestational

Age(weeks)] and smaller fetal zone volume in comparison with their controls (p<0.001). In the same study, he demonstrated that a smaller Adrenal Gland Volume and a higher fetal zone/adrenal ratio in FGR fetuses were associated with an adverse perinatal outcome(56).

In a related study involving 406 pregnant women (343 controls and 63 FGR fetuses), the mean cortex width and the adrenal gland ratio were higher in FGR fetuses (P < 0.001; P = 0.036, respectively).

It may seem these adaptive changes occur in fetuses that have FGR after continuous exposure to a chronic hypoxic intrauterine environment due to uteroplacental dysfunction. Failure of the fetus to undergo these changes may be predictive of a poor perinatal outcome(55).

2.5 Adrenal gland size in growth-restricted fetuses

Fetal Growth Restriction (FGR) is described by the Delphi Consensus as Abdominal Circumference (AC) or Estimated Fetal Weight (EFW) of less than the 3rd centile or absent/reversed EDF irrespective of the fetal growth percentile. When less than the *10th centile (but > 3rd centile)* is used, a *Pulsatility Index* (PI) greater than the *95th Centile* for uterine artery and (or) umbilical is needed to confirm the diagnosis for Early-onset FGR. For late onset FGR, two out of three of the following criteria are needed to make a diagnosis of FGR; the EFW or AC less than the *10th centile,* AC/EFW crossing centiles greater than 2 quartiles and Umbilical Artery Doppler PI greater than the 95th centile(64).

Table 2.5 1 Consensus-based definition for early and late fetal growth restriction (FGR) in the absence of congenital anomalies(64).

Early FGR: *GA < 32 weeks, in absence of congenital anomalies*	*Late FGR:* *GA ≥ 32 weeks, in absence of congenital anomalies*
AC/EFW < 3rd centile *or* UA-AEDF	AC/EFW < 3rd centile
Or 1. AC/EFW < 10th centile *combined with* 2. UtA-PI > 95th centile *and/or* 3. UA-PI > 95th centile	*Or at least two out of three of the following* 1. AC/EFW < 10th centile 2. AC/EFW crossing centiles >2 quartiles on growth centiles* 3. CPR < 5th centile *or* UA-PI > 95th centile

*Growth centiles are non-customized centiles. AC, fetal abdominal circumference; AEDF, absent end-diastolic flow; CPR, cerebroplacental ratio; EFW, estimated fetal weight; GA, gestational age; PI, pulsatility index; UA, umbilical artery; UtA, uterine artery.

FGR can be due to structural anomalies, infections, genetic abnormality, and placental dysfunction, and may have a significant impact on perinatal morbidity and mortality(12). Placental dysfunction may serve as chronic intrauterine stress for the ~~f~~etus; thus, activating the Fetal Stress System. The fetal stress system is composed of the adrenal glands, the HPA axis, and the sympathetic-adrenal medullary system. The adrenal cortex produces glucocorticoids while the medulla produces catecholamines. The process of fetal adaptation to chronic intrauterine stress involves the redistribution of blood flow to the brain, heart, and fetal adrenals. Some authors assert that fetuses having growth restriction develop larger fetal adrenals than those with poorer outcomes (12,56). Physiologic autoregulation severe enough will result in FGR, but poorer outcomes or perhaps adrenal insufficiency may be seen in fetuses without this compensation(65). The fetal adrenal gland measurement in ultrasonography has been proposed as a predictor of preterm birth (66). Several studies have investigated the association between Fetal Growth Restriction and ultrasound measurement of the fetal adrenal gland (12,55,56). On the contrary, a study done by Blue et al found no association between adrenal gland size and FGR-related morbidity(65).

2.6 Imaging modalities for the human fetal adrenal gland

Several imaging modalities are available for the human fetal adrenal gland. The human fetal adrenal and its abnormalities can be visualized easily using ultrasound(67). At about 9 weeks gestation the human fetal adrenal gland can be confused with the fetal kidneys. They can be imaged at the end of the first trimester, but reliable visualization can be done after 20 weeks of gestation(68). In most published studies, the fetal adrenal gland has been evaluated during fetal ultrasound using a transabdominal technique (12,45,47,69). A few papers have also adequately visualized the fetal adrenal gland via the transvaginal approach(70). The transvaginal ultrasound generally produces better image quality due to higher frequencies but with a limited field of vision(71). Other authors have also compared ultrasound measurements of the fetal adrenal gland using 2-dimensional and 3-dimensional ultrasound. “The authors found that there was a significant correlation between 3-D and 2-D methods (ICC = 0.979; 95% confidence interval [CI]: 0.971 to 0.984). The coefficient of repeatability for the 3-D was better as compared to the 2-D method (intra-observer 3-D: 30.8, 2-D:57.6; interobserver 3-D:12.2, 2-D: 15.6)(72).

There have been documented reports of the use of Magnetic Resonance Imaging in the assessment of the fetal adrenal gland. The visibility of the T2-weighted images of the gland up to 30 weeks is high (90.3-97.2%). In the second trimester, however, the signal intensity of the T2- Weighted images was lower but became less distinct in the third trimester(73). Magnetic Resonance Imaging can distinguish soft tissue excellently. Its use is limited by availability, cost, and expertise to interpret fetal MRI.

There are no documented studies on the use of Computerized Tomography obviously due to higher fetal radiation which may increase the risk of teratogenicity and oncogenicity (74). Due to the above reasons, CT scanning is not currently recommended for imaging of the fetal adrenal gland. It is important to consider safer alternatives.

Two-dimensional ultrasonography or B-mode was used for this study because of its safety, availability, and ability to visualize the fetal adrenal gland. The B-mode or two-dimensional ultrasonography does not require any special equipment or transducer and can easily be integrated into routine ultrasound protocol. The fetal adrenal gland parameters have been shown to have good interobserver and intra-observer correlation coefficients and as in previous studies, measurements were obtainable in all cases(12).

2.7 Technique for the ultrasound measurement of the human fetal adrenal gland

To complete this study, as explained in the previous section the two-dimensional ultrasonography approach was chosen because of its safety, availability, effectiveness, and ease of integration into routine ultrasound protocols.

The fetal adrenal gland has been visualized by authors using the three axial planes. The adrenal gland can easily be visualized at the level of the axial plane used for the accurate measurement of the Abdominal Circumference. The gland is in the axial plane above the kidneys. It is superior and medial to the kidney and is seen as a pyramidal (sagittal and coronal views) structure having two zones; an outer hypoechoic zone and an inner hyperechoic zone the gland proximal to the probe is measured and this can be either the left or right fetal adrenal gland. The probe is moved(sweeping) cephalad on the fetus after obtaining a transverse section of the kidneys in the axial or transverse plane. There is no difference between the left and the right

fetal adrenal gland from a previous study(75). The gland is then measured in the axial (length), sagittal (depth) and coronal(width) plane(75–77).

The gland can also be accurately measured using two orthogonal planes. The length and width are measured in the transverse plane while the depth is measured in the sagittal plane by carefully rotating the probe through an angle of 90 degrees. The callipers are placed from the outer border to the outer border(78). The volume of the gland is calculated using the ellipsoid formula or the three-dimensional Virtual Organ Computer-Aided analysis method (VOCAL)(79).

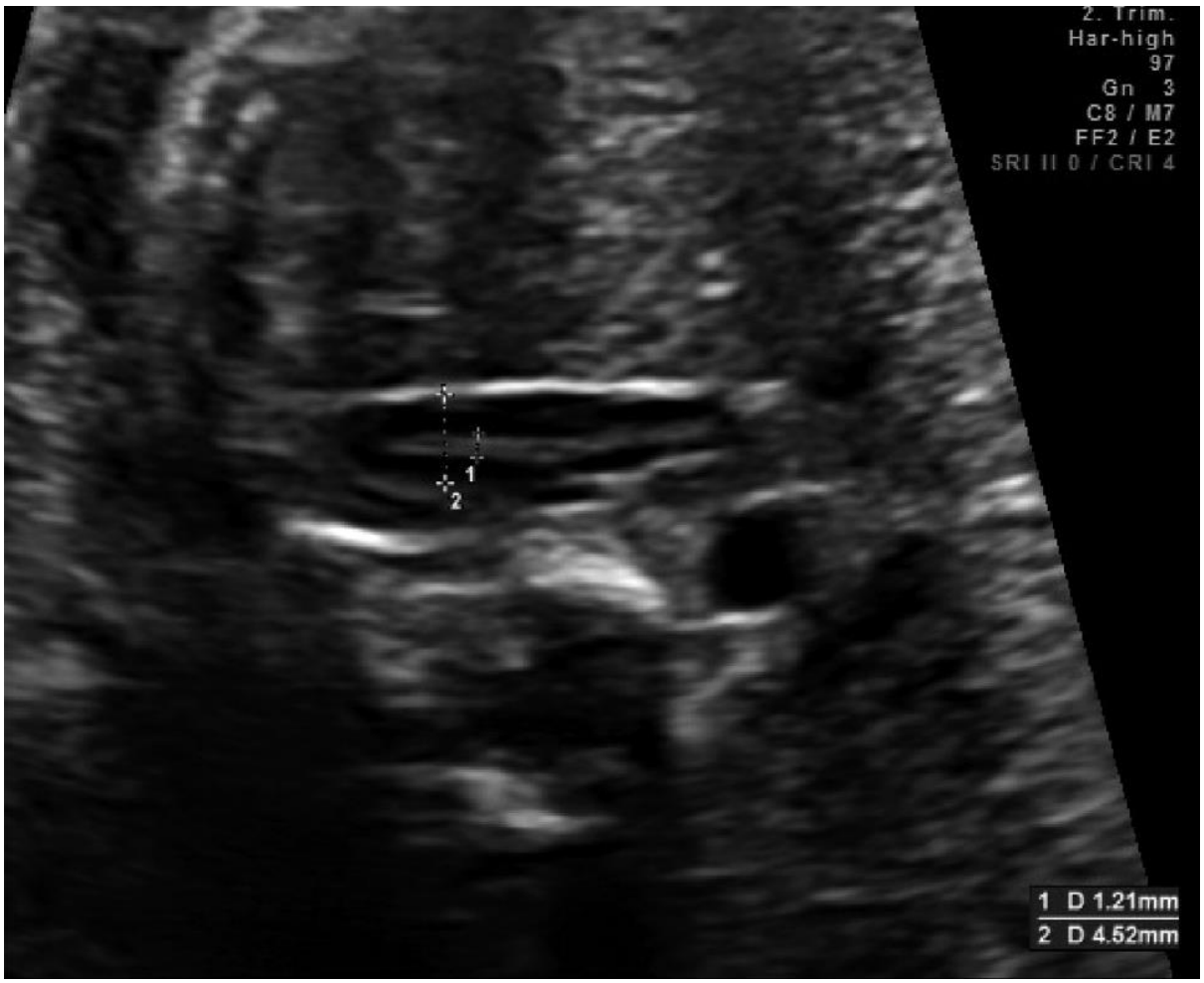


Figure 2.7 1 “Image of the fetal adrenal gland in the axial or transverse plane. Fetal Width (1) and Total Gland Width” (2).

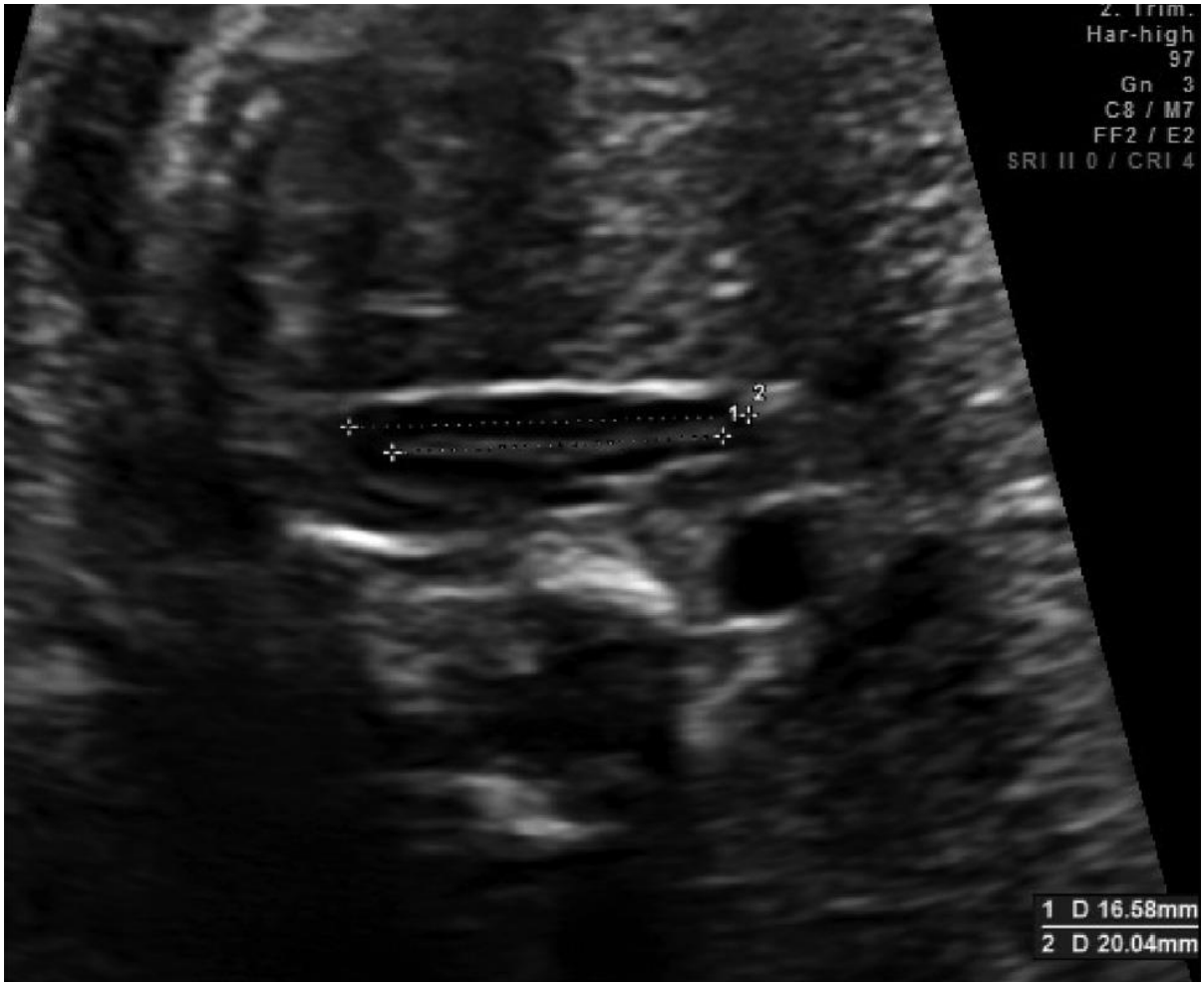


Figure 2.7.2 Image of the fetal adrenal gland in the transverse or axial plane. Fetal Zone Length (1) and Total Adrenal gland (2).

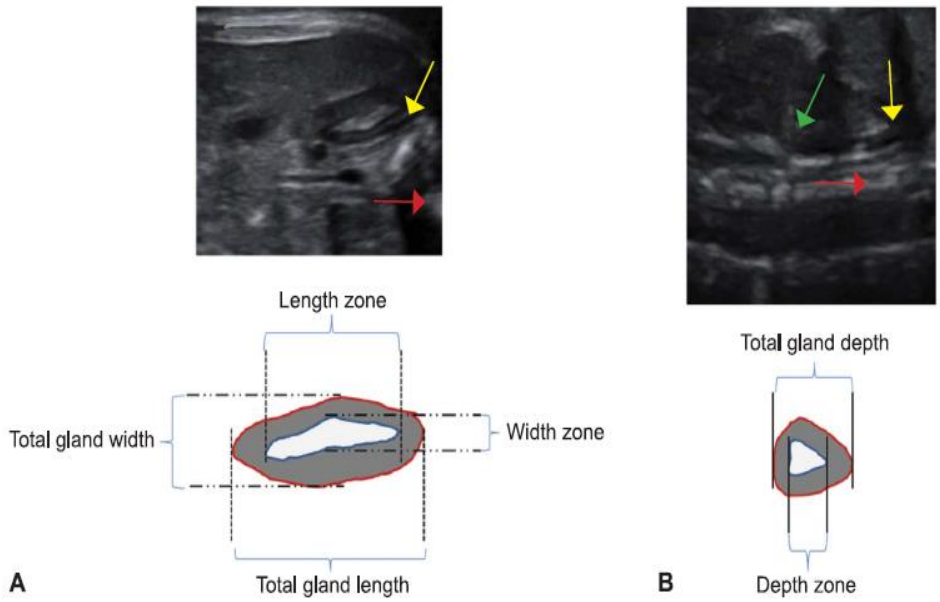


Figure 2.7.3 “Technique for measuring the fetal adrenal gland. A. Transverse measurements. Yellow arrow, adrenal gland; red arrow, spine. B. Sagittal measurements. Yellow arrow, adrenal gland; red arrow, spine; green arrow, kidney”(51).

2.8 Fetal adrenal gland sizes in fetuses of mothers with preeclampsia.

According to the International Society for the Study of Hypertension in Pregnancy 2018 guidelines, the diagnostic criteria for preeclampsia include “gestational hypertension accompanied by one or more of the following new-onset organ dysfunction at or after 20 weeks’ gestation”. The fourth criterion is “Uteroplacental dysfunction (such as fetal growth restriction, abnormal umbilical artery Doppler waveform analysis, or stillbirth)”(80).

The link between preeclampsia and fetal growth restriction cannot be overemphasized. In preeclampsia, there is defective deep placentation “which is characterized by a significant increase in the number of junctional zone myometrial spiral arteries with absent or partial transformation. There is a restriction of trophoblastic invasion of spiral arterioles and obstructive lesions in spiral arteries in the junctional zone of the myometrium. This leads to an increase in placental vascular tone and resistance, decreased perfusion and placental ischemia. “This phenomenon has been associated with a spectrum of pregnancy complications like pre-eclampsia, intrauterine growth restriction, pre-term birth, pre-term premature rupture of

membranes, late sporadic miscarriage and abruptio placentae"(81). The increase in resistance is evidenced by notching in the uterine artery waveform around 20 weeks of gestation(82).

Pre-eclampsia is generally associated with placental lesions. The primary vascular manifestations as described above, the existence of oxidative stress and endothelial damage, adversely impact uteroplacental blood flow and possibly cause fetal growth restriction with underlying hypoxia and acidosis(82).

A study described "the outcomes of 31 normotensive growth-restricted fetuses, 31 growth-restricted fetuses with pre-eclampsia and 120 control fetuses. The research evaluated the following indices: umbilical artery, middle cerebral artery, ductus venosus Pulsatility index, aortic isthmus blood flow index, E–A ratios, left modified myocardial performance index, and combined cardiac output(83). "The outcomes showed no difference in uteroplacental and cardiovascular indices among normotensive growth-restricted fetuses and those associated with pre-eclampsia. Therefore, the author thought it appropriate to extrapolate findings on growth-restricted fetuses with growth-restricted fetuses of women with preeclampsia"(82).

Another researcher also found similar pathophysiologic mechanisms in terms of cardiovascular remodelling and dysfunction in fetuses of mothers with preeclampsia as had been previously described for growth restriction (84,85).

Based on these research findings one can hypothesize that adrenal gland size changes in growth-restricted fetuses are like the changes of growth-restricted fetuses of mothers with preeclampsia. In the current study, we expect similar changes as found in growth-restricted fetuses.

In an earlier study done among 346 Japanese pregnant women, 9 had fetal growth restriction mostly from gestational hypertension. They found that fetuses with poor outcomes had smaller Fetal Adrenal Gland Area about $\pm$ 2SD below the mean. They concluded that the Fetal Adrenal Gland Area may help to identify fetuses at high risk of perinatal morbidity and mortality(86).

"Farzad Mohajeri et al did a study among 97 pregnant women (48 with fetal growth restriction and 49 controls) during the third trimester. 2-Dimensional Ultrasonography of the fetal adrenal gland was done and Total Adrenal Gland Volume and Fetal Adrenal Gland Volume were determined and corrected for Estimated Fetal Weight. Corrected AGV 393.9 ± 58.5 (mm3/kg)

(Mean ± SD), Corrected FZV 59.1 ± 8.4 (mm3/kg) (Mean ± SD), Fetal zone/adrenal ratio 0.15 ± 0.02 (Mean ± SD)"(56).

Sennaiyan et al found in their study that small for gestational fetuses have measurable changes in their fetal adrenal gland size. Total gland volume and Adrenal gland ratio have statistically significant differences between Appropriate for Gestational Age Fetuses as well as Small for Gestational Age fetuses(11). FGV: TGV ratio 0.02(−0.26, 0.29) .910, TGV (mm3) 0.65 (0.45, 0.78), FZV (mm3) 0 .43(0.17, 0.63), cTGV (mm3/kg) −0.12 (−0.38, 0.17), cFZV (mm3/kg) −0.02 (−0.29, 0.26)

In addition, Heese et al also found in their study where they compared 64 FGR fetuses with 343 normal or healthy fetuses. They compared the adrenal sizes between the two groups and found that the cortex width and total width were higher in growth-restricted fetuses. Total width [3.89 (3.13, 4.75) vs. 3.33 (2.69, 4.21), P = 0.001]; Cortex width [1.40 (1.10, 1.70) vs. 1.10 (0.90, 1.40), P < 0.001](12).

In the study done by Kaya et al among 44 pregnant women with FGR and 44 healthy controls, adrenal gland sizes were compared among the two groups. The computed Z scores where there was a statistically significant difference between the z scores of those with Intrauterine Growth Restriction and Healthy Controls are shown respectively as follows; the total length 0.78 (-1.08–2.67) vs -0.65 (-1.62–0.61) p<0.001, total width 0.67(-1.73–2.59) vs -0.47 (-1.97–0.79) p <0.001, medulla length 0.3(-2.21–2.06) vs -0.04 (-1.58–1.81) p=0.607, medulla width -0.52(-2.22–1.85), 0.49 (-1.2–2.86) p<0.001, cortex width 0.81(-0.97–2.47) vs -0.73 (-1.95–0.26) p <0.001, total width/medulla width 0.61 (-0.22–4.34) vs -0.81(-1.45–0.04) p<0.001(55)

On the contrary, there was no statistically significant relationship between corrected Total Adrenal Gland Area, Total Adrenal Gland Area, corrected Fetal Zone Area, Fetal Zone Area, Fetal Zone Ratio and Risk of morbidity in Fetal Growth Restriction fetuses as found by Blue et al. Their study involved 1709 neonates of which 120 of them had fetal growth restriction. (65) . Their study used Total adrenal gland Area and not Adrenal Gland Volume. The level of fetal growth restriction was also not stated in their study which may have also differed with regards to the distinct study population involved in the study. cTAA 46.4 (35.2,61.3), TAA 446 (334.0, 594.2), FZR 2.61 (2.2, 3.1), cFZA 12.6 (9.4, 16.9). Those without composite morbidity. cTAA 43.4 (38.6, 48.8), TAA 403 (359, 452), FZR 2.96 (2.7, 3.2), cFZA 2.96 (2.7, 3.2). (65)

2.9 Adverse perinatal outcome in pregnancies complicated by preeclampsia.

Preterm birth and inadequate uteroplacental perfusion are known to result in poor newborn outcomes in preeclampsia-complicated pregnancies. The issue is much more severe in Lower Middle-Income Countries, where most settings lack the necessary resources and capacity to provide care for preterm infants(87). The worst outcomes of preeclampsia are found in Sub-Saharan Africa yet there is a paucity of research data in this population (88).

A secondary analysis of the World Health Organization Multi-Country Survey on Maternal and Newborn Health was done in 357 health facilities in over 29 countries conducting over 100 deliveries in Africa, Asia, South America, and the Middle East. There was a sum of 313 030 women in the database out of 8542(2.73%) were analysed as they had hypertensive disease in pregnancy. The following outcomes were seen in the study for preeclampsia and eclampsia respectively; Infant sex (male) 3445 (51.2%) vs 432 (49.8%), Birthweight <1500g 553 (8.2%) vs 117 (14.0%), Stillbirth 429 (6.4%) vs 133 (15.3%), Neonatal complications (at least one) 1388 (20.6%) vs 223 (25.5%), Apgar score at 5 minutes [≥7 - 5822 (92.1%) vs 578 (79.8%)], [4–6 - 389 (6.2%) vs 115 (15.9%)], [≤3- 108 (1.7) vs 31 (4.3)], Fetal death 429 (6.36%) vs133 (15.32%), NICU admission 1634 (25.84%) vs 235 (32.02%), Preterm birth 2079 (30.89%)vs 339 (39.84%)(89)

In a study to assess perinatal outcomes in hypertensive disease in pregnancy done in Accra, "Women who had pre-eclampsia had a significantly higher rate of emergency Caesarean section (88.9% vs. 50%, P = 0.04), they also had a higher risk for low-birth-weight infants (aRR 7.95, 95% CI 1.41–44.80) and a higher neonatal death risk (aRR 18.41, 95% CI 1.20–283.22)"(37).

A secondary analysis of data obtained from a randomized controlled trial done at the Korle-Bu Teaching Hospital found that poor neonatal outcomes were experienced by more than half of patients with preeclampsia. The following poor outcomes were found in the study; NICU admissions 470 (49.4%), low Apgar scores <7, birthweight <1500g 200(18.5%), stillbirth 123 (11.3%), preterm birth 566 (52.7%), 142 (14.9%), NICU stay 8.0 (3.0-15.0), composite of poor neonatal outcomes 623 (56.9%)(90)

A recent cohort study conducted at a Tertiary referral facility in Southwestern Uganda between January 2019 to November 2019 also found the following perinatal outcomes; Intrapartum

stillbirth 5 (4.8%), Antepartum stillbirth 16 (15.5%), "Admission to Neonatal Intensive Care Unit 38 (36.9%), Death of infant before discharge1 (1.1%)", One or more adverse perinatal outcome 60 (58%). The study however did not segregate the perinatal outcome data into the various categories of Hypertensive disease in pregnancy(91).

2.10 Relationship between the fetal adrenal gland dimensions and adverse perinatal outcome in preeclampsia.

There have been a few studies that have sought to evaluate the relationship between fetal adrenal gland size and perinatal outcomes, especially concerning Fetal Growth Restriction.

Kathrin Oelmeier et al did a study among 445 women with singleton pregnancies between 23 and 40 weeks of gestation. 67 had Fetal Growth Restriction 378 were normal fetuses. "Their study showed that adrenal gland ratio was increased in FGR fetuses compared to normal controls (3.670 [3.062, 4.640] vs. 3.190 [2.871, 3.740], p=0.0002)". "PI of the umbilical artery and the fetal adrenal gland ratio were shown to be significantly associated with fetal FGR (odds ratio umbilical artery PI 0.012 [0.002–0.057], p<0.001 in logistic regression". "It is interesting to note that Adrenal gland ratio showed no relationship with any of the outcome variable including gestational age at ultrasound examination"(62).

A study conducted by Sennaiyan et al in Australia among 153 women between gestational ages of 18-34 weeks. The study participants were grouped into either "Small for Gestational Age or Appropriate for Gestational Age based on their Estimated Fetal Weight being less than the 10^{th} centile. "Total Gland Volume (P = .003) and Fetal Zone Volume (P = .001) were noted to be increased in Small for Gestational Age group compared to the Appropriate for Gestational Age Fetuses". The Adrenal gland ratio was also shown to be significantly increased (P = .006) in the SGA group. They also found potential cut-offs for clinically relevant values for cTGV, cFZV and "FZV/TGV (FZV:TGV ratio 10 sensitivity 82%, specificity 32%, cTGV 1.5 sensitivity 84%, specificity 24%, cFZV 0.36 sensitivity 80%, specificity 24%)"(76).

A secondary analysis of the NuMoM2b study among 1709 fetuses was done. In the 7% (n=120) of the participants had Fetal Growth Restriction and 14% (n=251) of the participants experienced perinatal morbidity. In this study, the Corrected Adrenal Gland Volumes were not used, instead Total [TAA 46.4 (35.2,61.3) versus 43.4 (38.6, 48.8) p=0.649] and Fetal Adrenal

Gland Area [FZA 121 (88.1, 166.0) versus128 (112,147) 0.721] were used and they were corrected for Estimated Fetal Weight yet there was no association between Adrenal Gland size and morbidity. The outcome was similar to the Fetal Zone Ratio (2.61 (2.2, 3.1) versus 2.96 (2.7, 3.2) p=0.19). The Area Under the Curve was 0.52 (0.38, 0.67) for Corrected Total Adrenal Gland Area(92). The results may have been different if other parameters of the fetal Adrenal Gland like the volume were used.

Karsli et al conducted a study on new-born infants with comparable results to fetuses in-utero. 99 neonates were recruited in the study and were between Gestational Ages of 24 to 41 weeks. Measurements were done between Day 1 to Day 4 of birth. "Similarly hypertensive mothers gave birth to infants whose adrenal glands were smaller (1140 ± 784 mm3 versus 1428 ± 998 mm3)". "Adrenal Fetal Zone with a beta coefficient (95% CI) of 0.041 (0.024; 0.057) with a p <0.001 and -0.203 (-0.401; -0.005) p=0.045 respectively. "Gestational age and preeclampsia were the only independent variables associated with the size of the adrenal glands with a beta coefficient (95% CI) of 121.31 (96.41; 146.22) with a p<0.001 and 479.49 (196.72; 762.26) with a p=0.001 respectively"(93).

A study by Mohajeri et al. has been referenced in a few articles that evaluate the size of the fetal adrenal gland and its relationship to perinatal outcomes. Their study was a prospective cohort of 97 pregnancies. 48 had Growth-restricted fetuses and 49 healthy controls. All mothers had a 2D ultrasound assessment of the fetal adrenal gland and were followed up to delivery. "The Total Adrenal and Fetal Zone Volumes were measured and adjusted for Estimated Fetal Weight. Corrected AGV (mm3/kg) (Mean ± SD) [393.9 ± 58.5 296.5 ± 26.4 p<.001], Corrected FZV (mm3/kg) (Mean ± SD) [59.1 ± 8.4 versus 80.3 ± 17.2 <.001], Fetal zone/adrenal ratio (Mean ± SD) [0.15 ± 0.02 versus 0.27 ± 0.04 <.001]". "Fetuses with Fetal Growth Restriction had a smaller Adrenal Gland Volume and a larger fetal zone volume. This group also was made up of FGR fetuses with adverse perinatal outcomes including non-reassuring fetal heart status, preterm birth, very low birth weight delivery and admission to neonatal intensive care unit (p<.01)"(94).

This review of literature has established the significance, the various dimensions, and the gaps in the application of the ultrasound measurement of the fetal adrenal gland and perinatal outcomes. Fewer studies have evaluated this in preeclampsia and no data has been found yet

in our setting. The next section of this thesis will seek to look at the most feasible, most cost-effective methods for conducting robust research to further explore this subject.

CHAPTER THREE
METHODOLOGY

3.0 Study design

This was a hospital-based cross-sectional study. The study involved women in their third trimesters of pregnancy who were on admission and were receiving care for preeclampsia. The study was conducted in the High Dependency Ward where patients with Preeclampsia are managed. Those mothers who fulfilled the inclusion criteria and consented were selected and followed up till 1 week post-delivery. Mothers were assessed within 72 hours of admission. Three measurements of the fetal adrenal gland were done at the time of recruitment and at each fetal surveillance ultrasound examination. Ultrasound measurements of the fetal adrenal glands were done during routine fetal surveillance assessment for preeclampsia and the measurement closest to the time of delivery was utilised. Gestational age and obstetric risk factors were obtained from the Antenatal or Maternal Health record books. The management, timing, and route of delivery were as per standard protocol and not part of the research protocol. Delivery outcomes were obtained from delivery records at the High Dependency Ward, Labour Ward, Neonatal Intensive Care Unit and Obstetric Theatres. The study was conducted from February to May 2023. The study design was chosen because it was the most feasible and the most cost-effective design within the time frame chosen for the study.

3.1 Setting

The Ashanti Region of Ghana has only one tertiary referral centre, which is the Komfo Anokye Teaching Hospital (KATH). It is also the second biggest hospital in Ghana. The population of the Ashanti region is about 5,440,463(95). The strategic location of the hospital and the road network of the country make the facility accessible to 12 out of the 16 regions of Ghana as well as neighbouring countries. Unpublished data from the Ghana National Ambulance Service places the Komfo Anokye Teaching Hospital as the busiest in terms of referrals in the country. In the past year, the hospital received 4,388 referrals by the Ghana National Ambulance Service alone. This excludes other emergency referrals which were not done by the Ambulance Service. The figure is more than twice that of the second busiest hospital in the country(96).

KATH is a 1200-bed capacity hospital, which provides both general and specialist care for its numerous clients. The research was done in the Obstetrics and Gynaecology department, which conducts about 7000 deliveries every year. An average of 600 obstetric scans are done per

month in the facility. The research was done mainly in the A1 High Dependency Unit, which caters for cases of Hypertensive Disease in Pregnancy (HDP) and admits about 1400 women with HDP annually out of which 735 women have preeclampsia. It serves as an antenatal, intrapartum, and postnatal ward. It is also a regional Centre of excellence for the management of peripartum women with hypertensive disease in pregnancy. The ward has 31 beds and sees about 61 cases of preeclampsia monthly. Unpublished data from the Biostatistics Unit of the Obstetrics and Gynaecology Directorate for September 2022 showed that there were 37 deliveries for preeclamptic mothers that required NICU admissions, 11 fetuses required no NICU admissions, 6 were Intrauterine Fetal deaths(97).

3.2 Study population

Women who were diagnosed with Preeclampsia and admitted to the ward comprised the study population.

3.3 Inclusion criteria

1. Clients who give consent to participate in the study.
2. Pregnancy that is reliably dated either using the date of the last normal menstrual period or the presence of an early pregnancy dating scan.
3. Women aged 18 years and above.
4. Gestational age of 28 weeks and above.
5. Single non-anomalous pregnancy

3.4 Exclusion criteria

1. Presence of fetal structural anomalies or suspected chromosomal anomalies.
2. Women with Intrauterine Fetal Death at the time of recruitment.
3. Clients in the postpartum period.
4. Women who required emergency delivery or critical care at the time of recruitment.
5. Technical difficulties encountered in visualizing the fetal adrenal gland adequately.

3.5 Sonography

All ultrasound investigations were performed by the Principal Investigator with the help of a single experienced Registered Diagnostic Medical Sonographer (RDMS) with experience in performing Maternal Fetal Medicine ultrasound examinations. The measurements of the human fetal adrenal glands were done three times during a single visit to the ultrasound suite by study participants. The intra-class correlation coefficient was calculated to determine reliability. A value less than 0.50 was regarded as poor reliability, between 0.50- 0.75 was considered as moderate reliability while between 0.75-0.90 was high reliability. A value of 0.90 and above was regarded as excellent reliability. The standard protocol for a 2D ultrasound visualization and measurement of the Human Fetal Adrenal gland was used. A two-dimensional ultrasound of the fetus and fetal adrenals was obtained using the Siemens NX3 Acuson Elite machine with a CH5-2 transducer.

The HADLOCK formula was used to estimate the weight of the fetus by considering its Head Circumference, Biparietal Diameter, Abdominal circumference, and Femur Length. The growth percentile was assessed based on the INTER-GROWTH fetal growth curve and the known documented gestational age(98). FGR was defined as EFW $<10^{th}$ percentile with Doppler abnormalities or EFW or AC $<3^{rd}$ percentile(99).

The umbilical artery doppler Pulsatility Index was described as abnormal if the value of the parameter was greater than the 95^{th} centile for gestational age. This was done using an online calculator from the Fetal Medicine Foundation(100)

The adrenal glands were identified in all three planes: sagittal, transverse, and coronal planes. The fetal adrenal glands comprise two zones. The outer hypoechoic zone (cortex) and the inner echogenic zone (fetal zone). Identification of the gland in all three planes aided in the measurement of the length, width and depth of the cortex and fetal zones of the gland. The method of measurement was based on literature review(65,101,102).

The Adrenal Gland Volume, AGV, or Fetal Zone Volume was calculated using the following ellipsoid formula; *(Length x Width x Depth x 0.52) =mm^3*. The AGV and FZV were corrected for fetal weight *cAGV=AGV or FZV/EFW =mm^3/kg or cTAA*=TAA $(\pi \times L \times R)$/EFW. Adrenal Gland Ratio *(ratio of the total width to the medulla width or* Adrenal gland ratio = FZA/TAA*),* Total width, cortex width (half of the total width minus medulla width), medulla width.

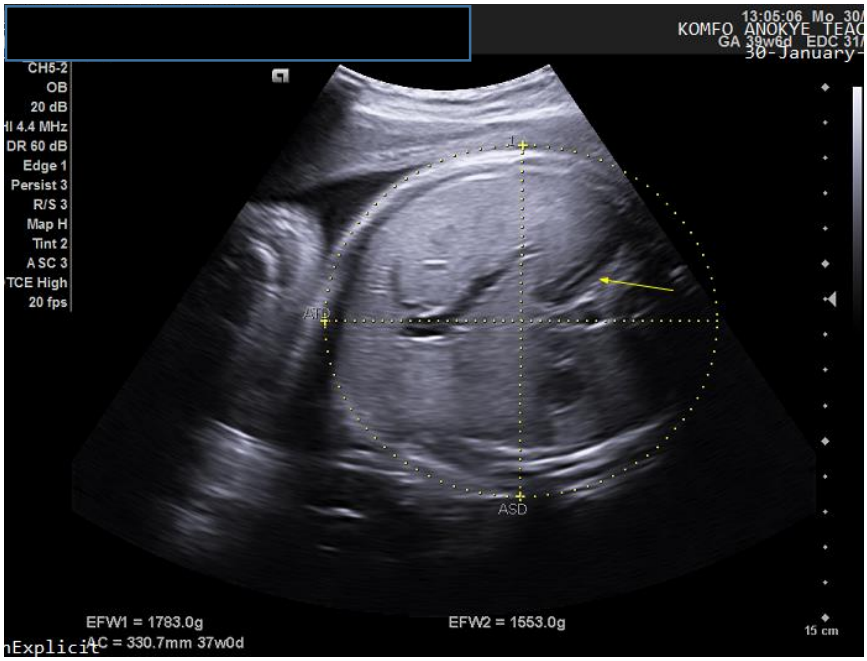


Figure 3.5 1 Adrenal gland visualised on axial plane of the fetal abdomen.

Source: Sonographic measurement of the fetal adrenal gland as a marker of adverse perinatal outcome in preeclampsia.

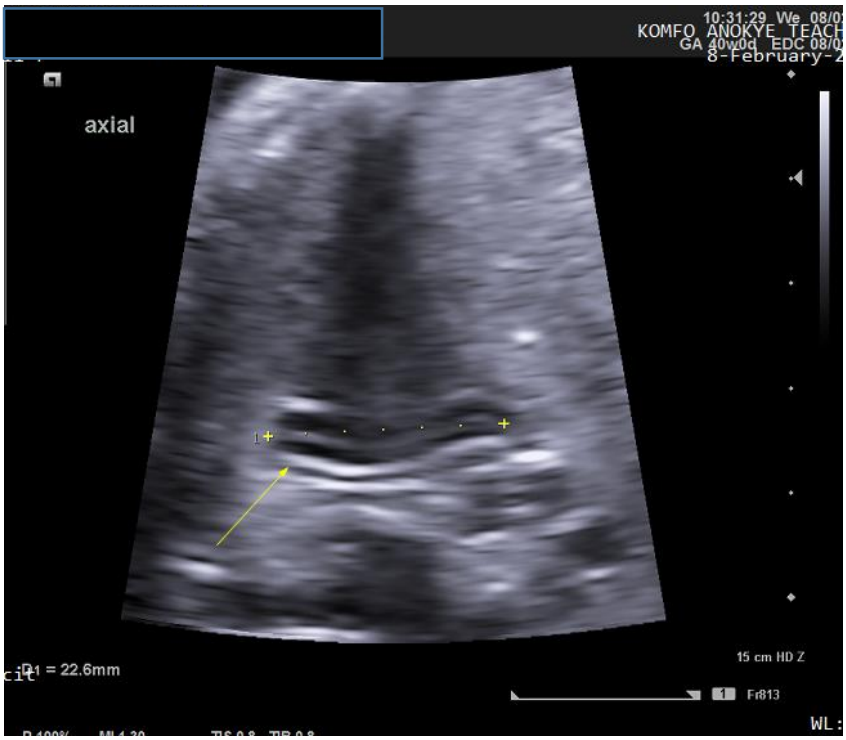


Figure 3.5 2 Magnified sonograph of the fetal adrenal gland in the axial plane.

Source: Sonographic measurement of the fetal adrenal gland as a marker of adverse perinatal outcome in preeclampsia.

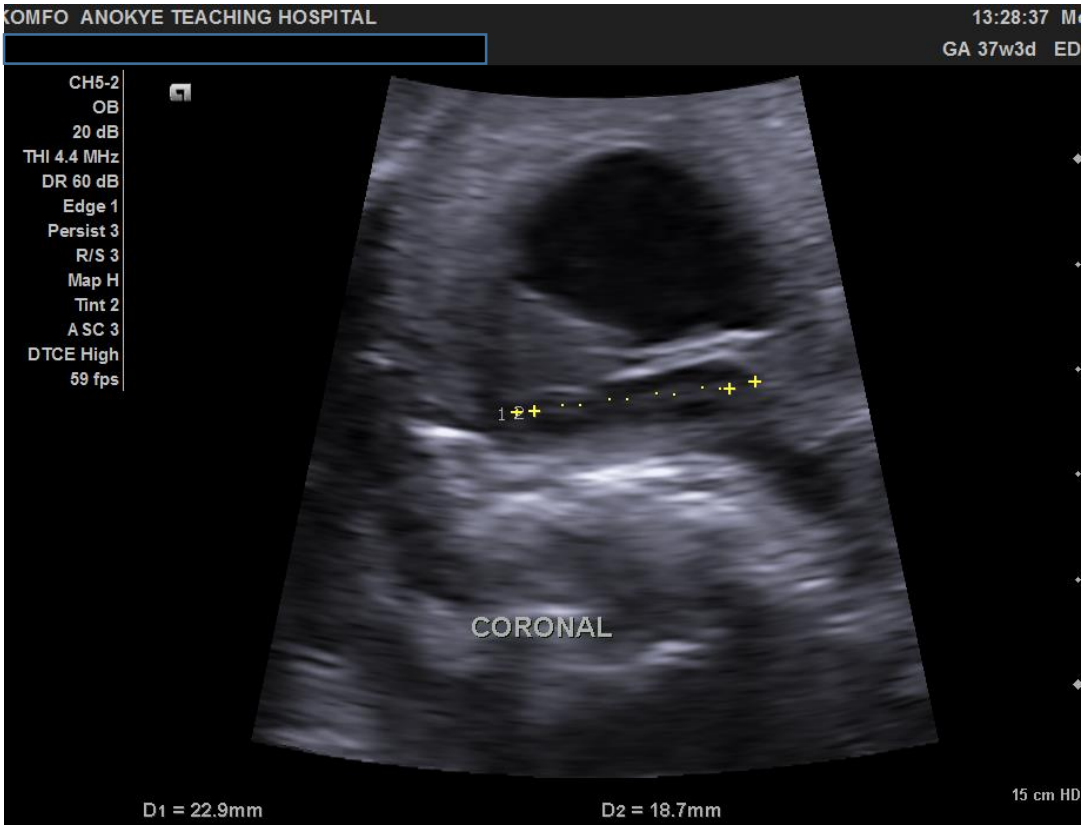


Figure 3.5 3 Sonograph of the human fetal adrenal gland in the coronal plane

Source: Sonographic measurement of the fetal adrenal gland as a marker of adverse perinatal outcome in preeclampsia.

3.6 Data collection tool

The Demographic information and other risk factors for adverse perinatal outcomes were collected through the use of a questionnaire. An electronic database was created in Microsoft Excel to assist in recording fetal parameters. Information on gestational age, parity, and the presence or otherwise of comorbid medical conditions were obtained from the Antenatal Record book. Data on the outcome of deliveries as well as perinatal outcomes were obtained from patient records and delivery registers found in the A1 High Dependency Unit, Labour Ward, obstetric theatres and Mother and Baby Unit

3.7 Data management and analysis

The data obtained were doubly entered into Microsoft Excel and cleaned up to correct errors, inconsistencies, and missing facts. The data were then exported into Stata Version 17.0 for analysis. Descriptive Analysis and logistic regression analysis were used to examine the demographic data and correlation between negative outcomes, respectively. A p-value <0.05 was considered statistically significant. Continuous variables were presented as means, median and standard deviation. Categorical variables were presented as frequencies with percentages. The two-sample t-test was used to assess the differences in the means between adrenal gland measurements and perinatal outcome. P-values less than 0.05 were considered statistically significant.

To assess the relationship between adrenal gland measurements and perinatal outcome several new variables were created using Stata including the composite perinatal outcome measure which was created using the following variables: fetal demise, stillbirth, low 5-minute APGAR scores (<7), neonatal death, seizures, intubation, low birth weight. These were first recoded into binary indicators to indicate the absence or otherwise of these conditions. The presence of any of these conditions was classified as adverse perinatal outcome.

3.8 Sample size and sampling strategy

The following parameters were employed to determine the required sample size: The
Mean (SD) corrected Fetal Adrenal Volume (cFAV) of 0.42(0.26) as reported by Helfer et al (69) in fetuses with good outcomes and the proportion of new-borns with adverse fetal outcome of 80% (unpublished data from A1 High Dependency Unit at KATH). To detect a difference in cFAV of 0.18cm between fetuses with adverse and good outcomes the formula below from Chow et al was used.

$$n_A = \kappa n_B \text{ and } n_B = \left(1 + \frac{1}{\kappa}\right)\left(\sigma \frac{z_{1-\alpha/2} + z_{1-\beta}}{\mu_A - \mu_B}\right)^2$$

where

• μA is the mean cFAV in babies with poor outcome of 0.6

• μB is the mean cFAV in babies with good outcome of 0.42

• σ is combined standard deviation of 0.26

• nA is the sample size in babies with poor outcome

• nB is the sample size in babies with good outcome

• $\kappa = nA/nB$ is the matching ratio, which was 4

• α is the type I error rate of 0.05

• β is the type II error rate of 0.2, (and thus a power of 0.81)

The minimum sample size for babies with poor outcomes was determined to be 84 and for babies with good outcome as 21. Assuming a non-response rate of 10%, a minimum sample size of 116 was needed for the study. Overall, 120 study participants were recruited for the study. However, 8 participants were excluded on account of technical difficulties in visualising the fetal adrenal gland adequately as well as missing data.

In this study, there was no sampling involved. There was consecutive recruitment of study participants who met the inclusion and exclusion criteria as described above in sections 3.3 and 3.4 until the desired sample size was obtained. The reason was to make sure the participants who were selected did not possess any factors such as other medical conditions in pregnancy which could have impacted the results of the study. Recruitment efforts were continued until the desired sample size was achieved to ensure sufficient representation.

Prospective study participants admitted to the ward were initially approached and the details of the study were explained to them. They were then screened using the inclusion and exclusion criteria and informed consent was sought before participation in the study.

3.9 Variables

Independent Variables obtained from study participants included age, ethnicity, parity, other medical conditions, and gestational age on admission/diagnosis.

Maternal and fetal monitoring data that was used in the study included highest and lowest blood pressure, Liver Function Tests, Renal Function Tests, Full Blood Count, fetal Doppler: Umbilical Artery Doppler Velocimetry s/d ratio, Pulsatility Index, Resistive Index, Cardiotocography findings, adrenal measurements (length, width, depth), (absent variability, decelerations prolonged and late) weight centile, Amniotic Fluid Index, and Estimated Fetal Weight. Maternal symptoms including severity of headache, visual disturbance and epigastric pain were obtained. Study participants were asked to score the headache they were experiencing using a 10-point scale. A score of 0 was regarded as no headache, 1-3 mild headache, 4-6 moderate headache and 7-10 severe headache. This was used as part of exploratory data analysis.

Outcome variables measured in the study were NICU admission, low APGAR scores (<7) at 5^{th} minutes, neonatal death, oxygen therapy, stillbirth, preterm birth, seizures, and intubation.

In this study, the main outcome variable was Perinatal outcome. Perinatal outcome was a composite including the following outcome variables; NICU admission, low APGAR scores (<7) at 5^{th} minutes, neonatal death, oxygen therapy, stillbirth, seizures, and intubation.

Adverse perinatal outcome was defined as 1 or more of the outcome variables being answered with a 'Yes'. However, fetuses without any of these variables being answered with a 'Yes' that is had the answer 'no' for the outcome variables were regarded as having good perinatal outcomes. Secondary outcomes included the individual components of the poor neonatal outcome composite.

The exposure variables in this study were the various adrenal gland dimensions. These were adrenal gland length, adrenal width, adrenal gland depth, and adrenal gland volume.

The following were regarded as confounding variables sex of baby, duration of first stage, duration of 2^{nd} stage, mode of delivery.

3.10 Pretesting

Pretesting was done using 16 participants at the Kumasi South Hospital which also serves as the Regional Hospital of the Ashanti Region of Ghana. The pretesting afforded the study team to have a hands-on experience on how the actual research would be conducted. Data obtained

from pretesting were used to identify discrepancies in the study protocol which were subsequently rectified.

3.11 Ethical considerations

The research was conducted upon receipt of ethical clearance from the Komfo Anokye Teaching Hospital Institutional Review Board and approval of the research proposal by the assessors at the Ghana College of Physicians and Surgeons. Full approval was given with the reference KATH IRB/AP/173/22.

All respondents were taken through a mandatory informed consent process in a language well understood by the respondents before being allowed to partake in the research. Refusal of consent/participation in the study did not affect the quality of care. Clients were made to understand that they were free to opt-out at any time. Women who were not able to read and write had access to a translator, and the option to thumbprint while literates signed.

Prior to giving consent or assent, the objectives of the study were explained to the patient in detail and allowance was given for questions to be asked. All patients were given Study Identification Numbers. Research documents containing patient identifiers were kept by the Principal Investigator separately from the primary research documents and not accessible to non-study team members except for the members of the Institutional Review Board for inspection.

All electronic forms or data were password protected and hardcopies of documents including informed consent materials were kept under lock and key in the Ward Nurse Manager's office. The information collected was used solely for the study.

Study participants had ultrasound examinations done as part of their routine care. The opportunity was taken, and fetal adrenal gland measurements were done during ultrasound examinations requested by the participants Attending Obstetrician. The clients were not surcharged or billed any extra amount for partaking in the study. To reduce waiting times in the queue for other clients who did not partake in the study, a less busy ultrasound suite meant for training students was mostly used for the study.

CHAPTER FOUR

RESULTS

This section presents the results of the study as follows.

4.1 Demographic and clinical characteristics of study participants

Table 4. 1 Sociodemographic characteristics of study participants

Variable		Frequency (N=120)	Percent
Age (years)	Age Category		
	<20	3	2.5
	20-25	18	15
	26-30	24	22
	31-35	45	37.5
	36-40	21	17.5
	41-45	9	7.5
Religion			
	Christian	107	89.17
	Muslim	13	10.83
	Traditional	0	0
	Other	0	0
Level of Education			
	None	5	4.9
	Primary	13	12.75
	Junior High School	39	38.24
	Senior High School	18	17.65
	Tertiary	27	26.47
Ethnicity			
	Akan	98	81.67
	Ewe	2	1.67
	Grusi	1	0.83
	Other	19	15.83
Marital Status			
	Single	19	15.83
	Cohabiting	14	11.67
	Married	87	72.5
Parity			
	0	36	30.00
	1	29	24.17
	2-4	43	35.83
	>=5	12	10.00

Source: Sonographic measurement of the fetal adrenal gland as a marker of adverse perinatal outcome in preeclampsia.

There was a total of 120 participants in the study. Majority of participants 37.50% (n=45) were between the ages of 31-35years. This was followed by the 26–30 year-old group 22.00% (n=24). The extremes of age had fewer participants <20 year 2.50% (n=3) and 41-45 years 7.50% (n=9). The mean age of study participants is 31.58 years with a standard deviation of 5.73 years. The minimum age was 19 years and the Maximum- 45 years.

Many of the respondents were Christians 89.17% (n=107). This was followed by Muslims 10.83% (n=13). There were no respondents from traditional religion or belonging to other religions.

Approximately 38.24% (n=39) of respondents in the study had completed Junior High School education. Participants who had completed their tertiary education formed 26.47% (n=27) of respondents. This was followed by those who had completed Primary school 12.75% (n=13). About 4.90% (n=5) had received no formal education.

Most study participants were Akans 81.67% (n=98), followed by Ewes who formed about 1.67% (n=2). There were other ethnic groups which formed about 15.83% (n=19) of all ethnic groups.

Many of study participants 72.50% (n=87) were married, 15.83% (n=19) were single and 11.67% (n=14) were Cohabiting.

Majority of respondents had parity between 2-4 35.29% (n=42). This was followed by the nullipara who formed 30.25% (n=36) and the primipara respectively 24.37% (n=29). The least among the respondents were the grand multipara who 10.08% (n=12). The mean parity of the respondents was 1.725$\pm$1.70 with the highest parity being 6 deliveries.

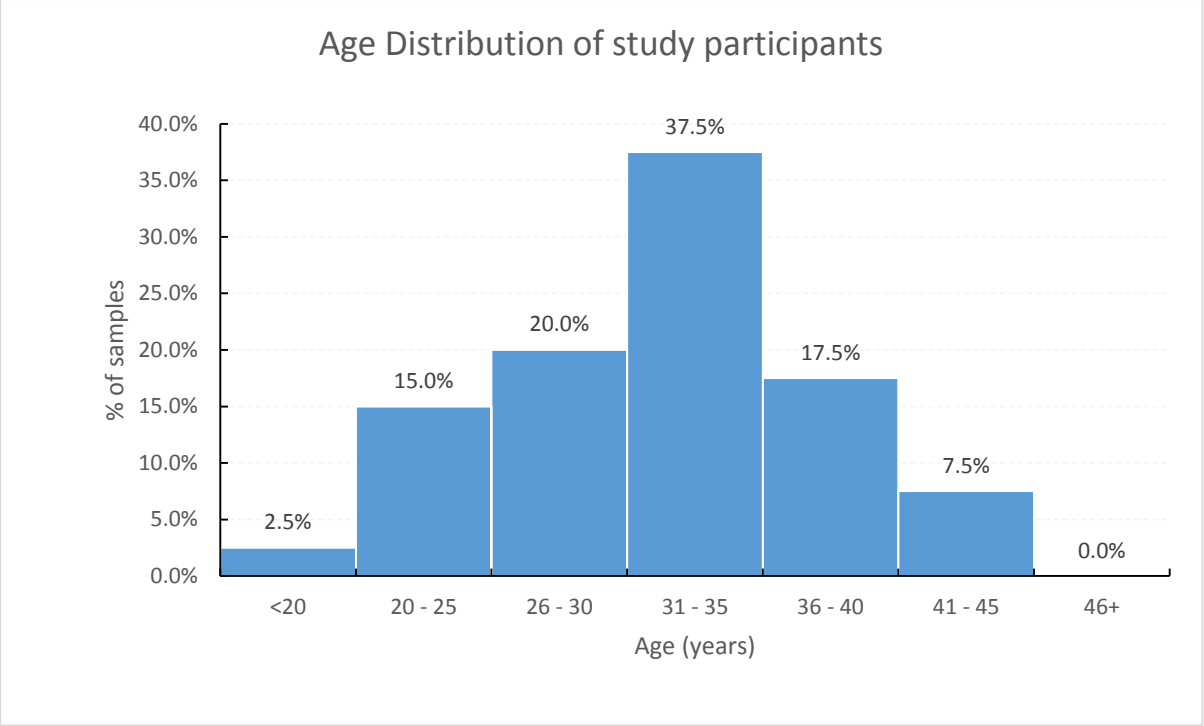


Figure 4. 1 Age distribution of study participants

Source: Sonographic measurement of the fetal adrenal gland as a marker of adverse perinatal outcome in preeclampsia

The figure above shows the age distribution of study participants in a bar chart. The highest peak is the 31-35 age group which has the highest. The peaks for the various age groups decrease as one moves away from the centre or modal age group. This gives the impression of a normal distribution.

Table 4. 2 Maternal clinical characteristics

Variable (N=120)	Obs	Mean	Std. Dev.	Min	Max
Gravidity(n=120)	120	3.725	2.033	1	10
Gest age(n=120)	120	33.275	3.623	28	42
Systolic(n=120)	120	160.767	23.875	99	220
Diastolic(n=120)	120	105.481	17.450	61	160
Creatinine (n=104)	104	72.554	34.737	19	258
Urea (n=103)	103	3.322	2.064	.7	10.24
AST (n=92)	92	67.191	105.665	16.3	603.3
ALT(n=92)	92	46.110	78.903	4.4	508
Platelet(n=116)	116	215.853	80.196	59	480
Haemoglobin(n=116)	116	11.922	1.739	7.1	15.7
Birth weight (n=120)	120	1905.633	855.283	270	4400
Est fetal weight(n=120)	120	1942.675	901.206	408	4544

Source: Sonographic measurement of the fetal adrenal gland as a marker of adverse perinatal outcome in preeclampsia

The above table shows the various maternal mean and standard deviation of the maternal clinical characteristics used in the study.

Table 4. 3 Distribution of maternal symptoms study participants.

Variable		Frequency(N=120)	Percent
	Severity of Headache		
No	No headache	61	50.83%
Yes	Mild	12	10%
	Moderate	28	23.33%
	Severe	19	15.83%
Epigastric pain	Yes	13	10.83
	No	107	89.17
Visual Disturbance	Yes	16	13.33
	No	104	86.67

Source: Sonographic measurement of the fetal adrenal gland as a marker of adverse perinatal outcome in preeclampsia

About 50.83% (n=61) had no headache. A similar proportion of the study participants had headache 49.17% (n=59) and 23.33% (n=28) had moderate headache. Approximately 15.83% (n=19) had severe headache and only 10.00%(n=12) had mild headache.

A greater proportion of study participants had no epigastric pain 89.17% (n=107). Only 10.83% (n=13) had symptoms of epigastric pain. Also with visual disturbance, majority of study participants 86.67% (n=104) had no visual disturbance, as against only 13.33% (n=16) who had symptoms of visual disturbance.

Table 4. 4 Distribution of participants' perinatal outcome.

Variable		Freq (N=120)	Percentage
Mode of delivery	Caesarean delivery	100	83.33
	Spontaneous Vaginal delivery	20	16.67
Sex of baby	Male	56	46.67
	Female	64	53.33
Apgar Score at 1min	Abnormal 0-6	43	35.83
	Normal 7-10	77	64.17
Apgar Score at 5min	Abnormal 0-6	21	17.5
	Normal 7-10	99	82.5
Birth Weight	Macrosomia >4000g	2	1.67
	Normal 2501-4000g	26	21.67
	Low Birth Weight 1501-2500g	43	35.83
	Very Low Birth Weight 1001-1500g	35	29.17
	Extremely Low Birth Weight <1000g	14	11.67

Birth Weight Categorisation using the Fenton growth chart for Preterm Boys and Girls	Small for Gestational Age (<10th Centile)	39	32.5
	Appropriate for Gestational Age (10-90th centile)	74	61.67
	Large for Gestational Age (>90th centile)	7	5.83
NICU Admission	No	28	25.45
	Yes	82	74.55
Oxygen therapy	No	53	48.18
	Yes	57	51.82
Preterm birth	No	28	23.33
	Yes	92	76.67
Seizures	No	109	99.09
	Yes	1	0.91
Intubation[a]	No	109	100
	Yes	0	0
Still birth	No	110	91.67
	Yes	10	8.33
Neonatal death[b]	No	99	91.67
	Yes	9	8.33

Outcomes within the 1st week of life	Well	65	59
	Still on admission	35	31.82
	Died	9	8.18
	Other	1	0.91

Source: Sonographic measurement of the fetal adrenal gland as a marker of adverse perinatal outcome in preeclampsia

[a] 1 missing value, [b] 2 missing values

Majority of the enrolled study participants 83.33% (n=100) underwent caesarean section for various obstetric indications. About 16.67.15 % (n=20) had Spontaneous Vaginal Delivery. In terms of the APGAR scores at 1 minute, 64.17% (n=77) had an APGAR score of $\geq$ 7 (normal) and 35.83%(n=43) had APGAR score of $\leq$ 6(abnormal). At 5 minutes new-borns with normal APGARS scores were 82.50% (n=99) and those with abnormal APGAR scores were 17.50%(n=21). There were more females births 53.33% (n=64) than male births 446.67% (n=56) among the fetuses delivered in the study-period. Approximately 35.83% (n=43) of fetuses delivered were Low birth weight, about 29.17% (n=35) were Very Low Birth Weight. The Extremely Low Birth Weight Categories formed about 11.67% (n=14) of the deliveries. About 1.67%(n=2) were macrosomic babies and the remaining were normal birth weight 21.67% (n=26). Using the Fenton Growth Charts for preterm Boys and Girls, most of the fetuses delivered were Appropriate for Gestational Age 61.67% (n=74). Those who were Small for Gestational Age were 32.50% (n=39). Only a few 5.83% (n=7) were Large for Gestational Age.

Most study participants 74.55% (n=92) had admission to the NICU and about 25.45% (n=28) were not admitted to the NICU. Of the babies born to study participants, 52.68% (n=59) received oxygen therapy for respiratory support. About 47.32% (n=53) did not receive oxygen therapy. Also, most of the study participants enrolled in the study, about 76.67% (n=92), had preterm birth that is they were delivered before 37 weeks. The remaining did not 23.33% (n=28) experience preterm birth. Only 0.91% (n=1) had a seizure in the neonatal period but none of all the remaining study participants experienced any seizure 99.09%

(n=1). No intubation was done for any fetuses delivered. A considerable number of the participants had stillbirths 8.33% (n=10) but, a greater percentage did not experience still births 91.67% (n=110). There were neonatal deaths, about 8.33% (n=9) among the study participants. Those who did not experience neonatal deaths were 91.67% (n=99). Approximately 59.00% (65) of the enrolled participants had their babies being well in the first week of life. About 31.82% (n=35) were still on admission at the NICU and 8.18% (n=9) had died and 0.91% (n=1) was lost to follow-up.

4.2 Fetal Adrenal Gland Dimensions and relationship with gestational age.

Table 4. 5 Adrenal gland Length (mm) by gestational age of mothers with preeclampsia.

	Total Length(mm)				
Gestational Age (Weeks)	**N**	**Mean**	**SD**	**Min.**	**Max.**
28	9	14.3	5.4	9.2	26.1
29	13	16.8	4.4	8.5	24.1
30	11	18.7	3.9	12.2	25.5
31	10	17.8	4.9	9.7	23.8
32	11	14.8	4.3	9.3	22.7
33	15	19.3	6.2	10.1	31.6
34	10	18.5	3.8	12.1	23.4
35	6	19.9	4.9	12.0	25.1
36	9	23.8	4.0	18.8	30.7
37	10	23.8	3.9	17.7	28.0
38	4	24.1	6.5	17.2	32.1
39	4	25.8	0.5	25.2	26.3
40	4	30.0	4.8	24.0	35.3
41	3	20.4	2.0	19.1	22.7
42	1	25.4	-	25.4	25.4

The table above shows the mean length of the fetal adrenal gland (mm) per gestational age from 28 weeks to 42 weeks.

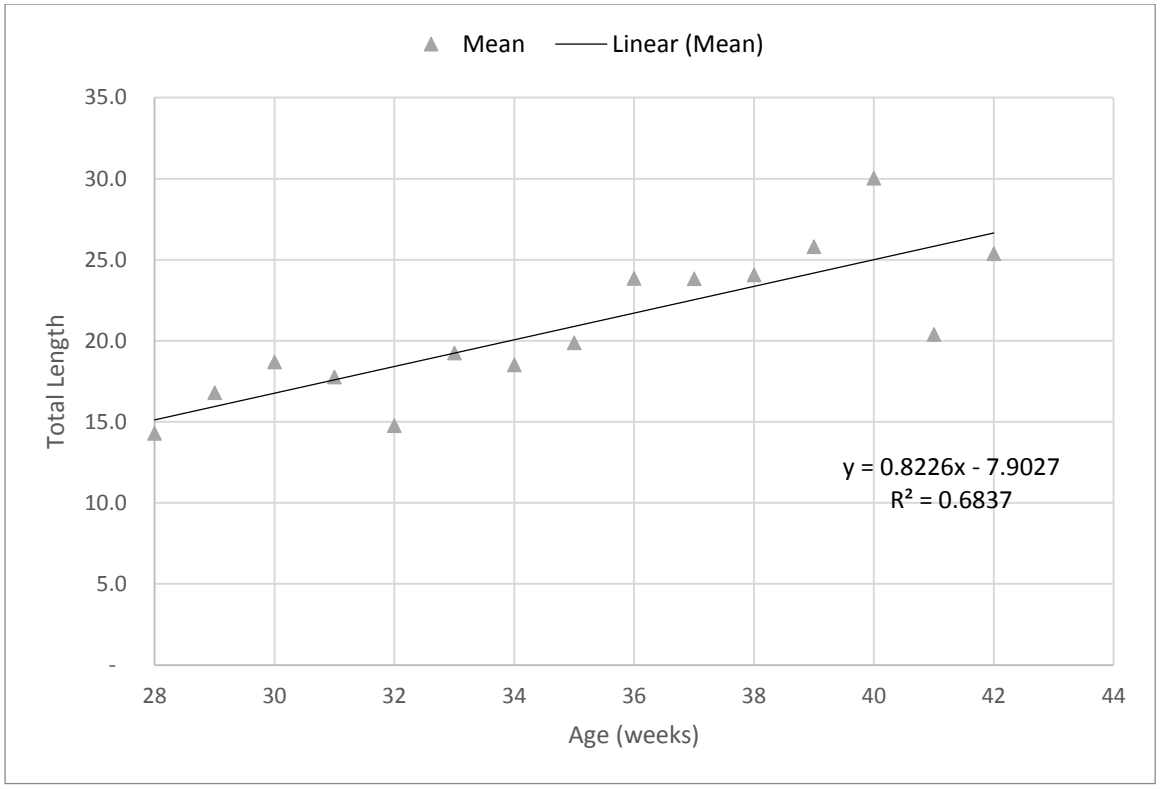


Figure 4. 2 Scatter diagram of the total adrenal length in mm versus gestational age in weeks.

The figure above is a scatter plot aimed to assess the relationship between the total length of the fetal adrenal gland in millimetres and gestational age in weeks. The gestational age (weeks) is on the x-axis and total length (mm) on the y-axis. The data points are scattered across the plot, exhibiting a moderate positive linear trend. The scatter plot suggests a positive correlation between gestational age and total length of the whole fetal adrenal gland, indicating that as gestational age increases the total length of the fetal adrenal gland also increases.

Table 4. 6 Fetal zone length of the fetal adrenal gland in millimetres and the gestational age in weeks

	Fetal Zone Length(mm)			
Gestational Age (Weeks)	**N**	**Mean**	**SD**	**Min.**	**Max.**
28	9	10.4	5.2	6.4	23.5
29	13	11.6	3.0	6.5	17.3
30	11	15.0	3.0	8.8	20.2
31	10	13.9	4.7	6.5	20.5
32	11	10.7	4.3	4.1	18.2
33	15	14.7	5.3	6.0	26.8
34	10	14.3	3.1	7.6	17.9
35	6	14.3	5.0	7.2	19.3
36	9	18.8	3.6	14.2	25.7
37	10	17.6	3.7	12.7	23.7
38	4	19.3	6.2	14.1	27.4
39	4	19.3	2.4	15.8	21.1
40	4	24.1	3.9	20.6	29.3
41	3	15.6	1.5	13.9	16.7
42	1	20.6	-	20.6	20.6

The table above shows the mean fetal zone length of the fetal adrenal gland (mm) per gestational age from 28 weeks to 42 weeks.

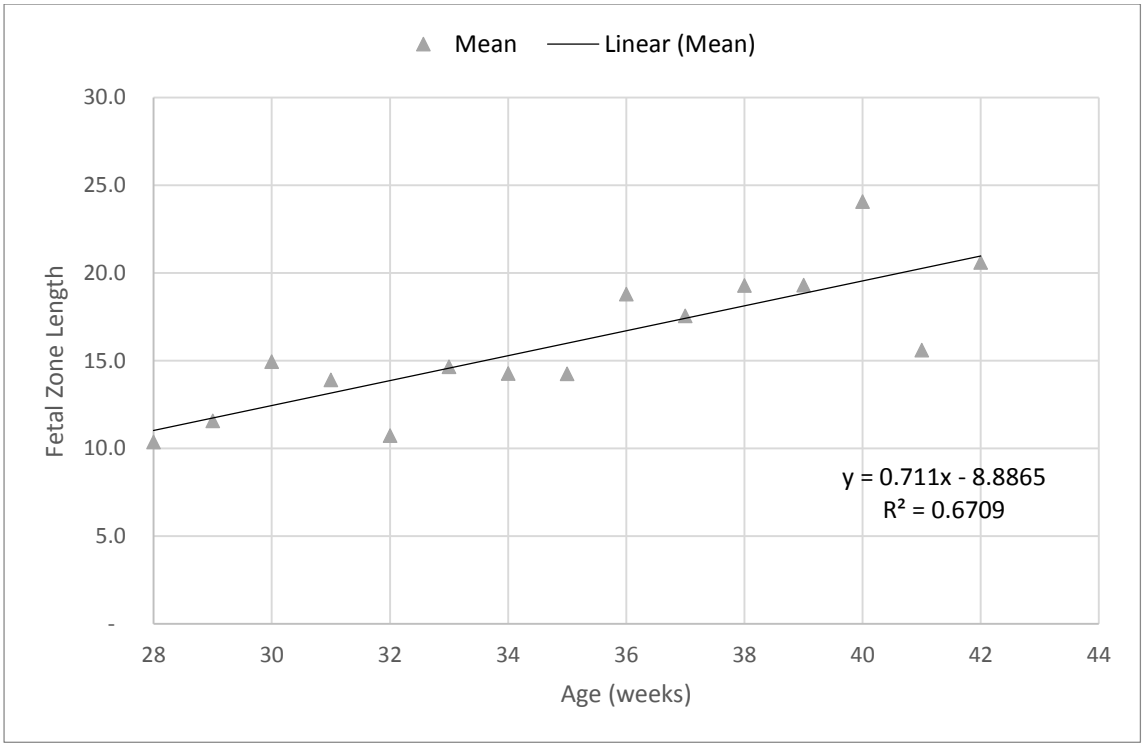


Figure 4. 3 Scatter plot showing the fetal zone length in millimetres versus the gestational age in weeks.

The figure above is a scatter plot was purposed to assess the relationship between the fetal zone length of the fetal adrenal gland in millimetres and gestational age in weeks. The gestational age (weeks) is on the x-axis and fetal zone length (mm) on the y-axis. The data points are scattered across the plot, exhibiting a moderate positive linear trend. However, there are a few outliers with the gestational age and the total length. The scatter plot suggests a positive correlation between gestational age and fetal zone length, indicating that gestational age increases with the fetal zone length.

Table 4. 7 Mean of Fetal Adrenal Gland Width of the whole fetal adrenal gland in millimetres and the gestational age in weeks.

		Adrenal Gland Width(mm)			
Gestational Age (Weeks)	**N**	**Mean**	**SD**	**Min.**	**Max.**
28	9	2.3	0.8	1.0	3.3
29	13	3.0	1.0	1.4	5.7
30	11	4.2	1.4	2.6	7.8
31	10	3.7	2.8	1.9	11.4
32	11	3.0	1.0	1.6	5.1
33	15	3.7	1.4	1.9	6.6
34	10	5.9	5.4	3.0	20.7
35	6	5.5	2.4	2.8	9.3
36	9	4.5	1.0	3.2	6.2
37	10	6.2	3.1	2.6	11.7
38	4	5.2	3.0	1.9	9.2
39	4	5.1	2.2	3.1	8.2
40	4	9.6	8.8	2.7	22.2
41	3	7.7	5.8	2.7	14.0
42	1	8.5	-	8.5	8.5

The table above shows the mean width of the whole fetal adrenal gland (mm) per gestational age from 28 weeks to 42 weeks.

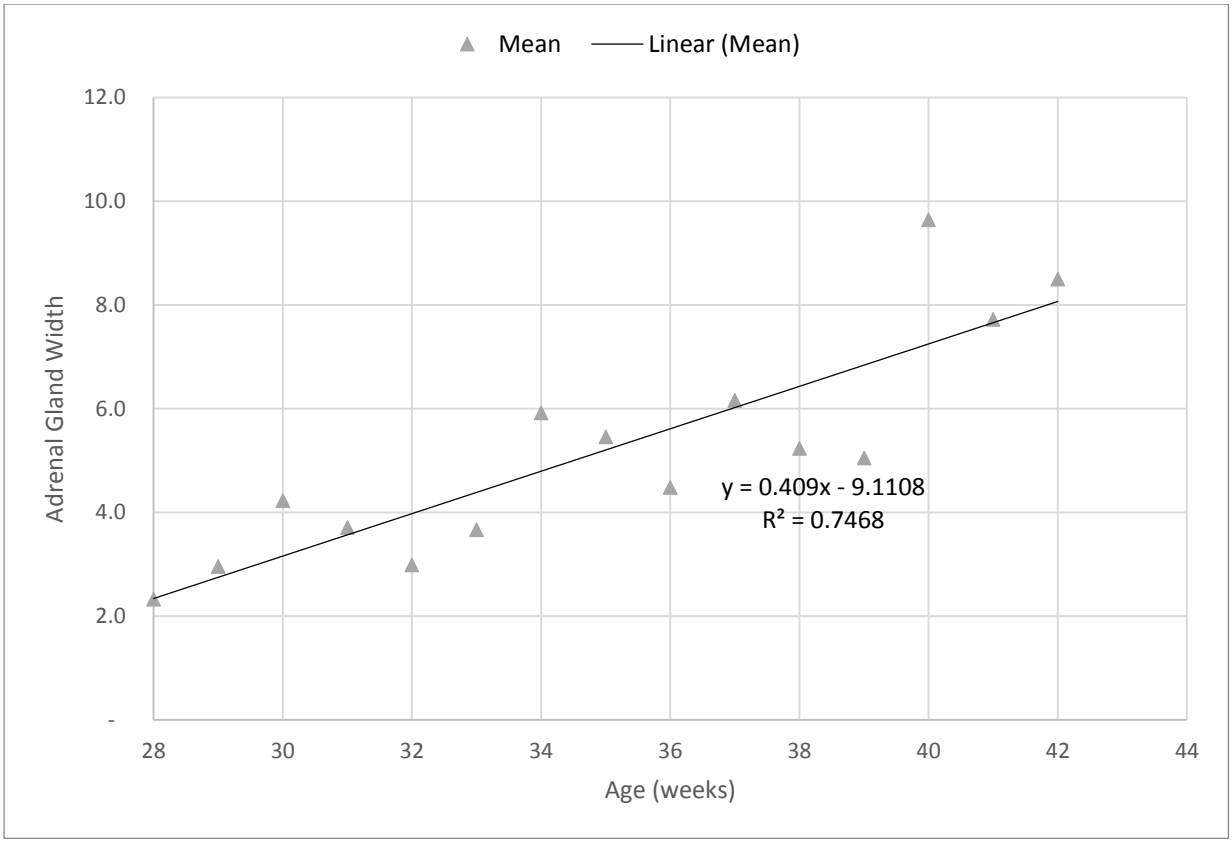


Figure 4. 4 Scatter plot showing the Fetal Adrenal Gland Width in millimetres versus the gestational age in weeks.

The figure above is a scatter diagram was aimed at assessing the relationship between the fetal adrenal gland width in millimetres and gestational age in weeks. The gestational age (weeks) is on the x-axis and fetal adrenal gland width is (mm) on the y-axis. However, there are a few outliers with the gestational age and the total length. The scatter plot suggests a positive correlation between gestational age and fetal zone width, indicating that gestational age increases with the fetal zone width.

Table 4. 8 Fetal Zone Width of the adrenal gland in millimetres and the gestational age in weeks.

		Fetal width			
Gestational Age (Weeks)	**N**	**Mean**	**SD**	**Min.**	**Max.**
28	9	1.0	0.3	0.6	1.5
29	13	1.0	0.5	0.3	2.2
30	11	1.9	1.2	0.9	5.0
31	10	1.5	1.2	0.9	4.7
32	11	1.4	0.4	0.8	2.0
33	15	1.7	0.9	0.8	4.5
34	10	3.1	3.5	0.9	12.7
35	6	1.9	1.2	1.1	4.4
36	9	1.6	0.6	1.0	2.9
37	10	3.0	2.4	1.1	9.3
38	4	2.2	1.0	1.0	3.3
39	4	1.6	0.4	1.2	2.2
40	4	6.7	8.3	1.3	18.9
41	3	3.7	3.7	1.2	7.9
42	1	6.9	-	6.9	6.9

The table above shows the mean fetal zone width (mm) per gestational age from 28 weeks to 42 weeks.

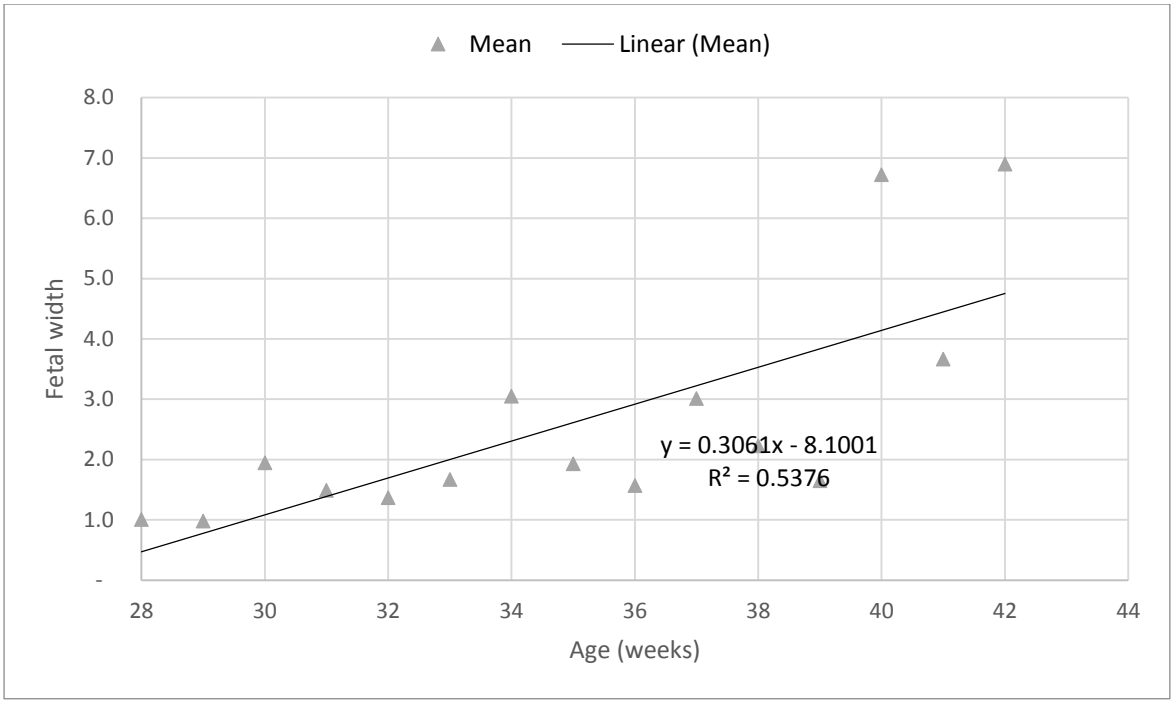


Figure 4. 5 Scatter plot showing the Fetal Zone Width in millimetres versus the gestational age in weeks.

The figure above is a scatter diagram that examined the relationship between the fetal zone width in millimetres and gestational age in weeks. The gestational age (weeks) is on the x-axis and fetal zone width (mm) on the y-axis. However, there are a few outliers with the gestational age and the total length. The scatter plot suggests a positive correlation between gestational age and fetal adrenal gland width, indicating that gestational age increases with the fetal adrenal gland width length.

Table 4. 9 Mean of Adrenal Gland Depth of the whole fetal adrenal gland in millimetres and the gestational age in weeks.

		Adrenal Gland Depth			
Gestational Age (Weeks)	**N**	**Mean**	**SD**	**Min.**	**Max.**
28	9	11.3	3.9	5.8	18.1
29	13	10.7	4.8	2.1	18.1
30	11	13.7	6.3	2.2	24.3
31	10	11.6	6.6	2.1	21.8
32	11	15.0	11.1	1.2	42.0
33	15	11.1	7.9	1.3	23.3
34	10	8.3	6.3	1.6	20.3
35	6	15.4	8.4	4.1	27.2
36	9	16.8	6.9	2.4	28.0
37	10	16.2	7.6	3.4	25.7
38	4	23.8	5.3	21.0	31.7
39	4	19.9	4.3	16.2	24.3
40	4	17.2	10.4	4.0	27.5
41	3	12.3	2.7	9.2	14.0
42	1	3.3	-	3.3	3.3

The table above shows the mean fetal adrenal gland depth (mm) per gestational age from 28 weeks to 42 weeks.

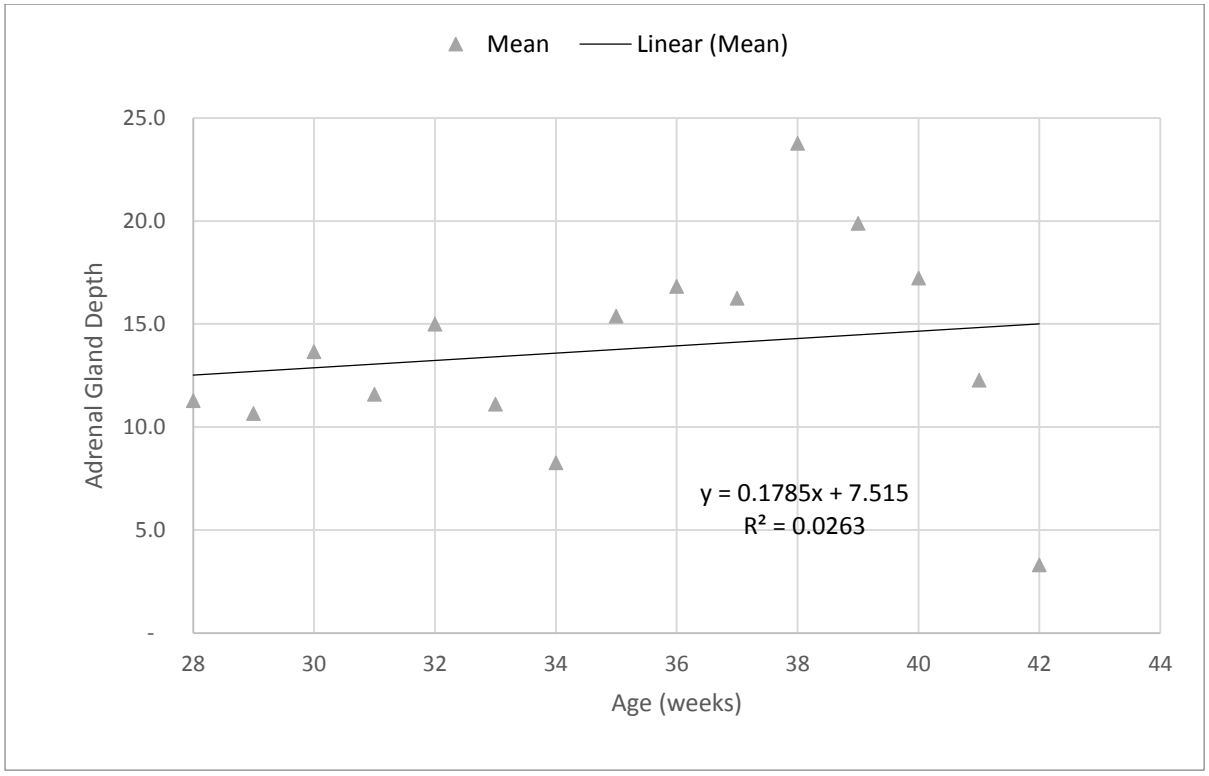


Figure 4. 5 Scatter plot showing the Fetal Adrenal Gland Depth in millimetres versus the gestational age in weeks.

The figure above is a scatter diagram that examined the relationship between the fetal adrenal gland depth in millimetres and gestational age in weeks. The gestational age (weeks) is on the x-axis and fetal adrenal gland depth (mm) on the y-axis. The data points are scattered around the plot, exhibiting a weak positive linear trend. There are some outliers with the adrenal gland depth especially after 39 weeks. The scatter plot suggests a weak positive correlation between gestational age and fetal adrenal gland depth.

Table 4. 10 Mean of Fetal Zone Depth in millimetres and the gestational age in weeks.

	Fetal Zone Depth			
Gestational Age (Weeks)	**N**	**Mean**	**SD**	**Min.**	**Max.**
28	9	7.6	2.6	4.2	11.9
29	13	6.8	3.7	0.4	12.9
30	11	9.6	5.8	0.8	21.0
31	10	8.9	5.9	0.9	18.5
32	11	11.0	9.4	0.8	35.0
33	15	7.1	6.1	0.7	20.9
34	10	5.1	4.9	0.5	15.3
35	6	19.9	27.0	1.4	73.0
36	9	10.0	4.6	0.6	15.5
37	10	12.1	6.6	1.2	19.7
38	4	17.9	4.7	14.0	24.3
39	4	15.1	4.0	12.4	21.0
40	4	12.7	8.3	1.8	20.1
41	3	8.0	2.9	4.7	10.0
42	1	1.0	-	1.0	1.0

The table above shows the mean fetal adrenal gland depth (mm) per gestational age from 28 weeks to 42 weeks.

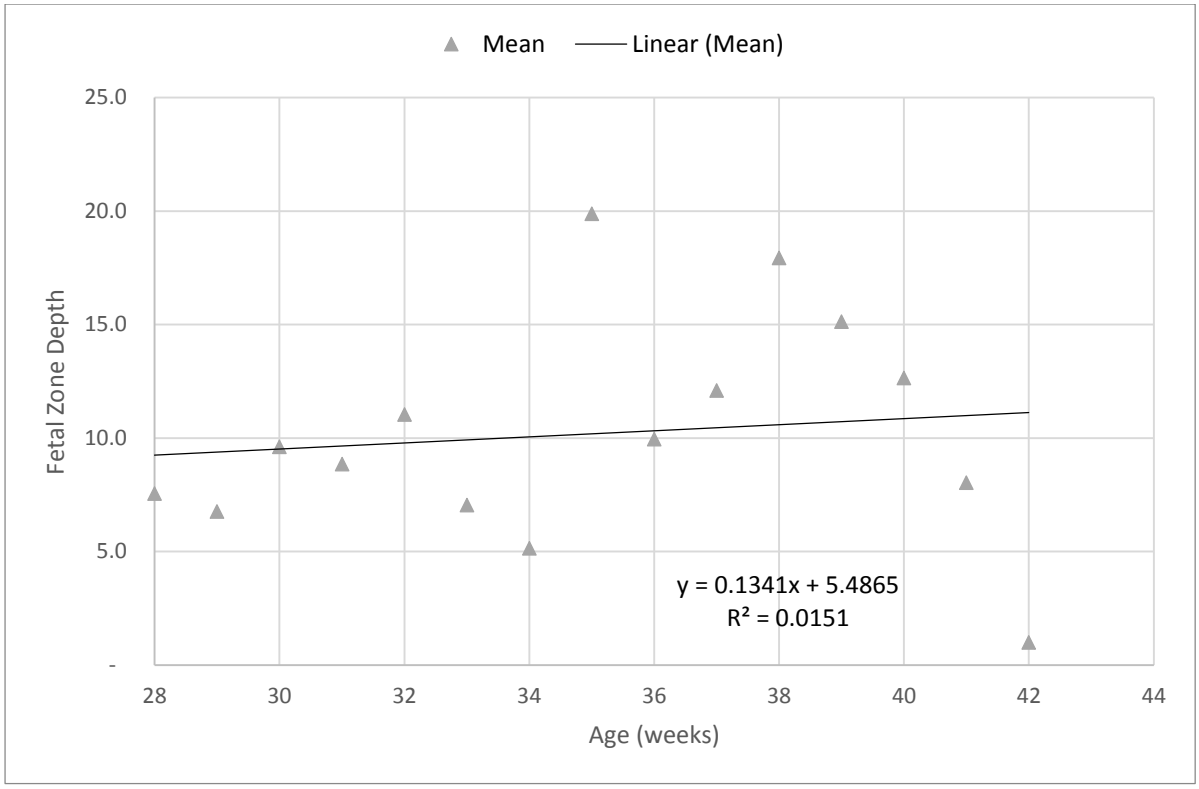


Figure 4. 6 Scatter plot showing the Fetal Zone Depth in millimetres versus the gestational age in weeks.

The figure above is a scatter plot that assessed the relationship between the fetal adrenal gland depth in millimetres and gestational age in weeks. The gestational age (weeks) is on the x-axis and fetal zone depth (mm) on the y-axis. The data points are scattered around the plot, exhibiting a very weak positive linear trend. There are some outliers with the fetal zone depth especially after 39 weeks. The scatter plot suggests a weak positive correlation between gestational age and fetal adrenal gland depth.

Table 4. 11 The fetal adrenal gland composite measurements and ratios.

	Mean	Std. Dev.	min	max	Median	p25	p75
Adrenal gland volume (mm^3)	694.211	785.591	25.99	4885.693	470.263	216.491	822.241
Fetal adrenal gland volume (mm^3)	160.342	233.962	1.34	1653.715	81.363	34.875	183.706
Corrected adrenal gland volume (mm^3/g)	.356	.389	.019	3.269	.278	.146	.426
Corrected fetal zone volume (mm^3/g)	.081	.12	.001	.87	.051	.026	.093
Adrenal gland ratio	.213	.121	.027	.958	.198	.132	.271
Cortex width (mm)	.208	1.052	-7.783	1.95	.3	0	.667
Adrenal Gland width Ratio	.425	.132	.2	.85	.41	.321	.5

Source: Sonographic measurement of the fetal adrenal gland as a marker of adverse perinatal outcome in preeclampsia.

The table above shows the mean, standard, deviation, median and interquartile ranges of the composite fetal adrenal gland dimensions.

4.3 Adverse perinatal outcome in preeclampsia.

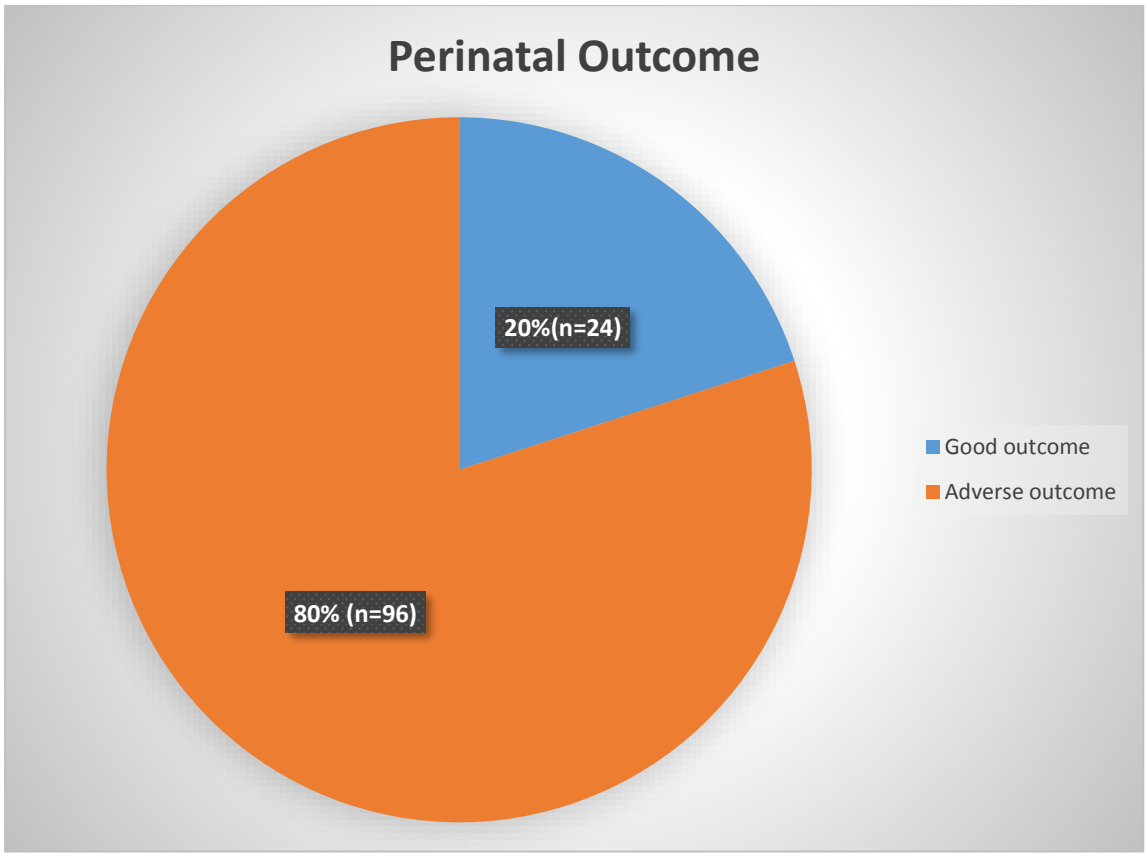


Figure 4. 7 Distribution of study participants according to the composite perinatal outcome.

The pie chart displayed the distribution of perinatal outcomes, with two sections representing the distinct categories. The larger section accounted for 80.00% of the chart, indicating the proportion of participants with adverse perinatal outcome. The smaller section represented 20.00% of the chart.

Table 4. 12 Relationship between perinatal outcome and selected fetal clinical parameters as well as maternal socioeconomic variables.

		Perinatal Outcome			
		Adverse perinatal outcome	**Good outcome**	**Total**	**p- value**
Growth Centile category	FGR	2	30	32	0.027
	AGA	62	20	82	
Umbilical artery PI centile category	Normal	45	18	63	0.009
	Abnormal	34	1	35	
Birth weight Centile Category	SGA	34	5	39	0.160
	AGA	58	1	74	
	LGA	4	3	7	
Birth weight Category	Extreme Low Birth Weight	14	0	14	0.001
	Very Low Birth Weight	35	0	35	
	Low Birth Weight	36	7	43	
	Normal	11	15	26	
	Macrosomia	0	2	2	
Age Category	<20	3	0	3	0.605
	20-25	18	0	18	
	26-30	17	7	24	
	31-35	35	10	45	
	36-40	16	5	21	
	41-45	7	2	9	
Religion	Christian	85	22	107	0.660
	Muslim	11	2	13	
Level of Education	None	2	3	5	0.169
	Primary	12	1	13	
	Junior High School	31	8	39	
	Senior High School	15	3	18	
	Tertiary	20	7	27	
Ethnicity	Akan	75	22	97	0.487
	Ewe	2	0	2	
	Grusi	1	0	1	
	Other	18	2	20	
Marital Status	Single	18	1	19	0.173
	Cohabiting	12	2	14	
	Married	66	21	87	

Source: Sonographic measurement of the fetal adrenal gland as a marker of adverse perinatal outcome in preeclampsia

The table above shows the relationship between the perinatal outcome and fetal clinical parameters and maternal sociodemographic variables. growth centile category(p=0.027), umbilical artery pi centile category(p=0.002), birth weight centile category(p=0.002), birth weight category (p=0.000) was statistically significant with a p-value of <0.05. However, age category(p=0.231), religion (p=0.660), level of education, ethnicity(p=0.169), marital status (0.150).

4.4 Fetal Adrenal gland Size and relationship with perinatal outcome.

Table 4. 13 Two-sample sample t test comparing fetal adrenal gland dimensions with perinatal outcome.

Variable	Perinatal Outcome	N=120	Mean	Std. dev.	[95% conf.	interval]	t-value	p-value
Total Adrenal Gland Length	Good	24	24.662	4.259	22.863	26.461	5.377	**0.001**
	Adverse	96	18.262	5.421	17.164	19.361		
Fetal Zone Length								
	Good	24	19.055	4.063	17.339	20.771	2.684	**0.008**
	Adverse	96	14.371	8.284	12.692	16.049		
Total Adrenal Gland Width								
	Good	24	6.637	4.121	4.897	8.377	3.986	**0.0001**
	Adverse	96	3.926	2.630	3.394	4.459		
Fetal Zone Width								
	Good	24	3.242	3.782	1.645	4.839	2.951	**0.0038**
	Adverse	96	1.739	1.651	1.405	2.074		
Total Adrenal Gland Depth								
	Good	24	17.062	8.461	13.490	20.635	2.227	**0.0279**
	Adverse	96	12.901	8.121	11.256	14.547		
Fetal Zone Depth								
	Good	24	12.557	7.224	9.507	15.608	1.832	0.0696
	Adverse	96	9.0148	8.751	7.241	10.788		
Adrenal Gland Volume								
	Good	24	1486.344	1228.689	967.514	2005.174	6.819	**0.001**
	Adverse	96	467.740	408.292	385.012	550.467		
Fetal Zone Volume								
	Good	24	343.615	377.842	184.066	503.163	5.111	**<0.001**
	Adverse	96	104.632	132.603	77.765	131.500		
Corrected Adrenal Gland Volume								
	Good	24	0.473	0.335	0.332	0.615	1.916	0.0578
	Adverse	96	0.311	0.378	0.235	0.388		

Corrected Fetal Zone Volume								
	Good	24	0.111	0.101	0.069	0.154	1.609	0.110
	Adverse	96	0.070	0.116	0.046	0.093		
Adrenal Gland ratio								
	Good	24	0.221	0.078	0.187	0.254	0.389	0.698
	Adverse	96	0.210	0.122	0.186	0.235		
Cortex Width								
	Good	24	0.119	1.985	-0.719	0.958	-0.5511	0.583
	Adverse	96	0.251	0.625	0.123	0.377		
Adrenal Gland Width Ratio								
	Good	24	0.433	0.161	0.365	0.501	0.2293	0.819
	Adverse	95	0.426	0.125	0.401	0.452		

Source: Sonographic measurement of the fetal adrenal gland as a marker of adverse perinatal outcome in preeclampsia

The table above shows a two-sample t-test result that was done to determine whether there was a statistically significant mean difference for the fetal adrenal gland dimensions and perinatal outcome.

The means of the Total Adrenal Gland Length, Total Adrenal Gland Width, Total Adrenal Gland Depth, Fetal Zone Length, Fetal Zone Width, Fetal Zone Depth, Adrenal Gland Volume showed a statistically significant difference between fetuses with good outcome and those with adverse perinatal outcome. The t-value was positive in all these cases meaning fetuses with good perinatal outcome had comparably larger fetal adrenal glands than those who had a poor outcome, and this difference was statistically significant p value <0.05.

Table 4. 14 Mean, Median and Interquartile range for the various adrenal gland parameters.

	Mean	Std. Dev.	min	max	Median	p25	p75
Adrenal Gland Length(mm)	19.548	5.787	8.5	35.3	19.183	15.833	23.5
Fetal Zone Length(mm)	15.325	7.924	4.1	80.467	14.7	10.967	18.2
Adrenal Gland Width(mm)	4.516	3.204	1	22.233	3.633	2.7	5.05
Fetal Zone Width(mm)	2.05	2.341	.34	18.9	1.367	1	2.05
Adrenal Gland Depth(mm)	13.871	8.449	1.3	50.4	13.6	8	19.6
Fetal Zone Depth(mm)	9.831	8.728	.4	73	8.685	4.7	13.333
Adrenal Gland Volume(mm^3)	694.211	785.591	25.99	4885.693	470.263	216.491	822.241
Fetal Adrenal Gland Volume(mm^3)	160.342	233.962	1.34	1653.715	81.363	34.875	183.706
Corrected Adrenal Gland Volume(mm^3/g)	.356	.389	.019	3.269	.278	.146	.426
Corrected Fetal Zone Volume(mm^3/g)	.081	.12	.001	.87	.051	.026	.093
Adrenal Gland Ratio	.213	.121	.027	.958	.198	.132	.271
Cortex width	.208	1.052	-7.783	1.95	.3	0	.667
Width ratio	.425	.132	.2	.85	.41	.321	.5

The above table shows the mean, median and Interquartile ranges for the different adrenal gland dimensions.

Table 4. 15 Unadjusted logistic regression model for Fetal Gland Dimensions and Logistic Regression Model Adjusted for Gestational Age

	Unadjusted				Adjusted			
Variable	**Odds ratio**	**[95% conf.**	**interval]**	**P>z**	**Odds ratio**	**[95% conf.**	**interval]**	**P>z**
Total Adrenal Gland Length	0.791	0.71	0.882	**0.001**	0.818	0.675	0.99	**0.039**
fetal Zone Length	-----	-----	-----	-----	-----	------	-----	-----
Total Adrenal Gland Width	0.784	0.666	0.922	**0.003**	0.912	0.766	1.086	0.302
Fetal Zone Width	0.787	0.638	0.972	**0.026**	0.931	0.732	1.184	0.563
Total Depth	0.945	0.896	0.996	**0.036**	0.987	0.912	1.068	0.753
Fetal Zone Depth	-----	-----	-----	-----	-----	-----	-----	-----
Adrenal Gland Volume	0.998	0.997	0.999	**0.001**	0.999	0.997	0.999	**0.035**
Fetal Adrenal Gland Volume	0.995	0.992	0.998	**0.001**	0.999	0.996	1.001	0.306

Source: Sonographic measurement of the fetal adrenal gland as a marker of adverse perinatal outcome in preeclampsia.

The above table shows the shows the unadjusted and adjusted logistic regression model for adrenal gland dimensions. The Total Adrenal Gland Length (p=0.039) and adrenal Gland Volume (p=0.035) were still significant after adjusting for gestational age.

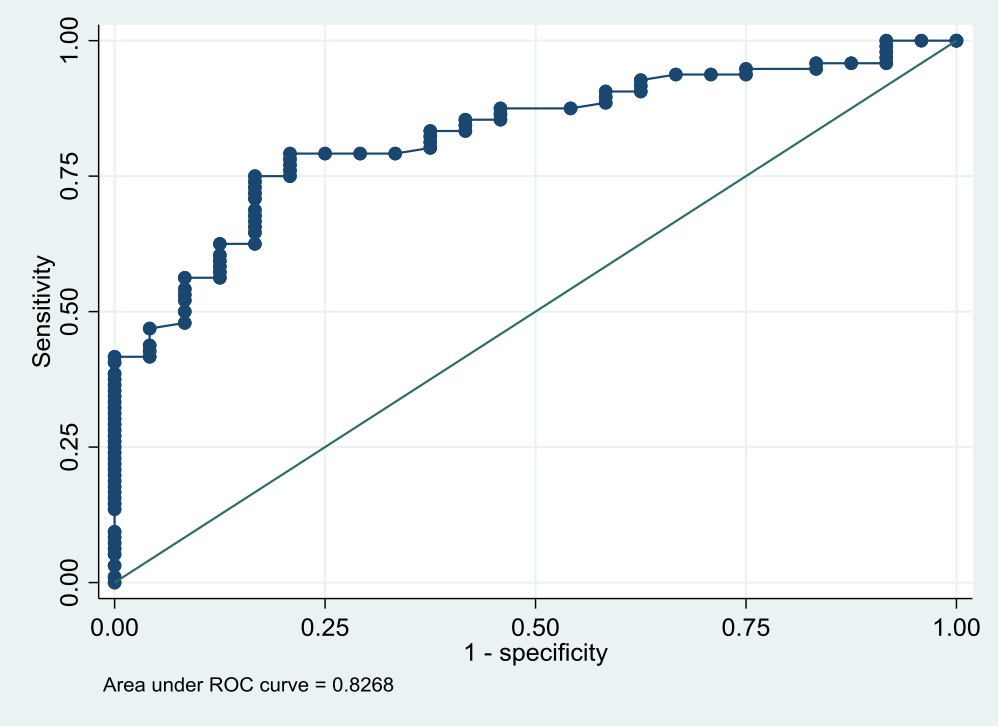


Figure 4. 8 ROC curves depicting the predictive ability of the total adrenal gland length in the prediction of adverse perinatal outcome.

Source: Sonographic measurement of the fetal adrenal gland as a marker of adverse perinatal outcome in preeclampsia.

The AUROC obtained was 0.8268 which depicts a relatively good performance of the fetal adrenal gland length in distinguishing between adverse and good perinatal outcome.

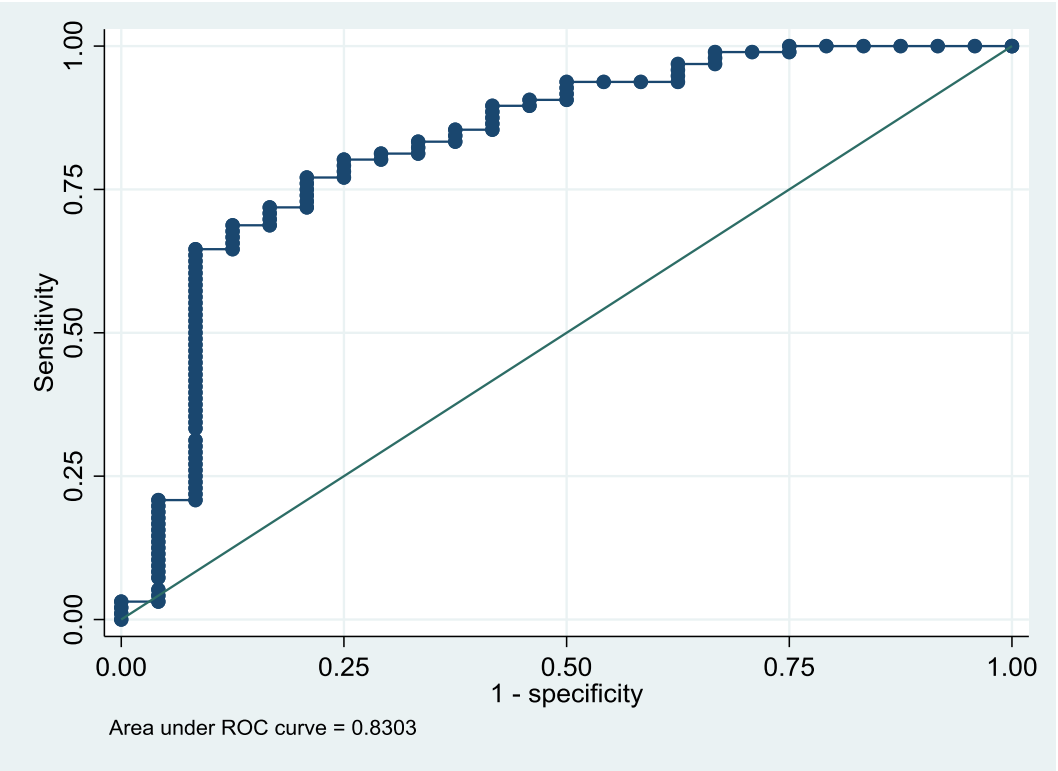


Figure 4. 9 ROC curves depicting the sensitivity and specificity of the total adrenal gland volume in the prediction of adverse perinatal outcome.

Source: Sonographic measurement of the fetal adrenal gland as a marker of adverse perinatal outcome in preeclampsia

The AUROC obtained was 0.8303 which depicts a relatively good performance of the fetal adrenal gland volume in distinguishing between adverse and good perinatal outcome.

CHAPTER FIVE

DISCUSSION

5.0 Maternal Sociodemographic Characteristics

The results of the study show that over 60% of the study participants who were all patients with preeclampsia were above 30 years of age. Dassah et al and Adu-Bonsaffoh et al had similar findings in their study done at KATH and KBTH respectively(6,9) The finding in this study supports the fact that advancing maternal age is a recognized risk factor for the development of preeclampsia as reported in many studies. The relative risk of developing preeclampsia was found to be increasing with advancing maternal age in the study done by Bartsch et al (age ≥35: RR 1.2, 95% CI 1.1-1.3; age ≥40: RR 1.5, 95% CI 1.2-2.0)(26) Patients with advancing maternal age have comorbidities like obesity, chronic hypertension and Diabetes Mellitus which predispose them to having preeclampsia in pregnancy. Some experts have argued that a similar incidence is found at a younger maternal age. One large systematic review by Macedo et al involving 291,247 adolescents, found the prevalence of preeclampsia among adolescents to be 6.7%(27) but this evidence is inconclusive as some systematic reviews support an association while others do not (28). In current study, very few study participants fell in the category which involved adolescents 2.5%(n=3).

In terms of religious beliefs of the study participants, many of the study participants were Christians 89.17% (107). This was followed by Muslims 10.83% (13). There were no study participants from the traditional religion or belonging to other religions. These findings were similar to the findings of the study undertaken in the same setting by Dassah et al(6). This reflects the general religious distribution in the study area as well as the country where majority of the population are Christians. No study participants belonged to the traditional religious beliefs and other minority religions. This may also depict the increasing influence of Christianity and Islam religion which are more prevalent now than the traditional religion.

With respect to the level of education, approximately 38.24% (n=39) of the study participants had completed Junior High School education. Participants who had completed their tertiary education formed 26.47% (n=27) respondents. This was followed by those who had completed Primary school 12.75% (n=13). About 4.90% (n=5) had received no formal education. The distribution of the level of education found in this study is quite similar to the study done by Dassah et al, 5.8% who had received no formal education and majority of study participants

61.2% had received basic education. A study undertaken by Silva et al found that women who had a low socioeconomic status that is a low level of education, were five times more likely to have preeclampsia (29). A study done in Sweden involving 46,618 pregnancies also concluded that lower socioeconomic status is associated with risk of preeclampsia(103). It is interesting to note that these studies were done in countries with universal healthcare where health care especially maternal care is free and accessible to all women and yet women who fall within the lower socioeconomic bracket have the highest risk of preeclampsia. Reasons for this association are unclear but may be due to improved health seeking behaviour among women of higher socioeconomic status due to adequate knowledge about the complications of preeclampsia. Also, these women are likely to seek pre-conceptional care which will eventually lead to prevention of preeclampsia and improved maternal and perinatal outcomes. Despite all these factors some studies do not support the association of lower socioeconomic status with preeclampsia and rather link this association to the influence of BMI other causes (30–35).

The majority of study participants were Akans 81.67% (n=98), followed by Ewes who formed about 1.67% (n=2). There were other ethnic groups which formed about 15.83% (n=19). The setting of the study, which was in Kumasi, the Capital of the Ashanti Region is predominantly occupied by Ashantis who are Akans. This is similar to data obtained from the Population Housing Census from the Ghana Statistical Service where Ashantis is classified as subgroup of the Akan ethnic group formed 80.7% of the population. Ewes forms about 3.6% of the population. Almost other ethnic groups are found within the Kumasi Metropolis which makes it culturally and ethnically diverse(104).

Majority of study participants 72.50% (n=87) were married, 15.83% (n=19) were single and 11.67% (n=14) were Cohabiting. In the study done by Adu-Bonsaffoh et al which assessed perinatal outcomes in Hypertensive disorders of pregnancy reported that 80% of their study participants were either married or cohabiting and 20% were single(9). A much higher marital rate was found by Dassah et al 95.9% in the same setting. This may be because, they considered pregnant women and those who were cohabiting together. When it comes to the subject of relationships as a risk factor for preeclampsia, research papers in the past have focused on acquisition of a new partner within a year of pregnancy and duration of sexual cohabitation before first pregnancy. These have been based on an Immunological theory which states that prolonged exposure to paternal seminal antigens elicits a maternal immunological response

which when occurs over an extended period of time, leads to maternal tolerance and a reduction in the incidence of preeclampsia. Opinion is divided on this theory, and it was also not the focus of this study.

Olv et al in their review of 209,423 pregnancies, found that the risk of preeclampsia in the first, second and third pregnancies was 3.9%,1.7% and 1.8% respectively.

5.1 Maternal Clinical Characteristics

Concerning parity, many of the respondents had parity between 2-4 35.83% (n=43). This was followed by the nullipara who formed 30.00% (n=36) and the primipara respectively 24.17% (n=29). The least among the respondents were the grand multipara who formed 10.00% (n=12). The mean parity of the respondents was 1.725±1.70 with the highest parity being 6 deliveries. Comparable results were found by Adu-Bonsaffoh et al in their study. About 52.1% of their respondents had a parity of between 1-3 compared to 40.7% who were nulliparous. Only 7.1% had had more than 4 deliveries(9).

From the comparison of the two studies, the results suggest that quite a considerable proportion of nulliparous women have preeclampsia. A study by Bartsch et al found nulliparous women to have two times higher the risk of having preeclampsia (RR 2.1, 95% CI 1.9-2.4) (26) It is also not clear what the effect of new partners is in this study, duration of cohabiting sex as well as the duration in between pregnancies. The proponents of nulliparity being a risk factor for preeclampsia are of the view that the immune system of nulliparous women has had limited exposure to paternal seminal antigens, and the inadequate exposure to these antigens does not give the maternal immune system enough sensitization(105). Olv et al in their review of 209,423 pregnancies, the risk preeclampsia in the first, second and third pregnancies was 3.9%,1.7% and 1.8% respectively(106)Rather than nulliparity, some experts are of the notion that it is rather the period or interval between pregnancies that is implicated in preeclampsia in that the longer the period the higher the risk , a new partner may come in after a period of waiting. They argue that the protective effect of multiparity is only transient and falls sharply with a longer interval between pregnancies. This they said was not a recommendation for shorter interpregnancy intervals which have their inherent risks as well and that risk of an interpregnancy interval of 10 years is similar to that seen in the nulliparous (106).

The mean blood pressure for mothers with preeclampsia recruited in the study was 160.767mmHg while the diastolic blood pressure was 105.808mmHg. All patients with preeclampsia have a high blood pressure except for a few who do not satisfy all the diagnostic criteria. The blood pressure is usually ≥ 140/90mmHg, and those with severe hypertension having blood pressure of >_160//110mmHg(80). In the study by Dong et al among 172 patients with severe preeclampsia, their mean blood pressure was a systolic of 153.7 ± 22.5mmHg and diastolic of 103.5 ± 17.8mmHg(107). The results obtained by Dong et al though lower were similar to the means obtained in this study. This may be because their study was conducted in a developed country and their patients may have easy access to health facilities compared to the setting in our present study. In preeclampsia, there is formation of defective placental vasculature or abnormal trophoblastic invasion of spiral arterioles. There is relative placental under perfusion, oxidative stress and release of antiangiogenic factors and endothelial dysfunction in the maternal circulation eventually leads to the clinical manifestation of hypertension with an increase in peripheral vascular resistance.

The participants in the study had an average Creatinine of 73.369±34.785µmol/L. The lowest and highest level of creatinine being 19 µmol/L and 258 µmol/L. About 16.67% (n=17) of the study participants had creatinine >90µmol/L. Dong et al also had an average serum creatinine of 64.6 ± 20.0 µmol/L among the 172 patients with preeclampsia that were studied in Shengjing Hospital of China Medical University. Again, their mean creatinine was much lower compared to this study. This could be due to the fact that Asians have a lower muscle mass compared to Africans. “Creatinine is a breakdown product of Creatinine Phosphate from muscle and protein metabolism” (108). This could also be from the diet of Asians which is in rich in vegetables rather than meat. The mean ages in both studies were comparable and could not explain the reason for the difference in the level of creatinine.

The mean liver transaminases for the women with preeclampsia in this study were AST (67.191±105.665U/L) and ALT (46.110±78.903U/L). Transaminases found in the heart, liver, skeletal muscle, gall bladder, kidneys, red blood cells and the brain are responsible for catalysing the chemical reaction of transferring α amino group from aspartate to glutamate. The study done in China by Dong et al to also had lower mean transaminases (AST (U/L) 41.7 ± 65.5 and ALT (U/L) 27.4 ± 51.5)(107). This may also be attributed the lower muscle mass of Asians compared to Africans.

Study participants in this study had a mean haemoglobin of 11.922+1.739g/dL. This is comparable to the mean value obtained by the study in China HB (g/dL) 11.71 ± 2.4(107).

Mothers with preeclampsia who were enrolled in the study had been assessed for their symptoms. About 50.83% (n=61) had no headache. A similar proportion of the study participants had headache 49.17% (n=59) and 23.33% (n=28) had moderate headache. Approximately 15.83% (n=19) had severe headache and only 10.00%(n=12) had mild headache Most of the patients who were admitted to the ward were also referred from other hospitals where they may have had initial treatment administered as a result, it is not surprising most of the patients did not have headache. Though the diagnostic criteria from the American College of Obstetricians suggests the definition of headache of preeclampsia as "new-onset headache unresponsive to medication and not accounted for by alternative diagnoses"(109), absence of headache or a resolving headache does not exclude preeclampsia. Headache is one of the commonest symptoms which move clients with preeclampsia especially in the post-partum period to seek clinical care. Though common, its pathophysiology is poorly understood. It has been linked to cerebral oedema, cerebral ischemia, and haemorrhagic changes. Some experts have noted endothelial dysfunction which leads to cerebral vasospasm or loss of cerebral autoregulation from a dangerously high blood pressure(110–112). In this study, apart from 50.83%% (n=61) that had no headache, the rest 49.17% had headache out of which 15.83%(n=19) had severe headache. In a review done among postpartum patients with preeclampsia, the most common complaint at the time of presentation in 70% of their study subjects was headache(113,114). A study by Dong et al among 172 patients with severe preeclampsia found that 52.9%(n=91) experienced headache which is similar to the rate found in this study, although slightly higher(107).

A greater proportion of study participants had no epigastric pain 89.17% (n=107). Only 10.83% (n=13) had symptoms of epigastric pain. This symptom also reflects disease at the severe end of the spectrum. It may come about as a consequence of the stretching of the Glisson's capsule which can be due to liver swelling or bleeding. Rarely, the cause may be from liver rupture especially when the pain is of sudden onset. Yen et al also conducted a study among 2023 women, in which they used maternal symptoms to predict adverse maternal and perinatal outcomes. About 18.6% (n=381) had symptoms of right upper quadrant pain and this value was higher than 10.83% as was obtained in this study(115). This difference may be

attributed to problems of recall since patients who may have had resolved symptoms may not report when asked later in the course of the disease. Also with visual disturbance, majority of study participants 86.67% (n=104) had no visual disturbance, as against only 13.33% (n=16) who had symptoms of visual disturbance. When visual symptoms are present, in a patient with preeclampsia, it depicts disease in the severe range of the spectrum. The causes of visual disturbance include photopsia, scotomata, blurry vision, and amaurosis fugax. All these may be the clinical manifestations of Posterior Reversible encephalopathy Syndrome(116). In the study by Dong et al, 28.5% (107) had visual disturbances which was higher than the rate found in this study. This is reasonable since visual disturbances are self-reported and the study by Dong et al only focused on patients in the severe end of the spectrum.

5.2 Perinatal outcomes in Preeclampsia

Pregnancies that are complicated by Preeclampsia have a higher risk of adverse perinatal outcomes(9,90). In this study, majority of the fetuses were delivered via caesarean-section 83.33% (n=100) for various obstetric indications. About 16.67% (n=20) were delivered through Spontaneous Vaginal Delivery. The world over, caesarean section rates continue to rise and WHO states that Caesarean deliveries account for about 1 in 5 deliveries, approximately 25% of all deliveries(117). This is a worrying trend that must be looked at circumspectly. With this trend, has there been any corresponding improvement in both maternal and perinatal morbidity and mortality? Compared to the study done by Dassah et al a lower rate of 55.5% was found(6) . A recent study at the Korle Bu Teaching Hospital by Lawrence et al found a higher rate of 66.5% (90)but not as high as in this study. The high rate of babies delivered by Caesarean section in preeclampsia in this study could be attributed to the fact that, preeclampsia is a complication of pregnancy which cannot be treated in the same way as non-complicated pregnancies. Fetal surveillance is usually instituted and some of the fetuses in preeclampsia have various degrees of placental insufficiency and as such labour and delivery will offer a precarious path with a high risk of poor outcomes. There is equipment available to monitor fetuses who could have been delivered by spontaneous vaginal delivery, but this equipment is inadequate making monitoring less efficient. In the dispensation of increasing lawsuits and bids to improve perinatal outcomes, obstetricians will usually resort to caesarean sections as the safest route. Again, routine use of fetal surveillance such as Cardiotocography to decide on the route of delivery or the timing of delivery of a patient with

preeclampsia may have had an influence on the high caesarean section rate. Cardiotocography is known to have a high false positive rate of about 60% which may increase the risk of unnecessary interventions(118). A great proportion of fetuses are also in the peri-viability period of around 28 weeks, very preterm (28-31weeks). The Caesarean Section rate is also high at this gestational age. Again, as described in the setting, KATH receives the highest number of referrals as a tertiary referral hospital in Ghana and most of the cases are unfortunately in a severe and compromised state because they were deemed not fit to be managed in the referring facilities. Some of the reasons may be due to malpresentation. Nevertheless, the Caesarean Section rate as found in this study is high and critical steps must be engaged to reduce the rate including researching into the indications for such caesarean sections which is beyond the scope of this study.

There were more females births 53.33% (n=64) than male births 46.67% (n=56) among the fetuses delivered in the study-period but the ratio is about 8:7 in favour of females. This is at variance with the sex ratio at birth in Ghana which is about 1.03males/females according to data from the Ghana Statistical Service(104). Scientific opinions are divided on the association of sex or gender with preeclampsia. In the study by Taylor et al, women with early onset preeclampsia had a higher odds (ORadj. 3.2, 95% CI 1.1–9.6) of carrying a female fetus and women without preeclampsia were found to have lower odds (ORadj. 0.5, 95% CI 0.3–0.9). The study also found that the female sex is associated with anti-inflammatory and regulatory cytokines(119). In a study by Mirzakhani et al, they examined if maternal race had an impact on the relationship between fetal sex and risk of preeclampsia. Their findings were that preeclampsia was not more common in mothers with female or male fetuses, but the interaction was with African American mothers carrying male fetuses and this was significant after adjusting for potential confounders(120).

In terms of the APGAR scores at 1 minute, 67.14% (n=77) had an APGAR score of > 7 (normal) and 35.83% (n=43) had APGAR score of < 6(abnormal). At 5 minutes new-borns with normal APGARS scores were 82.50% (n=99) and those with abnormal APGAR scores were 17.50%(n=21). In the study by Dassah et al done at the Komfo Anokye Teaching Hospital, at 1 minute and 5 minutes, the proportion of new-borns that had abnormal APGAR scores were 35% and 10.0% respectively(6). The rate of abnormal APGAR scores was similar compared at 1 minute but there was a higher proportion of abnormal APGARS at the 5th minute

in this study. This may possibly be due to the high proportion of preterm new-borns in this study. The study by Lawrence et al and Adu-Bonsaffoh et al at the Korle Bu Teaching Hospital had the proportion of new-borns with abnormal APGAR scores at 5minutes being 14.9% and 20.7% (8,88)respectively. These rates obtained by the studies done in KBTH were somewhat similar to the rates found in KATH. The APGAR score is used as a universally accepted tool to assess new-born health status immediately after birth. The score has 5 variables including heart rate, respiratory rate, muscle tone, reflex irritability, and colour of the skin. A score of 7-10 would virtually require no further intervention for the newborn. Those newborns who score 6 and below will require further evaluation and possible intervention. Though there is an association between low APGAR scores and morbidity and mortality. Its predictive ability for neonatal outcomes is poor and as such is not used as a prognostic tool(121)

Approximately 35.83% (n=43) of fetuses delivered were Low birth weight, about 29.17% (n=35) were Very Low Birth Weight. The Extremely Low Birth Weight Categories formed about 11.67% (n=14) of the deliveries. About 1.67% (n=2) were macrosomic babies and the remaining were normal birth weight 21.67% (n=26). Using the Fenton Growth Charts for preterm Boys and Girls, most of the fetuses delivered were Appropriate for Gestational Age 61.67% (n=78). Those who were Small for Gestational Age were 32.50% (n=39). Only a few 5.83% (n=7) were Large for Gestational Age. The findings in this study suggest that mothers, with preeclampsia had a majority of their babies being born with low birth weights though most of them were appropriate for gestational according to the Fenton Growth Chart for Preterm Boys and Girls, respectively. This can possibly be attributed to the earlier Gestational Ages at which these deliveries took place. New-born weights were found as Appropriate according to their Gestational ages but overall, most of the fetuses were of Low Birth Weight(<2500g). The proportion of new-borns who fell below the Normal birth weight category was even alarming (76.67%), if all the low-birth-weight categories were considered together in this study. A much lower proportion of low-birth-weight new-borns (40.7%) were found in the study by Adu-Bonsaffoh et al. They considered all the low-birth-weight groups (<2500g) together in their study as is described by the WHO (9). Low birth weight has its commonest causes as Fetal Growth Restriction and prematurity or both. The latter is mostly the case in preeclampsia. New-borns with low birth weight are at risk of a range of adverse health outcomes. It is intricately linked to new-born mortality and morbidity and new-borns with low birth weight have 20 times higher risk of mortality compared to new-borns with normal weight. Its effects are also far

reaching and not only limited to neonatal life but extends to later in life. Low birth weight infants are at substantial risk of Non-Communicable Diseases, inhibited growth and Cognitive development in life(122) To improve neonatal morbidity and mortality and also to improve the Quality of life of infants in the future, steps must be taken to reduce the rates of preterm birth and low birth weights.

Most of the new-borns who had mothers enrolled into the study 74.55% (n=82) had admission to the NICU. About 25.45% (n=28) did not need admission to the NICU. This is not surprising as a greater proportion of these new-borns in this study were either preterm (76.67%) or had low birth weight(<2500g) (76.66%). Lawrence et al found a lower rate of NICU admission (50.3%) in their study on neonatal outcomes in preeclampsia done at the Korle Bu Teaching Hospital(90). Adu-Bonsaffoh et al also found a NICU admission rate of 36.4%(9) In the same setting as this study, Dassah et al also found a much lower rate of 29.6%(6). In all these studies, the rate of preterm birth and prematurity was much lower than in this current study because a significantly lower NICU admission rate was observed. The main reasons for NICU admissions, include supportive care for the preterm new-borns such as respiratory support, monitoring of vital signs, passage of feeding tube to facilitate feeding for new-borns who have a poor suckling reflex, administration of medications, placement in an incubator to help maintain body temperature and many other reasons.

With regards to respiratory support, 52.68% (n=59) received oxygen therapy for respiratory support. About 47.32% (n=53) did not receive oxygen therapy. Research data from the Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network which involved 9575 very low birth weight infants according to gestational age. The analysis of the data suggests that 93% of the very low birth weight infants had respiratory distress at birth (123) . Thus, it is not surprising that 52.68% percent of the infants born to preeclamptic mothers in the study required oxygen therapy. The main cause of respiratory distress syndrome (RDS) in preterm new-borns is the lack of pulmonary surfactant whose production starts from around the 20th week of gestation and is known to reduce surface tension in the alveolar thereby increasing the surface area for gas exchange by allowing lung expansion and preventing atelectasis(123). The management of RDS in the infant requires skill, experience, and modern oxygen delivery equipment. The management modalities may include, use of Antenatal Corticosteroids, supplemental oxygen, nasal continuous positive airway

pressure (nCPAP) or nasal intermittent positive pressure ventilation (NIPPV), administration of surfactant which is very costly in our setting and not covered by the National Health Insurance Scheme. New-borns who do not respond to these will require bag and mask ventilation and escalation to intubation and mechanical ventilation. In this study, no intubation was done for any of fetuses delivered. Reasons could be lack of well-functioning equipment and unavailability of pulmonary surfactant which is an important adjunct to the success of the management of RDS.

In this study, most of the newborns 76.67% (n=92), were delivered preterm that is before 37 weeks of gestation. The remainder did not experience preterm birth 23.33% (n=28). The study by Adu-Bonsaffoh et al had a preterm rate of 35% which is lower than that obtained in this study(9). Lawrence et al also found a rate of 52.7%(88) . Dassah et al found a high rate of 62.0% of preterm birth in their study (6) Trends from the studies discussed and, in this study, show a rise in preterm birth rate. Preterm birth is not without complications. Some of the short-term complications include Respiratory Distress Syndrome, Bronchopulmonary Dysplasia, Necrotizing Enterocolitis, Intraventricular Haemorrhage, Periventricular Leukomalacia, Patent Ductus Arteriosus and many more(123). Attainment of Sustainable Development Goal 3 and target 3.2 which aims at ending preventable deaths of newborns and children under 5 years will be a mirage without tackling this problem of preterm births through preventive efforts and effective management.

Only 0.91% (n=1) had a seizure in the neonatal period, none of all the remaining study participants experienced any seizure 99.09% (n=109).

There were a significant number of stillbirths 8.33% (n=10) and, a greater percentage did not experience still births 91.67% (n=110). A systematic review involving 25,356,688 pregnancies among 92 research studies found women with preeclampsia to have double the risk of stillbirth (RR 2.4, 95% CI 1.7-3.4) (26)A higher still birth rate of 14.2% was found by Dassah et al. Again, Adu-Bonsaffoh et al found a similar stillbirth rate of 9.3% (9) and Lawrence et al found a rate of 11.3%(90). Another systematic review by Atamamen et al found a similar still birth rate of 9.88% in several studies across the African continent(124) . Still birth in preeclampsia may be attributed to severe forms of placental insufficiency and placental abruption.

There were neonatal deaths, about 8.33% (n=9) among the current study's participants. Those who did not experience neonatal deaths were 91.67% (n=99).

The preterm neonates were followed up till 7 days of life for the purposes of this study. Approximately 59.00% (n=65) of the preterm neonates were well in the first week of life. About 31.82% (n=35) were still on admission at the NICU by Day 7 of life and 8.18% (n=9) had died and 0.91% (n=1) was lost to follow-up. The main outcome of this study was a composite of adverse neonatal outcomes, defined as 1 or more of the following: NICU admission, Low APGAR scores (<7) at 5th minute, preterm birth, neonatal death, oxygen therapy, Stillbirth, Seizures, intubation, and low Birth weight. There was an adverse outcome of rate of 91.9%. In the study by Lawrence et al., a composite of poor neonatal outcomes including "stillbirth, very low birthweight (<1500 g), 5-minute Apgar score <7, neonatal intensive care unit admission, or a live birth with a subsequent death before discharge". The composite of poor neonatal outcomes was experienced by 58.2% of the neonates (90). This is much lower than the rate obtained in this study. The possible reasons are that a few more adverse outcome measures were used in this study which were not in the study by Lawrence et al. Again, the inclusion of oxygen therapy among preterm newborns who have an extremely elevated risk of Neonatal Respiratory Distress Syndrome (93.2%)(123) could have been responsible. This study also had a remarkably high preterm and low birth weight rate, thus the very high composite of adverse outcomes.

5.3 Adrenal Gland sizes in fetuses of mothers with preeclampsia and relationship with gestational age.

Fetal adrenal measurements were done for both the whole of the adrenal gland and the fetal zone. For the purposes of this study. The length, width, depth, adrenal gland volume, fetal zone volume, adrenal gland ratio was measured and computed. From literature review, the measurements stated above were all described as gestational age dependent. The adrenal gland volume and fetal zone volume were all corrected for fetal weight. The width ratio and cortex width were also computed.

In terms of the total adrenal gland length, that is the mean of the length of the whole adrenal gland in millimetres found in this study was similar to the mean of the whole adrenal gland length found by Pattanapanyasat et al in their study to determine the mean of the various adrenal

gland measurements and their relationship with different gestational ages between 25 to 37 weeks(125). Both the scatter plots in the study by Pattanapanyasat et al and in this study showed a positive relationship between gestational age (weeks) and total length (mm), but the plot by Pattanapanyasat et al exhibited a stronger and more concentrated pattern while the plot in this current study showed a moderate to strong concentration pattern. The correlation between gestational age and total length appeared to be more pronounced in the study by Pattanapanyasat et al compared with what we found in this study. The correlation coefficient in this study was lower (R^2=0.68) and that by Pattanapanyasat et al was higher (R^2=0.85). This may be due to a smaller sample size and technique of measurement. Both scatter plots demonstrated a positive relationship between gestational age and total length of whole fetal adrenal gland. As the gestational age increases one would expect the total length of the fetal adrenal gland to also increase. As the fetus develops the growth of the fetal adrenal gland is regulated by the hormones released by the hypothalamus, pituitary, and placenta. The hormones that are produced especially Adrenocorticotropic hormone stimulate the proliferation and differentiation of the adrenal thus the increasing glandular size. The fetal adrenal gland also produces cortisol which is also required by several organ systems for their maturation. As the fetus grows, the demand for cortisol increases. There is hyperplasia and enlargement of the gland to meet the heightened demand. The level of cortisol is also increased in periods of intrauterine stress(126).

With regards to the fetal zone length, the scatter plots in the study by Pattanapanyasat et al and in this study show a positive relationship between gestational age (weeks) and the fetal zone length (mm), but the plot by Pattanapanyasat et al also showed a much stronger and more concentrated pattern while the plot in this study showed a moderate to strong concentration pattern. The correlation between gestational age and fetal zone length appeared to be more pronounced in the study by Pattanapanyasat et al compared to what we found in this study. The correlation coefficient in this scatter plot of fetal zone length versus gestational age in this study was lower (0.67) and that by Pattanapanyasat et al was higher (R^2=0.80). This may be attributed to a smaller sample size and heterogeneity in this current study since fetuses with adverse outcomes and good outcomes were included in the study. these have significantly different mean adrenal gland dimensions. Overall, the scatter plots showed a positive relationship between gestational age and fetal zone length. Gestational age would increase with increasing fetal zone length. The fetal zone is the most steroidogenic portion of the fetal adrenal gland and

is known to occupy about 80-90% of the gland in the second trimester. These are exclusively expressed in the Fetal Zone; cytochrome P450 17A1 (CYP17A1) and Sulfotransferase Family 2A Member 1 (SULT2A1) through 7 weeks gestation. This increases with glandular size and gestational age(42)

Taking into consideration the Fetal Adrenal gland Width, the scatter diagram in the study by Pattanapanyasat et al and in this study showed a positive relationship between gestational age (weeks) and Fetal Adrenal Gland Width (mm). Both plots showed a similar pattern of concentration. The correlation coefficient in this study was similar (R^2=0.74) though a little higher than that by Pattanapanyasat (R^2= 0.70)(125). This may be due to fewer errors in the technique of measurement and fewer outliers. Both scatter plots demonstrated a positive relationship between gestational age and Fetal Adrenal Gland Width. The gestational age increases as the Fetal Adrenal Gland Width also increases. This can be explained by the increase in steroidogenic activity of the fetal adrenal gland especially the Fetal Zone and the Transitional Zone as the demands by other organ systems increase with increasing gestational age(42).

Considering, the Fetal Zone Width, Both the scatter plots in the study by Pattanapanyasat et al and in this study show a positive relationship between gestational age (weeks) and Fetal Zone Fetal Zone Width (mm), the plot by Pattanapanyasat and the plot in this study showed similar strength and concentration. The correlation coefficient in this study was similar (R^2 =0.538) to that by Pattanapanyasat et al (R^2 =0.497). This may be due to a smaller sample size and technique of measurement. Both scatter plots demonstrated a positive relationship between gestational age and Fetal Zone Width of whole fetal adrenal gland. As the gestational age increases one would expect the Fetal Zone Width of the fetal adrenal gland to also increase.

Fetal Adrenal Gland Depth and Fetal Zone Depth versus gestational age on the scatter plot both showed a very weak positive correlation. The study by Pattanapanyasat et al exhibited a moderate positive correlation with correlation coefficient R^2=0.651 and R^2= 0.506(125) The reason for the difference could be accounted for by the heterogeneity in our study population which included pregnant women with preeclampsia as well as various severe forms of fetal growth restriction. These were all excluded in the study by Pattanapanyasat et al. Another reason could be technique of measurement and smaller sample size in this study.

5.4 Proportion of pregnancies with adverse perinatal outcomes in pregnant women with preeclampsia who are on admission.

In order, to capture the multiple aspects of the adverse perinatal outcomes in a condition like preeclampsia, a composite of outcomes was used. In this study, the composite outcome that is adverse perinatal outcome, included the following outcome variables; NICU admission, Low APGAR scores (<7) at 5 minutes, preterm birth, neonatal death, oxygen therapy, stillbirth, seizures, intubation. Adverse perinatal outcome for the purposes of this study was defined as, any 1 or more of the up listed outcomes.

In so doing, by combining multiple outcome measures into one composite outcome. The aim was to improve the statistical power and improve the efficiency of the analysis of this study. Each component of the composite outcome provided an important and different aspect of adverse outcome in preeclampsia, and this facilitated the capturing of a comprehensive image of adverse outcome in preeclampsia.

However, it is important to acknowledge some of the limitations of employing a composite outcome measure. The various aspects of the composite outcomes were given equal weights and did not matter how many of the individual components a study participant had. This had the potential of over amplification of the outcome measure.

In this study, out of the 120 study participants, 80.00%(n=96) were classified as having adverse perinatal outcome and 11.67%(n=14), had a good outcome. Compared to the study by Lawrence et al at the Korle Bu Teaching, they found a composite of poor neonatal outcome of 56.9% for preeclampsia. In their study, they used fewer individual components for the composite outcome measure which included “stillbirth, very low birthweight (<1500 g), 5-minute Apgar score <7, NICU admission, or a live birth with a subsequent death before discharge”(90). A much lower unfavourable perinatal outcome of 46.5% was also found by Misganaw et al in their study to assess perinatal outcomes in the Amhara referral hospitals in North-Western Ethiopia. Any of the following complications of preeclampsia was regarded as unfavourable outcome, Low Birth Weight, Low APGAR, Stillbirth, Preterm birth, Birth asphyxia, Miscarriage. They did not have NICU admission or Oxygen therapy as part of the adverse outcome (127). In essence they had fewer outcome measures in comparison with this current study. In another study done in KATH, where maternal and perinatal outcomes were

assessed, 87% had adverse maternal or perinatal outcomes (6) The adverse outcomes were high because they considered maternal or perinatal outcomes.

The perinatal outcomes in this study and the studies that have been discussed confirm that preeclampsia has an unacceptably high perinatal morbidity and mortality. The morbidity and mortality increase when preeclampsia reaches the severe end of the spectrum(128). The hallmark of preeclampsia is endothelial dysfunction. There is abnormal cytotrophoblast invasion of spiral arterioles, aberrant angiogenesis, inflammation The vessels instead of becoming very large high capacitance vessels maintain their narrow nature and this leads to hypoperfusion of the placenta. This phenomenon is responsible for the spectrum fetal effects including oligohydramnios, fetal growth restriction, placenta abruption, preterm birth, low birth weight, stillbirth, neonatal morbidity, and mortality(81,129,130)

Preterm birth which is a major consequence of preeclampsia has been shown to have a strong association with the disease as has been confirmed by several research papers. This association has been noticed to increase with worsening severity of hypertension(6,9,90,128). The same can be said of still birth which can result of from a hostile intrauterine environment from chronic hypoxia and from placental abruption. Systematic reviews, population-based studies have assessed stillbirth in preeclampsia as part of general perinatal outcome(6,9,90,124).. Prevention, timely recognition, management of preeclampsia and proper timing of delivery is likely to reduce adverse perinatal outcomes. As discussed earlier, preterm birth and fetal growth restriction are the main contributors to the adverse neonatal outcome. In Lower- and Middle-Income Countries, the burden of preeclampsia and preterm birth is disproportionately higher partly due to the lack of quality neonatal intensive care services(4). Neonates born to mothers with preeclampsia have increased risk of intraventricular haemorrhage, respiratory distress syndrome and NICU admissions. These adverse outcomes may be improved by improving the quality of neonatal care services.

Preeclampsia is plagued with significant perinatal complications as discussed and found in this study. A clear understanding of the pathophysiology of preeclampsia and is implication on fetal growth restriction, preterm birth, still birth and adverse neonatal outcomes will be important in finding an effective intervention to reduce the impact of these outcomes. It is essential to prevent preeclampsia, diagnose it early, promptly manage it and timely delivery will in no

doubt improve outcomes. Capacity for further research is also needed in settings like ours where the burden of the disease is highest.

5.5 Relationship between the fetal adrenal gland dimensions and adverse perinatal outcome in preeclampsia.

In terms of the total adrenal gland length, the obtained t-test results provided important insights into the research question under investigation. The significant difference between Adverse outcome and good outcome ($t = 5.377$, $p = <0.001$) suggests that there are meaningful distinctions between the two groups. This finding had significant implications for the research hypothesis, which posited that Adverse outcomes and good outcomes would differ in their dimensions.

The positive t-value ($t = 5.377$) indicated that the mean of the total adrenal gland length for those with Adverse outcome was lower than those with good outcome.

Moreover, the p-value of <0.001 indicated that the observed difference between the means of the total adrenal gland length for those with adverse and good outcome was statistically significant. This means that the likelihood of obtaining such a significant difference by chance alone is less than 5%. The p-value still remained significant even after adjusting for the effect of gestational age $p=0.0066$. Again, the odds obtained during logistic regression was 0.818 which indicated that as the total adrenal gland length increases the lesser the odds of obtaining an adverse outcome. Thus, we may have enough evidence to reject the null hypothesis and conclude that there is a true difference between the mean of the adrenal gland lengths between those with adverse outcome and good outcome.

The total adrenal gland volume had the similar characteristics with the two-sample t-tests. There was a statistically significant difference between the means of fetuses that had a good outcome and those fetuses who had an adverse perinatal outcome. Thus, the positive t-value 6.819, $p=0.000$. The Total Adrenal Gland Volume remained statistically significant after logistic regression ($p<0.001$). The level of significance was still present after adjusting for gestational age ($p=0.035$).

These findings somewhat agree with what was found by Mohajeri et al. However, in their study they found that the Adrenal Gland Volume, Corrected Fetal Zone Volume showed a

significant difference. Their study looked at the difference between Fetal Growth Restricted Fetuses and Healthy Controls(56). Similar results were also found by Kaya et al who also found a statistically significant Total Adrenal Gland Length. All fetuses in the current study were exposed to stressful conditions in-utero from exposure to preeclampsia. Those who were able to have a comparably larger adrenal size that is a better adrenal response to the stress had a better outcome than those fetuses whose adrenal response was inadequate that is a smaller total fetal adrenal volume and length comparably. Blue et al did not find any adrenal gland dimensions having a relationship with perinatal morbidity though they had a larger sample size. This may be the case, because of the population used in their study as well as the variables involved in the classification of the composite adverse perinatal outcome.

As discussed earlier, some papers have suggested a larger adrenal gland size in growth restricted fetuses (12,55,56,76). The fetuses with adverse outcome may be posited to have a smaller adrenal gland response hence smaller adrenal gland size. Hata et al studied fetal adrenal gland sizes in 346 healthy fetuses and 12 abnormal fetuses (8 out of 12 had FGR). All 12 fetuses were found to have the mean of their Fetal Adrenal Gland area below -2SD. About 33.3% of the FGR fetuses in their study had intrauterine fetal death or neonatal death, and 2 newborns (16.7%) had NICU admissions(86). Their results were similar to the findings in the current study. Based on the results of the adjusted logistic regression for Total Adrenal Gland Length and Volume we may have enough evidence to reject the null hypothesis

The Fetal Zone Length, Fetal Zone Width, Fetal Zone Depth, Total Adrenal Gland Width, Total Adrenal Gland Depth, Adrenal Gland Ratio, Fetal Zone Volume all lost their statistical significance after adjusting for gestational age. This may be attributed to the mediation of other confounding variables during the initial statistical significance. It could also be due to the fact that there was not enough statistical power to detect a significant association between the fetal zone length and perinatal outcome. These findings are similar to what Blue et al found in their study where there was no statistically significant association between adrenal gland size and neonatal morbidity(65). These findings were also at variance with what was found by Mohajeri et al. This may be because of differences in population and also the study by Mohajeri et al did not adjust for gestational age.

Based on the findings in this current study we do not have enough evidence to reject the null the hypothesis. A high-powered multicentre study with further statistical analysis will be needed to establish the true relationship between fetal zone length and perinatal outcome as well as calibrate its use for clinical practice.

This study aimed to assess the potential of adrenal gland size as a predictive marker for adverse perinatal outcomes. The Total Adrenal Gland Length and Total Adrenal Gland Volume were used since they still remained statistically significant even after adjusting for the effect of gestational age. The obtained AUROC was 0.8303 for Total Adrenal Gland Volume and 0.8268 for the total adrenal gland length. This suggests a relatively good performance of the model for fetal adrenal gland volume and fetal adrenal gland length in identifying fetuses of mothers with preeclampsia who may have adverse perinatal outcome. Oelmeier et al obtained a lower AUROC 0.6460 using the adrenal gland ratio. This may be because, the population used in the study as well the sample size was different. Larger sample sizes and strict adjustment for confounding would further elucidate the predictive value of the adrenal gland length and volume.

5.6 Strengths of the study

This study was conducted prospectively, this helped to reduce the incidence of recall bias especially for the maternal symptoms. This also helped to improve the precision of data collection.

A holistic picture of adverse perinatal outcome was achieved by using a composite measure. This improved the statistical power and improved the efficiency of the analysis of this study. Each component of the composite outcome provided an important and different aspect of adverse outcome in preeclampsia, and this facilitated the capturing of a comprehensive image of adverse outcome in preeclampsia. Again, using a composite of adverse perinatal outcome was probably a more useful indicator of clinical health status than single components of the composite.

The study involved participants with severe forms of Fetal Growth restriction, and this offered insights into adrenal gland changes in severely growth restricted fetuses.

The study site was a tertiary facility which is about the busiest in the country. In 2022, the hospital received 4,388 referrals by the National Ambulance Service alone. This was twice as high as the second busiest referral centre in the country. Consequently, there was an uncommon opportunity of studying a sizeable group of pregnancies complicated by preeclampsia with diverse neonatal outcomes. This may not have been possible elsewhere given the time frame of the study and the severity of cases.

5.7 Limitations of the study

In every study, it is important to acknowledge the limitations that may have been encountered in the course of the study. these limitations are factors that may have influenced the design, conduct, and interpretation of the study results. Acknowledgement of such gives a better context within which to interpret the findings of the study. In this part of the study, the discussion will centre on the potential limitations in the conduct of the research so as to provide a thorough understanding of the potential implications, validity, and generalizability of the study findings.

This study was conducted in the largest tertiary facility in the middle and Northern belt of Ghana. The situation as described in the study according to its findings may not be what pertains in lower-level facilities. For instance, there are consultants, specialists, residents, the presence of multidisciplinary team care and other equipment for neonatal care services that may influence perinatal morbidity and mortality that are not available in other facilities. This limits the generalizability of the study findings.

In terms of the exclusion criteria, if there were technical difficulties in visualising the fetal adrenal gland by ultrasound, such women were excluded from the study. These could still offer valuable information and their total exclusion could have introduced some bias into the sampling and recruitment of clients for the study. In so doing, valuable perspectives that could have provided a better understanding of the study may have been overlooked.

Neonatal outcomes were only assessed within the first week of life. Any other occurrences beyond this period were outside the scope of this study. The epigenetic changes that happen to the fetal adrenal gland and its adaptation are known to outlast the neonatal period and have an effect on the incidence of medical conditions later in life.

The weakness in the usage of a composite outcome measure could have introduced challenges in interpreting the relative contributions of each individual variable and the overall clinical importance of each. Having only one variable being present, was regarded as adverse outcome. Having more than one variable being present was not considered.

The interpretation of our results must be viewed and applied inside the perspective of these limitations.

CHAPTER SIX

6.1 Conclusion

The primary objective of this study was to assess the ultrasound measurement of the human fetal adrenal gland size and adverse perinatal outcomes in pregnancies complicated with pre-eclampsia.

The main findings of the study were that over 60% of the study participants were over the age of 30 years. Also, 35.29% of the study participants had a parity of between 2-4 deliveries. Again, the mean blood pressure of study participants was a systolic blood pressure of 161.0mmHg and a diastolic blood pressure was 106.0mmHg.

Most of the fetuses about 83.3% were delivered via caesarean section and 17.5% had abnormal APGAR scores at 5 minutes. There were 76.67% of the new-borns who were born preterm and had birth weight below 2500g (Low Birth Weight). Among newborns 74.55% were admitted to the NICU and 52.68% needed respiratory support. In all 8.33% experienced stillbirths and 8.18% died before the first of week of life.

The study used a composite adverse perinatal outcome where study participants who had any one of the following were regarded as having adverse outcome; NICU admission, Low APGAR scores (<7) at 5th minutes, neonatal death, oxygen therapy, stillbirth, seizures, intubation. In all 80.00% were classified as having adverse perinatal outcome and 20.00% had good perinatal outcome.

The mean of the Total Length of the Fetal Adrenal Gland (19.548mm$\pm$5.787mm, R2=0.68), length of the fetal zone (15.325mm$\pm$7.924, R^2=0.67), Total adrenal gland Width (4.516mm$\pm$3.204, R^2=0.75), Fetal Zone Width (2.05mm$\pm$2.341mm, R^2=0.54). These parameters showed moderate to strong positive correlation with gestational age.

In terms of the relationship of the sonographic measurement of the fetal adrenal gland size with perinatal outcomes, results from the study found that there was statistically significant differences between the means of the fetuses that had an adverse perinatal outcome and good perinatal outcome in terms of the total length, fetal zone length, total width, fetal zone width , Total depth, Fetal Zone Depth, Adrenal Gland Volume, Fetal Zone Volume, Corrected Adrenal Gland Volume and corrected fetal zone volume with p-value <0.05. Only the Total Adrenal

gland Length and Total adrenal gland volume remained statistically significant after adjusting for the effect of gestational age. An AUROC of 0.8268 and 0.8303 were obtained respectively for the two dimensions. Based on these findings we may have had enough evidence to reject the null hypothesis of no difference between the means of fetuses with adverse and good perinatal outcome for the two dimensions.

The study also found that fetuses with adverse outcome had smaller adrenal gland length and volume compared to the fetuses with good outcome. All fetuses in the study were exposed to stressful conditions in-utero from exposure to preeclampsia. Perhaps those who were able to have a larger adrenal gland size that is a better adrenal response to the stress had a better outcome than those fetuses whose adrenal response was inadequate that is a smaller fetal adrenal gland length and fetal adrenal gland volume.

This study highlights the value of the use of the sonographic measurement of the adrenal gland size as a tool that may be able to predict outcomes in preeclampsia and further research is needed to firmly establish its implications.

6.2 Recommendations

Based on the findings of the study that highlight the statistically significant difference between the means adrenal gland sizes of the new-borns with adverse perinatal outcome and those with good perinatal outcome, it is recommended that the Ministry of Health and supporting agencies should consider funding research into the role of the sonographic measurement of the fetal adrenal gland and its role in preeclampsia.

It is also recommended that the Maternal Fetal Medicine Unit of the Obstetrics Gynaecology Department of the Komfo Anokye Teaching should consider periodic training and refresher courses to train their staff that is Consultants, Specialists, Residents and Sonographers to accurately measure the size of the fetal adrenal gland to establish nomograms for our population and further strengthen its role in the prediction of outcomes in preeclampsia and possibly other high-risk pregnancies.

6.3 Areas for further research

Further research is needed to study the various changes that the fetal adrenal gland undergoes during fetal deterioration or when there is worsening maternal disease.

This current study can also be replicated on a larger scale using a longitudinal and multicentre approach to improve generalizability and acceptance of the results.

Apart from the sonographic measurement of the fetal adrenal gland size further research can be conducted into the level of stress hormones produced by the fetal adrenal gland in these hostile intrauterine conditions both in adverse and good perinatal outcome.

This study can also be replicated with a different study design for example a case control approach to determine if the results will be similar.

REFERENCES

1. August P, Sibai BM. Preeclampsia: Clinical features and diagnosis - UpToDate [Internet]. 2021 [cited 2021 Aug 14]. Available from: https://www.uptodate.com/contents/preeclampsia-clinical-features-and-diagnosis?search=preeclampsia with severe features&source=search_result&selectedTitle=2~122&usage_type=default&display_rank=2
2. Turbeville HR, Sasser JM. Preeclampsia beyond pregnancy: long-term consequences for mother and child. https://doi.org/101152/ajprenal000712020. 2020 Jun 1;318(6):F1315–26.
3. Skeith L, Blondon M, Ní Áinle F. Understanding and Preventing Placenta-Mediated Pregnancy Complications. Vol. 40, Hamostaseologie. Georg Thieme Verlag; 2020. p. 356–63.
4. Duley L. The Global Impact of Pre-eclampsia and Eclampsia. Semin Perinatol. 2009 Jun 1;33(3):130–7.
5. Abalos E, Cuesta C, Grosso AL, Chou D, Say L. Global and regional estimates of preeclampsia and eclampsia: a systematic review. Eur J Obstet Gynecol Reprod Biol [Internet]. 2013 [cited 2023 Oct 22];170(1):1–7. Available from: https://pubmed.ncbi.nlm.nih.gov/23746796/
6. Dassah ET, Kusi-Mensah E, Morhe ESK, Odoi AT. Maternal and perinatal outcomes among women with hypertensive disorders in pregnancy in Kumasi, Ghana. PLoS One [Internet]. 2019 Oct 1 [cited 2021 Aug 14];14(10):e0223478. Available from: https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0223478
7. Kwawununu FK, Morhe ES, Konney TO. Trends in maternal mortality at Komfo Anokye Teaching Hospital, Kumasi, Ghana, between 1998 and 2007. International Journal of Gynecology and Obstetrics. 2012;117:183–4.
8. Adu-Bonsaffoh K, Samuel OA, Binlinla G, Samuel OA. Maternal deaths attributable to hypertensive disorders in a tertiary hospital in Ghana. International Journal of Gynecology and Obstetrics. 2013;123(2):110–3.
9. Adu-Bonsaffoh K, Ntumy MY, Obed SA, Seffah JD. Perinatal outcomes of hypertensive disorders in pregnancy at a tertiary hospital in Ghana. BMC

Pregnancy and Childbirth 2017 17:1 [Internet]. 2017 Nov 21 [cited 2021 Sep 2];17(1):1–7. Available from: https://bmcpregnancychildbirth.biomedcentral.com/articles/10.1186/s12884-017-1575-2

10. Oros D, Figueras F, Cruz-Martinez R, Meler E, Munmany M, Gratacos E. Longitudinal changes in uterine, umbilical and fetal cerebral Doppler indices in late-onset small-for-gestational age fetuses. Ultrasound Obstet Gynecol [Internet]. 2011 Feb [cited 2023 May 6];37(2):191–5. Available from: https://pubmed.ncbi.nlm.nih.gov/20617509/
11. Sennaiyan UN, Sarah M, Rm JM, Mbbs CA, Kirby A, Mbbs TIA. Fetal adrenal gland: Total gland volume and fetal zone to total gland ratio as markers of small for gestational age. 2020;(January):1–11.
12. Heese S, Hammer K, Möllers M, Köster HA, Falkenberg MK, Eveslage M, et al. Adrenal gland size in growth restricted fetuses. J Perinat Med. 2018;46(8):900–4.
13. Boafor TK, Ntumy MY, Asah-Opoku K, Sepenu P, Ofosu B, Oppong SA. Maternal mortality at the Korle Bu Teaching Hospital, Accra, Ghana: A five-year review. Afr J Reprod Health. 2021;25(1):56–66.
14. Lee QY, Odoi AT, Opare-Addo H, Dassah ET. Maternal mortality in Ghana: A hospital-based review. Acta Obstet Gynecol Scand. 2012 Jan 1;91(1):87–92.
15. Melamed N, Baschat A, Yinon Y, Athanasiadis A, Romero R, Hod M. Mecacci 5 | Francesc Figueras 6 | Vincenzo Berghella 7 | Amala Nazareth 8 | Muna Tahlak 9. Int J Gynecol Obstet. 2021;152:3–57.
16. 2023 ICD-10-CM Diagnosis Code P22.0: Respiratory distress syndrome of newborn [Internet]. [cited 2023 Apr 29]. Available from: https://www.icd10data.com/ICD10CM/Codes/P00-P96/P19-P29/P22-/P22.0
17. Miller WL. The Hypothalamic-Pituitary-Adrenal Axis: A Brief History. Horm Res Paediatr [Internet]. 2018 Jun 1 [cited 2023 Apr 30];89(4):212–23. Available from: https://pubmed.ncbi.nlm.nih.gov/29719288/
18. Adrenal Glands | Johns Hopkins Medicine [Internet]. [cited 2023 Apr 29]. Available from: https://www.hopkinsmedicine.org/health/conditions-and-diseases/adrenal-glands

19. Lo JO, Mission JF, Caughey AB. Hypertensive disease of pregnancy and maternal mortality. Curr Opin Obstet Gynecol [Internet]. 2013 Apr [cited 2023 Apr 29];25(2):124–32. Available from: https://journals.lww.com/co-obgyn/Fulltext/2013/04000/Hypertensive_disease_of_pregnancy_and_maternal.6.aspx
20. Perinatal | definition of perinatal by Medical dictionary [Internet]. [cited 2023 Jun 29]. Available from: https://medical-dictionary.thefreedictionary.com/perinatal
21. Preeclampsia: Practice Essentials, Overview, Pathophysiology [Internet]. [cited 2023 Jun 29]. Available from: https://emedicine.medscape.com/article/1476919-overview
22. Christensen NJ. The biochemical assessment of sympathoadrenal activity in man. Clinical Autonomic Research [Internet]. 1991 Jun [cited 2023 Apr 29];1(2):167–72. Available from: https://link.springer.com/article/10.1007/BF01826215
23. Longo DL, Preeclampsia Laura Magee EA, Nicolaides KH, von Dadelszen P. Preeclampsia. Longo DL, editor. https://doi.org/101056/NEJMra2109523. 2022 May 11;386(19):1817–32.
24. L D. The global impact of pre-eclampsia and eclampsia. Semin Perinatol. 2009 Jun;33(3):130–7.
25. Noubiap JJ, Bigna JJ, Nyaga UF, Jingi AM, Kaze AD, Nansseu JR, et al. The burden of hypertensive disorders of pregnancy in Africa: A systematic review and meta-analysis. The Journal of Clinical Hypertension. 2019 Apr 1;21(4):479–88.
26. Bartsch E, Medcalf KE, Park AL, Ray JG, Al-Rubaie ZTA, Askie LM, et al. Clinical risk factors for pre-eclampsia determined in early pregnancy: systematic review and meta-analysis of large cohort studies. BMJ [Internet]. 2016 Apr 19 [cited 2023 Jun 5];353. Available from: https://pubmed.ncbi.nlm.nih.gov/27094586/
27. Macedo TCC, Montagna E, Trevisan CM, Zaia V, de Oliveira R, Barbosa CP, et al. Prevalence of preeclampsia and eclampsia in adolescent pregnancy: A systematic review and meta-analysis of 291,247 adolescents worldwide since

1969. Eur J Obstet Gynecol Reprod Biol [Internet]. 2020 May 1 [cited 2023 Jun 5];248:177–86. Available from: https://pubmed.ncbi.nlm.nih.gov/32283429/

28. Duckitt K, Harrington D. Risk factors for pre-eclampsia at antenatal booking: systematic review of controlled studies. BMJ [Internet]. 2005 Mar 12 [cited 2023 Jun 5];330(7491):565–7. Available from: https://pubmed.ncbi.nlm.nih.gov/15743856/
29. Silva LM, Coolman M, Steegers EAP, Jaddoe VWV, Moll HA, Hofman A, et al. Low socioeconomic status is a risk factor for preeclampsia: the Generation R Study. J Hypertens [Internet]. 2008 [cited 2023 Jun 5];26(6):1200–8. Available from: https://pubmed.ncbi.nlm.nih.gov/18475158/
30. Lawlor D, Morton S, … DNJ of E&, 2005 undefined. Association between childhood and adulthood socioeconomic position and pregnancy induced hypertension: results from the Aberdeen children of the 1950s cohort. jech.bmj.com [Internet]. 2005 Jan [cited 2023 Jun 5];59(1):49–55. Available from: https://jech.bmj.com/content/59/1/49.short
31. Haelterman E, Marcoux S, Croteau A, Dramaix M. Population-based study on occupational risk factors for preeclampsia and gestational hypertension. Scand J Work Environ Health. 2007;33(4):304–17.
32. Lisonkova S, Sabr Y, Mayer C, Young C, Skoll A, Joseph KS. Maternal morbidity associated with early-onset and late-onset Preeclampsia. Obstetrics and Gynecology. 2014 Oct 10;124(4):771–81.
33. Jaatinen N, Jääskeläinen T, Laivuori H, Ekholm E. The non-traditional and familial risk factors for preeclampsia in the FINNPEC cohort. Pregnancy Hypertens [Internet]. 2021 Mar 1 [cited 2023 Jun 5];23:48–55. Available from: https://pubmed.ncbi.nlm.nih.gov/33221706/
34. Lisonkova S, Joseph KS. Incidence of preeclampsia: Risk factors and outcomes associated with early-versus late-onset disease. Am J Obstet Gynecol [Internet]. 2013 Dec 1 [cited 2023 Jun 5];209(6):544.e1-544.e12. Available from: http://www.ajog.org/article/S0002937813008594/fulltext
35. Heshmati A, Mishra G, Koupil I. Childhood and adulthood socio-economic position and hypertensive disorders in pregnancy: The uppsala birth cohort

multigenerational study. J Epidemiol Community Health (1978). 2013;67(11):939–46.

36. Lawrence ER, Beyuo TK, Kobernik EK, Moyer CA, Oppong SA. A comparative analysis of neonatal outcomes in pregnancies complicated by preeclampsia and eclampsia in Ghana. AJOG Global Reports. 2022 Aug 1;2(3).
37. Browne JL, Vissers KM, Antwi E, Srofenyoh EK, Van der Linden EL, Agyepong IA, et al. Perinatal outcomes after hypertensive disorders in pregnancy in a low resource setting. Tropical Medicine & International Health. 2015 Dec 1;20(12):1778–86.
38. Selvaggi L, Loverro G, Schena FP, Manno C, Cagnazzo G. Long term follow-up of women with hypertension in pregnancy. International Journal of Gynecology & Obstetrics. 1988 Aug 1;27(1):45–9.
39. Brown DW, Dueker N, Jamieson DJ, Cole JW, Wozniak MA, Stern BJ, et al. Preeclampsia and the risk of ischemic stroke among young women: results from the Stroke Prevention in Young Women Study. Stroke. 2006 Apr;37(4):1055–9.
40. Poulter NR, Chang CL, Farley TMM, Meirik O. Risk of cardiovascular diseases associated with oral progestagen preparations with therapeutic indications. Lancet. 1999 Nov 6;354(9190):1610.
41. Vikse BE, Irgens LM, Leivestad T, Skjærven R, Iversen BM. Preeclampsia and the Risk of End-Stage Renal Disease. New England Journal of Medicine. 2008 Aug 21;359(8):800–9.
42. Melau C, Nielsen JE, Frederiksen H, Kilcoyne K, Perlman S, Lundvall L, et al. Characterization of Human Adrenal Steroidogenesis during Fetal Development. Journal of Clinical Endocrinology and Metabolism. 2019;104(5):1802–12.
43. Nicolaides NC, Kyratzi E, Lamprokostopoulou A, Chrousos GP, Charmandari E. Stress, the stress system and the role of glucocorticoids. Neuroimmunomodulation. 2015 Nov 7;22(1–2):6–19.
44. Bronshtein M, Tzidony D, Dimant M, Hajos J, Jaeger M, Blumenfeld Z. Transvaginal ultrasonographic measurements of the fetal adrenal glands at 12 to 17 weeks of gestation. Am J Obstet Gynecol. 1993 Nov 1;169(5):1205–10.
45. P J, F C, P G, JC H. Normal ultrasonic size and characteristics of the fetal adrenal glands. Prenat Diagn. 1984;4(1):21–8.

46. Turan OM, Turan S, Funai EF, Buhimschi IA, Campbell CH, Bahtiyar OM, et al. Ultrasound measurement of fetal adrenal gland enlargement: an accurate predictor of preterm birth. Am J Obstet Gynecol. 2011 Apr 1;204(4):311.e1-311.e10.
47. Turan OM, Turan S, Funai EF, Buhimschi IA, Copel JA, Buhimschi CS. Fetal Adrenal Gland Volume. Obstetrics & Gynecology. 2007;109(4):855–62.
48. Gabor M, Kunochova I, Krizko M, Alfoldi M, Feriancova M, Ferianec V. Simple ultrasound evaluation of fetal adrenal glands as a marker of imminent preterm birth: a preliminary report. Bratisl Lek Listy [Internet]. 2021 [cited 2023 May 4];122(10):721–6. Available from: https://pubmed.ncbi.nlm.nih.gov/34570573/
49. Lemos AP, Feitosa FE de L, Araujo Júnior E, Feitosa HN, Pereira JGD, Mota RMS, et al. Delivery prediction in pregnant women with spontaneous preterm birth using fetal adrenal gland biometry. J Matern Fetal Neonatal Med [Internet]. 2016 Dec 1 [cited 2023 May 5];29(23):3756–61. Available from: https://pubmed.ncbi.nlm.nih.gov/26820835/
50. Carvalho FHC, Lemos AP, De Feitosa FEL, Feitosa HN, Augusto LCC, Mota RMS, et al. Can fetal adrenal artery Doppler velocimetry predict delivery date in pregnant women with spontaneous preterm birth? Med Ultrason [Internet]. 2017 [cited 2023 May 5];19(3):295–301. Available from: https://pubmed.ncbi.nlm.nih.gov/28845496/
51. Hoffman MK, Turan OM, Parker CB, Wapner RJ, Wing DA, Haas DM, et al. Ultrasound Measurement of the Fetal Adrenal Gland as a Predictor of Spontaneous Preterm Birth. Obstetrics and gynecology [Internet]. 2016 Apr 1 [cited 2023 May 5];127(4):726–34. Available from: https://pubmed.ncbi.nlm.nih.gov/26959201/
52. Özdemir BG, Özdemir H, Atalay CR. The importance of fetal adrenal gland volume measurement in successful labor induction with oxytocin. Journal of Obstetrics and Gynaecology Research [Internet]. 2022 Oct 1 [cited 2023 May 3];48(10):2514–21. Available from: https://onlinelibrary.wiley.com/doi/full/10.1111/jog.15361

53. Mosbeh MH, Ibrahim EM, Mohamed EM, Ali AAA. Assessment of fetal adrenal gland volume as prediction of success of labour induction prospective observational study. MJMR. 2020;31(1):241–3.
54. Goletzke J, Pagenkemper M, Wiessner C, Rüber F, Arck P, Hecher K, et al. Longitudinal adrenal gland measurements and growth trajectories as risk markers for late preterm delivery. BMC Pregnancy Childbirth. 2020 Sep 29;20(1):1–9.
55. Kaya B, Polat İ. The investigation of fetal adrenal gland sizes in the pregnancies complicated with the intrauterine growth restriction. Perinatal Journal. 2019;27(3):176–82.
56. Mohajeri ZF, Aalipour S, Sheikh M, Hantoushzadeh S, Borna S, Khazardoost S. Ultrasound measurement of fetal adrenal gland in fetuses with intrauterine growth restriction , an early predictive method for adverse outcomes. The Journal of Maternal-Fetal & Neonatal Medicine [Internet]. 2017;0(0):1–7. Available from: https://doi.org/10.1080/14767058.2017.1410125
57. Kesrouani A, Abdallah W, Hatoum I, Khalil K, Nagib B, Choueiry E, et al. Association between Fetal Adrenal Gland Ultrasound Measurements in the 9th Month and Mode of Delivery. Am J Perinatol [Internet]. 2022 [cited 2023 Apr 30]; Available from: https://pubmed.ncbi.nlm.nih.gov/35240701/
58. Junhasavasdikul S, Panburana P, Bumrungphuet S, Dulyaphat W. The Correlation Between Three-Dimensional Ultrasound Measurement of Fetal Adrenal Gland and Maternal Serum Fructosamine Level in Gestational Diabetes Mellitus: Prospective Cohort Study. Int J Womens Health [Internet]. 2022 Oct 17 [cited 2023 Apr 30];14:1465–76. Available from: https://www.dovepress.com/the-correlation-between-three-dimensional-ultrasound-measurement-of-fe-peer-reviewed-fulltext-article-IJWH
59. Hetkamp T, Hammer K, Möllers M, Köster HA, Falkenberg MK, Kerschke L, et al. Fetal adrenal gland size in gestational diabetes mellitus. J Perinat Med [Internet]. 2019 [cited 2023 May 3];47(9). Available from: https://pubmed.ncbi.nlm.nih.gov/31562804/
60. Garcia-Flores J, Cruceyra M, Cañamares M, Garicano A, Espada M, Nieto O, et al. Sonographic Evaluation of Fetal Adrenal Gland in Gestational Diabetes:

Relation to Fetal Growth and Maternal Biochemical Markers. J Ultrasound Med [Internet]. 2017 May 1 [cited 2023 May 3];36(5):999–1007. Available from: https://pubmed.ncbi.nlm.nih.gov/28150324/

61. Buhimschi CS, Turan OM, Funai EF, Azpurua H, Bahtiyar MO, Turan S, et al. Fetal adrenal gland volume and cortisol/dehydroepiandrosterone sulfate ratio in inflammation-associated preterm birth. Obstetrics and gynecology [Internet]. 2008 Mar [cited 2023 May 3];111(3):715–22. Available from: https://pubmed.ncbi.nlm.nih.gov/18310376/
62. Oelmeier K, Möllers M, Köster HA, Willy D, Bormann E, Braun J, et al. Fetal adrenal gland size and umbilical artery Doppler in growth-restricted fetuses. J Perinat Med [Internet]. 2022 Mar 28 [cited 2023 May 3];51(3):340–5. Available from: https://pubmed.ncbi.nlm.nih.gov/35962947/
63. Esser T, Chaoui R. Enlarged adrenal glands as a prenatal marker of congenital adrenal hyperplasia: a report of two cases. Ultrasound in Obstetrics and Gynecology [Internet]. 2004 Mar 1 [cited 2023 May 5];23(3):293–7. Available from: https://onlinelibrary.wiley.com/doi/full/10.1002/uog.994
64. Gordijn SJ, Beune IM, Thilaganathan B, Papageorghiou A, Baschat AA, Baker PN, et al. Consensus definition of fetal growth restriction: a Delphi procedure. Ultrasound Obstet Gynecol. 2016;48(3):333–9.
65. Blue NR, Hoffman M, Allshouse AA, Parry S, Chung JH, Reddy U, et al. Antenatal Fetal Adrenal Measurements at 22 to 30 Weeks' Gestation, Fetal Growth Restriction, and Perinatal Morbidity. 1900;84132.
66. Janke C, Heim KM, Steiner F, Massaquoi M, Gbanya MZ, Frey C, et al. Beyond Ebola treatment units: severe infection temporary treatment units as an essential element of Ebola case management during an outbreak. BMC Infect Dis. 2017;17(1):124.
67. Fetal Adrenal Abnormalities | Radiology Key [Internet]. [cited 2022 Nov 13]. Available from: https://radiologykey.com/fetal-adrenal-abnormalities/
68. Fetal Adrenal Glands [Internet]. [cited 2022 Nov 13]. Available from: http://www.fetalultrasound.com/online/text/3-033.htm
69. Helfer TM, Rolo LC, Okasaki NA de BM, de Castro Maldonado AA, Rabachini Caetano AC, Perez Zamarian AC, et al. Reference ranges of fetal adrenal gland

and fetal zone volumes between 24 and 37 + 6 weeks of gestation by three-dimensional ultrasound. J Matern Fetal Neonatal Med. 2017 Mar 4;30(5):568–73.

70. Bronshtein M, Tzidony D, Dimant M, Hajos J, Jaeger M, Blumenfeld Z. Transvaginal ultrasonographic measurements of the fetal adrenal glands at 12 to 17 weeks of gestation. Am J Obstet Gynecol. 1993;169(5):1205–10.
71. MOORTHY R. TRANSVAGINAL SONOGRAPHY. Med J Armed Forces India. 2000 Jul;56(3):181.
72. Turan OM, Turan S, Buhimschi IA, Funai EF, Campbell KH, Bahtiyar OM, et al. Comparative Analysis of 2-D Versus 3-D Ultrasound Estimation of the Fetal Adrenal Gland Volume and Prediction of Preterm Birth.
73. Smitthimedhin A, Rubio EI, Blask AR, Loomis JM, Bulas DI. Normal size of the fetal adrenal gland on prenatal magnetic resonance imaging. Pediatr Radiol. 2020 May 1;50(6):840–7.
74. Radiation Exposure In Pregnancy - StatPearls - NCBI Bookshelf [Internet]. [cited 2023 Jan 23]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK551690/
75. Özgüner G, Sulak O, Koyuncu E. A morphometric study of suprarenal gland development in the fetal period. Surg Radiol Anat [Internet]. 2012 Sep [cited 2023 May 16];34(7):581–7. Available from: https://pubmed.ncbi.nlm.nih.gov/22430763/
76. Sennaiyan UN, Melov SJ, Arcus C, Kirby A, Alahakoon TI. Fetal adrenal gland: Total gland volume and fetal zone to total gland ratio as markers of small for gestational age. J Clin Ultrasound [Internet]. 2020 Sep 1 [cited 2023 May 15];48(7):377–87. Available from: https://pubmed.ncbi.nlm.nih.gov/32333815/
77. Jeantyt P, Chervenak F, Grannum P, Hobbins JC. NORMAL ULTRASONIC SIZE AND CHARACTERISTICS OF THE FETAL ADRENAL GLANDS*. Vol. 4, PRENATAL DIAGNOSIS. 1984.
78. Pattanapanyasat N, Sudjai D, Puttanavijarn L. Normal Ranges of Fetal Adrenal Gland at 25-37 weeks of Gestation. Vol. 29, Thai Journal of Obstetrics and Gynaecology. 2021.

79. De Sá Barreto EQ, Figuinha Milani HJ, Araujo E, Krajden Haratz K, Cristine Rolo L, MacHado Nardozza LM, et al. Reliability and Validity of In Vitro Volume Calculations by 3-Dimensional Ultrasonography Using the Multiplanar, Virtual Organ Computer-Aided Analysis (VOCAL), and Extended Imaging VOCAL Methods. Journal of Ultrasound in Medicine [Internet]. 2010 May 1 [cited 2023 May 18];29(5):767–74. Available from: https://onlinelibrary.wiley.com/doi/full/10.7863/jum.2010.29.5.767
80. Brown MA, Magee LA, Kenny LC, Karumanchi SA, McCarthy FP, Saito S, et al. The hypertensive disorders of pregnancy: ISSHP classification, diagnosis & management recommendations for international practice. Pregnancy Hypertens. 2018;13(xxxx):291–310.
81. Khong Y, Brosens I. Defective deep placentation. Best Pract Res Clin Obstet Gynaecol. 2011 Jun 1;25(3):301–11.
82. Gruslin A, Lemyre B. Pre-eclampsia: fetal assessment and neonatal outcomes. Best Pract Res Clin Obstet Gynaecol. 2011;25(4):491–507.
83. Crispi F, Comas M, Hernández-Andrade E, Eixarch E, Gómez O, Figueras F, et al. Does pre-eclampsia influence fetal cardiovascular function in early-onset intrauterine growth restriction? Ultrasound Obstet Gynecol. 2009 Dec;34(6):660–5.
84. Youssef L, Miranda J, Paules C, Garcia-Otero L, Vellvé K, Kalapotharakos G, et al. Fetal cardiac remodeling and dysfunction is associated with both preeclampsia and fetal growth restriction. Am J Obstet Gynecol. 2020 Jan 1;222(1):79.e1-79.e9.
85. Doppler studies in fetal hypoxemic hypoxia Based on Doppler in Obstetrics: by K Nicolaides, G Rizzo, K Hecher FETAL OXYGENATION.
86. Hata K, Hata T, Kitao M. Ultrasonographic identification and measurement of the human fetal adrenal gland in utero: clinical application. Gynecol Obstet Invest [Internet]. 1988 [cited 2023 May 5];25(1):16–22. Available from: https://pubmed.ncbi.nlm.nih.gov/3277902/
87. Mahran A, Fares H, Elkhateeb R, Ibrahim M, Bahaa H, Sanad A, et al. Risk factors and outcome of patients with eclampsia at a tertiary hospital in Egypt.

BMC Pregnancy Childbirth [Internet]. 2017 Dec 22 [cited 2023 May 11];17(1). Available from: https://pubmed.ncbi.nlm.nih.gov/29272998/

88. Lawrence ER, Beyuo TK, Kobernik EK, Moyer CA, Oppong SA. A comparative analysis of neonatal outcomes in pregnancies complicated by preeclampsia and eclampsia in Ghana. AJOG global reports [Internet]. 2022 Aug 1 [cited 2023 May 11];2(3). Available from: https://pubmed.ncbi.nlm.nih.gov/36276785/

89. Abalos E, Cuesta C, Carroli G, Qureshi Z, Widmer M, Vogel JP, et al. Pre-eclampsia, eclampsia and adverse maternal and perinatal outcomes: a secondary analysis of the World Health Organization Multicountry Survey on Maternal and Newborn Health. BJOG [Internet]. 2014 [cited 2023 May 8];121:14–24. Available from: https://onlinelibrary.wiley.com/doi/full/10.1111/1471-0528.12629

90. Lawrence ER, Beyuo TK, Kobernik EK, Moyer CA, Oppong SA. A comparative analysis of neonatal outcomes in pregnancies complicated by preeclampsia and eclampsia in Ghana. AJOG Global Reports [Internet]. 2022 Aug 1 [cited 2023 May 13];2(3). Available from: /pmc/articles/PMC9563915/

91. Lugobe HM, Muhindo R, Kayondo M, Wilkinson I, Agaba DC, McEniery C, et al. Risks of adverse perinatal and maternal outcomes among women with hypertensive disorders of pregnancy in southwestern Uganda. PLoS One [Internet]. 2020 Oct 1 [cited 2023 May 8];15(10). Available from: /pmc/articles/PMC7592727/

92. Blue NR, Hoffman M, Allshouse AA, Grobman WA, Simhan HN, Turan OM, et al. Antenatal Fetal Adrenal Measurements at 22 to 30 Weeks' Gestation, Fetal Growth Restriction, and Perinatal Morbidity. Am J Perinatol [Internet]. 2021 Jun 1 [cited 2023 May 16];38(7):676–82. Available from: https://pubmed.ncbi.nlm.nih.gov/31756754/

93. Karsli T, Strickland D, Livingston J, Wu Q, Mhanna MJ, Shekhawat PS. Assessment of neonatal adrenal size using high resolution 2D ultrasound and its correlation with birth demographics and clinical outcomes. J Matern Fetal Neonatal Med [Internet]. 2019 Feb 1 [cited 2023 May 16];32(3):377–83. Available from: https://pubmed.ncbi.nlm.nih.gov/28889777/

94. Farzad Mohajeri Z, Aalipour S, Sheikh M, Shafaat M, Hantoushzadeh S, Borna S, et al. Ultrasound measurement of fetal adrenal gland in fetuses with intrauterine growth restriction, an early predictive method for adverse outcomes. J Matern Fetal Neonatal Med [Internet]. 2019 May 3 [cited 2023 May 16];32(9):1485–91. Available from: https://pubmed.ncbi.nlm.nih.gov/29251009/

95.: : Ghana Statistical Service :: [Internet]. [cited 2023 Jun 6]. Available from: https://www2.statsghana.gov.gh/

96. National Ambulance Service G. Ministry of Health, Ghana- Annual Performance review. Accra; 2023 Apr.

97. Biostatistics Unit. Monthly Data. Kumasi; 2022.

98. INTERGROWTH_EFW_calculator_-_New.xlsx [Internet]. [cited 2023 May 14]. Available from: https://view.officeapps.live.com/op/view.aspx?src=https%3A%2F%2Fmedia.tghn.org%2Fmedialibrary%2F2019%2F08%2FINTERGROWTH_EFW_calculator_-_New.xlsx&wdOrigin=BROWSELINK

99. Gordijn SJ, Beune IM, Thilaganathan B, Papageorghiou A, Baschat AA, Baker PN, et al. Consensus definition of fetal growth restriction: a Delphi procedure. Ultrasound Obstet Gynecol [Internet]. 2016 Sep 1 [cited 2023 May 14];48(3):333–9. Available from: https://pubmed.ncbi.nlm.nih.gov/26909664/

100. The Fetal Medicine Foundation [Internet]. [cited 2023 Oct 20]. Available from: https://fetalmedicine.org/research/doppler

101. Pattanapanyasat N, Sudjai D, Puttanavijarn L. Normal ranges of fetal adrenal gland at 25-37 weeks of gestation. Thai Journal of Obstetrics and Gynaecology. 2021;29(4):217–26.

102. Turan OM, Turan S, Funai EF, Buhimschi IA, Campbell CH, Bahtiyar OM, et al. Ultrasound measurement of fetal adrenal gland enlargement: an accurate predictor of preterm birth. Am J Obstet Gynecol [Internet]. 2011 [cited 2023 Oct 22];204(4):311.e1-311.e10. Available from: https://pubmed.ncbi.nlm.nih.gov/21292230/

103. Mattsson K, Juárez S, Malmqvist E. Influence of Socio-Economic Factors and Region of Birth on the Risk of Preeclampsia in Sweden. Int J Environ Res Public

Health [Internet]. 2022 Apr 1 [cited 2023 Jun 5];19(7):4080. Available from: https://www.mdpi.com/1660-4601/19/7/4080/htm

104. Ghana Statistical Service. 2010 Population and Housing Census, Fertility. 2014;34.

105. Rich-Edwards JW, Ness RB, Roberts JM. Epidemiology of Pregnancy-Related Hypertension. Chesley's Hypertensive Disorders in Pregnancy, Fourth Edition. 2015 Jan 1;37–55.

106. Olv R, Kjaerven S, Llen A, Ilcox JW, Ie TL. The Interval between Pregnancies and the Risk of Preeclampsia. https://doi.org/101056/NEJMoa011379 [Internet]. 2002 Jan 3 [cited 2023 Jun 6];346(1):33–8. Available from: https://www.nejm.org/doi/full/10.1056/NEJMoa011379

107. Dong X, Nao J. Neurological manifestations and neuroimaging presentations in patients with severe preeclampsia: predisposing factors and clinical implications. Neurological Sciences [Internet]. 2019 Mar 19 [cited 2023 Jun 9];40(6):1245–53. Available from: https://link.springer.com/article/10.1007/s10072-019-03833-3

108. Creatinine test - Mayo Clinic [Internet]. [cited 2023 Jun 10]. Available from: https://www.mayoclinic.org/tests-procedures/creatinine-test/about/pac-20384646

109. Gestational Hypertension and Preeclampsia: ACOG Practice Bulletin, Number 222. Obstetrics and gynecology [Internet]. 2020 Jun 1 [cited 2023 Jun 7];135(6):e237–60. Available from: https://journals.lww.com/greenjournal/Fulltext/2020/06000/Gestational_Hypertension_and_Preeclampsia__ACOG.46.aspx

110. Zeeman GG. Neurologic complications of pre-eclampsia. Semin Perinatol [Internet]. 2009 Jun [cited 2023 Jun 7];33(3):166–72. Available from: https://pubmed.ncbi.nlm.nih.gov/19464507/

111. Zunker P, Ley- Pozo J, Louwen F, Schuierer G, Holzgreve W, Ringelstein EB. Cerebral hemodynamics in pre-eclampsia/eclampsia syndrome. Ultrasound Obstet Gynecol [Internet]. 1995 [cited 2023 Jun 7];6(6):411–5. Available from: https://pubmed.ncbi.nlm.nih.gov/8903916/

112. Mayama M, Uno K, Tano S, Yoshihara M, Ukai M, Kishigami Y, et al. Incidence of posterior reversible encephalopathy syndrome in eclamptic and patients with preeclampsia with neurologic symptoms. Am J Obstet Gynecol [Internet]. 2016 Aug 1 [cited 2023 Jun 7];215(2):239.e1-239.e5. Available from: https://pubmed.ncbi.nlm.nih.gov/26902987/

113. Al-Safi Z, Imudia AN, Filetti LC, Hobson DT, Bahado-Singh RO, Awonuga AO. Delayed postpartum preeclampsia and eclampsia: demographics, clinical course, and complications. Obstetrics and gynecology [Internet]. 2011 Nov [cited 2023 Jun 8];118(5):1102–7. Available from: https://pubmed.ncbi.nlm.nih.gov/21979459/

114. Redman EK, Hauspurg A, Hubel CA, Roberts JM, Jeyabalan A. Clinical Course, Associated Factors, and Blood Pressure Profile of Delayed-Onset Postpartum Preeclampsia. Obstetrics and gynecology [Internet]. 2019 Nov 1 [cited 2023 Jun 8];134(5):995–1001. Available from: https://pubmed.ncbi.nlm.nih.gov/31599846/

115. Yen TW, Payne B, Qu Z, Hutcheon JA, Lee T, Magee LA, et al. Using clinical symptoms to predict adverse maternal and perinatal outcomes in women with preeclampsia: data from the PIERS (Pre-eclampsia Integrated Estimate of RiSk) study. J Obstet Gynaecol Can [Internet]. 2011 [cited 2023 Jun 9];33(8):803–9. Available from: https://pubmed.ncbi.nlm.nih.gov/21846435/

116. Roos NM, Wiegman MJ, Jansonius NM, Zeeman GG. Visual disturbances in (pre)eclampsia. Obstet Gynecol Surv [Internet]. 2012 Apr [cited 2023 Jun 9];67(4):242–50. Available from: https://pubmed.ncbi.nlm.nih.gov/22495060/

117. Caesarean section rates continue to rise, amid growing inequalities in access [Internet]. [cited 2023 Jun 12]. Available from: https://www.who.int/news/item/16-06-2021-caesarean-section-rates-continue-to-rise-amid-growing-inequalities-in-access

118. Chandraharan E. Foetal electrocardiograph (ST-analyser or STAN) for intrapartum foetal heart rate monitoring: a friend or a foe? J Matern Fetal Neonatal Med [Internet]. 2018 Jan 2 [cited 2023 Jun 28];31(1):123–7. Available from: https://pubmed.ncbi.nlm.nih.gov/28027681/

119. Taylor BD, Ness RB, Klebanoff MA, Tang G, Roberts JM, Hougaard DM, et al. The impact of female fetal sex on preeclampsia and the maternal immune milieu. Pregnancy Hypertens. 2018 Apr 1;12:53–7.
120. Mirzakhani H, Weiss ST. Fetal sex and risk of preeclampsia: Dose maternal race matter? https://doi.org/101080/1476705820201818221 [Internet]. 2020 [cited 2023 Jun 12];35(17):3379–87. Available from: https://www.tandfonline.com/doi/abs/10.1080/14767058.2020.1818221
121. Overview of the routine management of the healthy newborn infant - UpToDate [Internet]. [cited 2023 Jun 13]. Available from: https://www.uptodate.com/contents/overview-of-the-routine-management-of-the-healthy-newborn-infant?search=apgar%20score&sectionRank=1&usage_type=default&anchor=H3&source=machineLearning&selectedTitle=1~108&display_rank=1#H3
122. Low birth weight [Internet]. [cited 2023 Jun 12]. Available from: https://www.who.int/data/nutrition/nlis/info/low-birth-weight
123. Stoll BJ, Hansen NI, Bell EF, Shankaran S, Laptook AR, Walsh MC, et al. Neonatal outcomes of extremely preterm infants from the NICHD Neonatal Research Network. Pediatrics [Internet]. 2010 [cited 2023 Jun 12];126(3):443–56. Available from: https://pubmed.ncbi.nlm.nih.gov/20732945/
124. Atamamen TF, Naing NN, Oyetunji JA, Wan-Arfah N. Systematic literature review on the neonatal outcome of preeclampsia. Pan Afr Med J [Internet]. 2022 Jan 1 [cited 2023 Jun 17];41(82):41. Available from: /pmc/articles/PMC8977357/
125. Pattanapanyasat N, Sudjai D, Puttanavijarn L. Normal Ranges of Fetal Adrenal Gland at 25-37 Weeks of Gestation. Thai Journal of Obstetrics and Gynaecology [Internet]. 2021 Jul 1 [cited 2023 Jun 14];217–26. Available from: https://he02-old.tci-thaijo.org/index.php/tjog/article/view/219442
126. Lanman JT. THE ADRENAL GLAND IN THE HUMAN FETUS An Interpretation of Its Physiology and Unusual Developmental Pattern. Pediatrics [Internet]. 1961 Jan 1 [cited 2023 Jun 15];27(1):140–58. Available from: /pediatrics/article/27/1/140/41223/THE-ADRENAL-GLAND-IN-THE-HUMAN-FETUS-An

127. Melese MF, Badi MB, Aynalem GL. Perinatal outcomes of severe preeclampsia/eclampsia and associated factors among mothers admitted in Amhara Region referral hospitals, North West Ethiopia, 2018. BMC Res Notes [Internet]. 2019 Mar 15 [cited 2023 Jun 16];12(1). Available from: /pmc/articles/PMC6420725/
128. Sibai BM. Preeclampsia as a cause of preterm and late preterm (near-term) births. Semin Perinatol [Internet]. 2006 Feb [cited 2023 Jun 17];30(1):16–9. Available from: https://pubmed.ncbi.nlm.nih.gov/16549208/
129. Preeclampsia: Pathogenesis - UpToDate [Internet]. [cited 2023 Jun 17]. Available from: https://www.uptodate.com/contents/preeclampsia-pathogenesis?search=preeclampsia%20complications&topicRef=6814&source=see_link#H16
130. Coppage KH, Sibai BM. Preeclampsia and Eclampsia. The Global Library of Women's Medicine [Internet]. 2009 [cited 2023 Jun 17]; Available from: http://www.glowm.com/section-view/heading/Preeclampsia and Eclampsia/item/158

APPENDIX

BUDGET AND RESOURCES

Activity		**Persons/ Design**	**FTE**	**Unit Cost Gh¢ per Recruitment**		**Duration(month)**	**Total cost Gh¢**	
Personnel								
Research Assistants		2	0.25	2	420	2	420	
Biostatistician		1	.25	500		1	125.00	
SUBTOTAL							**545.00**	
Research Equipment								
Tablets		2		Pre-owned			0.00	
Internet Modem		1		Pre-owned			0.00	
Laptop		1		Pre-owned			0.00	
Printer				Pre-owned			0.00	
SUBTOTAL							**0.00**	
Research Materials								
Pens		1 box		30			30.00	
Paper Clips		1box		10			10.00	
A4 sheets		1 ream		30			30.00	

Inkpad		2		15			30.00	
Mobile phone Airtime		MTN, VODAFONE, AIRTEL		100			100.00	
SUBTOTAL							**200.00**	
Administrative								
Ethical approval							150.00	
Institutional Administrative Cost							150.00	
Compensation				2 Ghana Cedis	233		466	
SUBTOTAL							**766.00**	
Publication and Dissemination								
Report printing		3		30			90	
IRB application		1		250			250	
SUBTOTAL							**340**	
Miscellaneous							**629**	
TOTAL							**2,880.00**	

PARTICIPANT INFORMATION LEAFLET

INFORMATION SHEET

Title of Research:

Sonographic measurement of the fetal adrenal gland as a marker of adverse perinatal outcome in preeclampsia.

Name(s) and affiliation(s) of researcher(s):

This study is being conducted by Dr. Opei Kwafo Adarkwa, Department of Obstetrics and Gynaecology, Komfo Anokye Teaching Hospital, Kumasi

Background:

Preeclampsia is a complication of pregnancy where affected pregnant women have high blood pressure and proteins in their urine. It is a major contributor to both ill-health and death in pregnancy. This may occur early in pregnancy and detecting it early, managing it well, and delivering affected women at the right time helps to improve the condition of the mother and baby after delivery. The study seeks to investigate additional tools that is the ultrasound measurement of the size your unborn baby's adrenal gland in the monitoring of such pregnancies. The fetal adrenal gland is a triangular structure located on top of the kidney of your baby which produces substances that help your baby to deal with stress that may be present due to the high blood pressure.

Purpose(s) of research:

The purpose of the research is to investigate the use of the ultrasound measurement of the unborn baby's adrenal gland as a tool for monitoring preeclampsia and being able to use it to tell what the baby's outcome around the delivery period may be especially for unborn babies that may not be doing so well.

Selection of participants:

This study involves women above 18 years of age, diagnosed of Preeclampsia, who are 28 weeks or more in the pregnancy. A study staff will ask you a few questions to know whether

you are eligible to take part in the study. Your permission is being sought for you to be part of the study because you have been diagnosed with preeclampsia in this pregnancy.

Procedure of the research, what shall be required of each participant and approximate total number of participants that would be involved in the research:

Once you agree and are selected to be part of the study, you will have your unborn baby's adrenal gland measured as part of your next routine ultrasound examination. These measurements will be done during your next scheduled work-up; as such, you will not be required to take any ultrasound scans outside what your doctor will need for the management of your condition. The research team will also need to know about the symptoms you are having and the results of the tests that your doctor will ask you to perform to help him manage the preeclampsia very well. In total, we expect to recruit 116 participants.

Risk(s):

There are no foreseeable risks when you take part in this study. You may have to spend a little longer at the ultrasound suite. Ultrasound is safe in pregnancy.

Benefit(s):

The goal of this research is to find out what the role of using the ultrasound to measure the adrenal gland of your baby and whether that can predict adverse or poor outcome. Your participation will help us to investigate this and allow us to improve our practice in the early detection, management, and optimal timing of delivery of cases of preeclampsia.

Confidentiality:

All information collected in this study will be given code numbers. All study documents will be under lock and key in the A1 ward-in-charge's office. Electronic data for analysis will be password protected. Data collected will be used only for the purposes of the study. No name or identifier will be used in any publication or reports from this study. However, as part of our responsibility to conduct this research properly, we may allow officials from the Ethics committees to have access to your records.

Voluntariness:

Taking part in this study should be out of your own free will. You are not under obligation to take part in the study. Participating in this study is entirely voluntary.

Alternatives to participation:

If you choose not to participate, this will not affect your treatment in this hospital/institution in any way.

Withdrawal from the research:

You may choose to withdraw from the research at any time without having to explain yourself. You may also choose not to answer any question you find uncomfortable or private.

Consequence of Withdrawal:

There will be no consequence, loss of benefit or care to you if you choose to withdraw from the study. Please note however, that some of the information that may have been obtained from you without identifiers, before you chose to withdraw, may have been modified or used in analysis reports and publications. These cannot be removed anymore. We do promise to make good faith effort to comply with your wishes as much as practicable.)

Costs/Compensation:

For your time and inconvenience while participating in the study, we will compensate you with a bottle of water.

Contacts:

In case you have any question(s) concerning this study, please do not hesitate to contact Dr. Opei Kwafo Adarkwa, the Principal investigator on this phone line 0244752405.

Further, if you have any concern about the conduct of this study, your welfare, or your rights as a research participant, you may contact:

The Office of the Chairman,

Komfo Anokye Teaching Hospital Institutional Review Board (KATH-IRB),

Research and Development Unit, Kumasi.

Tel: +233 3220 00617.

Email address: kathirb@kathhsp.org or kathirb25@gmail.com

CONSENT FORM

Statement of person obtaining informed consent:

I have fully explained this research to _____ and have given sufficient information about the study, including that on procedures, risks, and benefits, to make an informed decision.

DATE: _____ SIGNATURE: _____

NAME: _____

Statement of person giving consent:

I have read the information on this study/research or have had it translated into a language I understand. I have also talked it over with the interviewer to my satisfaction.

I have read the description of the research or have had it translated into language I understand. I have also talked it over with the interviewer to my satisfaction. I understand that my participation is voluntary. I know enough about the purpose, methods, risks, and benefits of the research study to decide that I want to take part in it. I understand that I may freely stop being

part of this study at any time. I have received a copy of this consent form and additional information sheet to keep for myself.

DATE: _____ SIGNATURE/THUMB PRINT: _____

WITNESS' SIGNATURE (if applicable): _____

WITNESS' NAME (if applicable): _____

PARENT/GUARDIAN'S SIGNATURE/THUMB PRINT: _____

PARENT/GUARDIAN'S NAME: _____

QUESTIONNAIRE

SONOGRAPHIC MEASUREMENT OF THE FETAL ADRENAL GLAND AS A MARKER OF ADVERSE PERINATAL OUTCOME IN PREECLAMPSIA.

The purpose of the research is to investigate the use of the ultrasound measurement of the unborn baby's adrenal gland as a tool for monitoring preeclampsia and being able to tell what the baby's outcome around the delivery period may be. Your responses will be needed to complete the research. Whether you participate or not in this study will not influence the care that you will be offered in the hospital. Feel at ease to answer the questions to the best of your abilities. Again, if you do not understand any question, please seek for explanation.

DEMOGRAPHICS	
STUDY ID	[__][__][__]
AGE	[__][__][__]
PARITY	[__][__][__]
GRAVIDITY	[__][__][__]
MISCARRIAGES	
EXPECTED DATE OF DELIVERY	DD/MM/YYYY [__] [__]/ [__] [__]/ [__][__][__][__]
GESTATIONAL AGE	[__] [__] WEEKS + [__] [__] DAYS
RELIGION	Christian-1 Muslim-2 Traditional-3 Other(specify)__
LEVEL OF EDUCATION	None Primary Junior High School

	Senior High School Tertiary Postgraduate
ETHNICITY	Akan-1 Ga/Dangme-2 Ewe-3 Mole-Dagbani Guan Grusi Gurma Mande Other(specify)_____
MARITAL STATUS	Single Cohabiting Married Divorced
MATERNAL CLINICAL FACTORS (To be filled by study staff)	
PRESENCE OF HYPERTENSIVE DISEASE IN PREGNANCY	Yes No
WHAT TYPE OF HYPERTENSIVE DISEASE DOES THE PATIENT HAVE?	Gestational Hypertension Pre-eclampsia Pre-eclampsia with severe features Chronic Hypertension superimposed with Pre-eclampsia with severe features. None Chronic Hypertension

ARE THERE ANY OTHER CHRONIC OR MEDICAL CONDITIONS?	Yes No
IF YES, PLEASE STATE THE CHRONIC OR MEDICAL CONDITION	_____
BLOOD PRESSURE	
BLOOD PRESSURE ON DAY OF REVIEW	SYSTOLIC [__] [__] [__] DIASTOLIC [__] [__] [__]
RENAL FUNCTION	
CREATININE	[__][__][__]
UREA	[__][__][__]
LIVER FUNCTION	
AST	[__][__][__]
ALT	[__][__][__]
COMPLETE BLOOD COUNT	
PLATELET	[__][__][__]
HEMOGLOBIN	[__] [__] [__] g/dl
MATERNAL SYMPTOMS	
SEVERE HEADACHE	[__] [__]/10 (please score out of 10)
VISUAL DISTURBANCES	[__] YES

	[__]NO
EPIGASTRIC PAIN	[__] YES [__]NO
FOETAL PARAMETERS at recruitment-1 and the last ultrasound before delivery-2	
ESTIMATED GESTATIONAL AGE-1	
ESTIMATED FETAL WEIGHT-1	[__][__][__]
GROWTH CENTILE-1	[__][__][__]
FETAL DOPPLER-1	
S/D RATIO-1	[__].[__][__]
UMBILICAL ARTERY DOPPLER-1	FORWARD WAVE FORM REDUCED FLOW ABSENT END-DIASTOLIC FLOW REVERSED END-DIASTOLIC FLOW
DUCTUS VENOSUS-1	
PULSATILITY INDEX PI-1 PI CENTILE-1	VALUE [__] [__] [__] [__][__][__]
DEXAMETHASONE ADMIN-1	Yes No

HUMAN FETAL ADRENAL GLAND MEASUREMENT	
LENGTH (total length)-1	LENGTH (total length)-1
LENGTH (total length)-2	LENGTH (total length)-2
LENGTH (total length)-3	LENGTH (total length)-3
WIDTH (total length)-1	WIDTH (fetal zone)-1
WIDTH (total length)-2	WIDTH (fetal zone)-2
WIDTH (total length)-3	WIDTH (fetal zone)-3
DEPTH (total length)-1	DEPTH (fetal zone)-1
DEPTH (total length)-2	DEPTH (fetal zone)-2
DEPTH (total length)-3	DEPTH (fetal zone)-3
AMNIOTIC FLUID INDEX (AFI)-1	[__][__][__]
CTG FINDINGS-1	Overall impression- reactive/non-reactive_____ Variability- absent/reduced/normal. Deceleration- yes/no, if yes (specify type) ____--- _____ Baseline Rate - [__] [__] [__]

OUTCOME DETAILS	
BIRTH WEIGHT	[__] [__] [__] [__]IN GRAMS
SEX OF BABY	**MALE** **FEMALE**
MODE OF DELIVERY	SVD ASSISTED VAGINAL DELIVERY CAESAREAN DELIVERY
DURATION OF 1ST STAGE OF LABOR	[__] [__] [__] minutes
WAS LABOUR AUGMENTED?	YES-1 NO-2…
DURATION OF 2ND STAGE OF LABOR	[__] [__] [__] minute
INDICATION FOR ASSISTED VAGINAL DELIVERY OR CAESAREAN SECTION	_____
GESTATIONAL AGE AT DELIVERY	[__] [__] WEEKS + [__] [__] DAYS
1ST MINUTE APGAR (<7)	[__] [__]/10
5TH MINUTE APGAR (<7)	[__] [__]/10
PRETERM BIRTH	Yes

	No
STILLBIRTH	Yes No
NEONATAL DEATH,	YES NO
NICU ADMISSION	
NICU admission	Yes No
DATE OF NICU ADMISSION	
SEIZURES	Yes No
INTUBATION	Yes No
DATE OF DISCHARGE FROM NICU	
OUTCOMES WITHIN THE 1ST WEEK OF LIFE	
	Well Still on admission Died Others _____

PLAN OF ACTIVITIES

ACTIVITIES	DECEMBER '22	JANUARY '23	FEBRUARY '23	MAY '23	JUNE '23	JULY '23
Proposal submission.						
Ethical Clearance.						
Data Collection.						
Data Analysis.						
Final write- up						
Submission of final work.						

ETHICAL APPROVAL

KOMFO ANOKYE
TEACHING HOSPITAL

P. O. Box 1934
Kumasi - Ghana
Tel: +233 - 3200-22301 - 4
Fax: +233 - 3220-24654 / 24621
Website: www.kathhsp.org

KATH IRB/AP/173/22
Our Ref. No.:.....

Your Ref... No:.....

Komfo Anokye Teaching Hospital Institutional Review Board

23th January 2023

Dr. Opei Kwafo Adarkwa
Department of Obstetrics and Gynaecology
Komfo Anokye Teaching Hospital,
Kumasi.

Dear Dr. Adarkwa,

Ethics Approval

Protocol title:	Sonographic Measurement of the Fetal Adrenal Gland as A Marker of Adverse Perinatal Outcome in Preeclampsia.
Study site:	Obstetrics &Gynaecology Directorate of the Komfo Anokye Teaching Hospital, Kumasi
Sponsor:	Self-funded

We write in response to your correspondence of 14th December 2022 requesting the Komfo Anokye Teaching Hospital Institutional Review Board (KATH IRB) to review the research study referenced above.

The proposed research study went through the Board review of 10th January 2023 and we are pleased to inform you that KATH IRB has given approval for the following study documents:

- *Protocol version 1.0 last updated 14th December 2022*
- *Informed consent form, version 1.0 last updated 14th December 2022*
- *Case report form version 1.0 last updated 14th December 2022*

Approval for the study is in effect until **22th January 2024** and it is the responsibility of the Principal Investigator to maintain the study in good standing at the Komfo Anokye Teaching Hospital. The Board anticipates to be notified of the actual start date of your project.

Prior to the expiration of the study approval, you must submit to the KATH IRB an "Application for Continuing Review" along with provision of "Annual Report" when the study is ongoing, or a "Termination Report" if the research has been completed.
You must hastily report to the KATH IRB should a modification to the research be proposed, and without delay if an unanticipated development occurs before the next required review. Regulations do not permit you to modify conduct of the study in its present form prior to ethics approval; except where urgent action is required to eliminate an apparent immediate hazard to

a study subject or other person. It is of utmost importance data generated from this study must be used for the intended purposes only.

Thank you.

Sincerely,

Prof. Kwabena Antwi Danso, BSc, MB ChB, FWACS, FGCS, FACOG
Chairman, KATH IRB