Fetal Cardiac Haemodynamics in Normal and Complicated Pregnancies

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DEDICATION:

To: Nazreen, Raeesa, Mehreen, Fathima, Mohammed and Maseeha who give meaning to my life and who are at the centre of my universe.

PUBLICATIONS AND PRESENTATIONS

The author is indebted to his co-workers for their contributions to the following publications, manuscripts submitted and scientific presentations

Journal Publications

1. I.E. Bhorat, J.S. Bagratee, T. Reddy. Gestational age-adjusted trends and reference intervals of the modified myocardial performance index (Mod-Mpi) with its interpretation in the context of established cardiac physiological principles*. Prenatal Diagnosis; DOI: 10.1002/pd.4414.*

2. I.E Bhorat, J.S Bagratee, Pillay M, Reddy T. Use of the myocardial performance index as a prognostic indicator of adverse fetal outcome in poorly controlled gestational diabetic pregnancies. *Prenatal Diagnosis; DOI:10.1002/pd.4471.*

3. Bhorat IE, Bagratee JS, Pillay M, Reddy T. Determination of the myocardial performance index in deteriorating grades of growth restriction and its link to adverse outcomes. *Prenatal Diagnosis: DOI: 10.1002/pd 4537.*

Manuscript submitted for Publication:

1. **Bhorat IE, Bagratee JS, Reddy T. Assessment of fetal myocardial performance across deteriorating stages of placental vascular resistance in severe early onset pre-eclampsia (EO-PET) and its link to adverse outcomes.**

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GLOSSARY

AFI	**Amniotic fluid index**
AEDF	**Absent End Diastolic Flow**
AUC	**Area under the curve**
CTG	**Cardiotocograph**
DV	**Ductus venosus**
E/A	**E wave/A wave peak velocity ratio**
EWF	**Expected weight of the fetus**
ET	**Ejection time**
ICT	**Isovolumetric contraction time**
IRT	**Isovolumetric relaxation time**
IQR	**Interquartile ranges**
IUGR	**Intra-uterine growth restriction**
IVH	**Intraventricular haemorrhage**
ms	**metre per second**
MCA	**middle cerebral artery**
MPI	**myocardial performance index**

Mod-MPI	**modified myocardial performance index**
NICU	**neonatal intensive care unit**
NVD	**normal vaginal delivery**
PET	**pre-eclampsia**
PI	**pulsatility index**
ROC	**receiver operating curve**
SB	**stillbirth**
UA	**umbilical artery**
Vent	**ventilation**

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Aim of Study:

The aim of the study is to establish normal gestational age –adjusted reference values (normograms) of a fetal cardiac parameter viz. the myocardial performance index (MPI) using real time 2-dimensional and Doppler ultrasonic techniques. The fetal MPI and diastolic function (early diastolic velocity /late diastolic velocity - E/A ratios) will be evaluated in high risk obstetric conditions to determine whether it is a prognostic marker of perinatal outcome.

Specific Objectives

To establish gestational age –adjusted normograms for the myocardial performance index in pregnancy.

To determine whether the MPI and E/A ratios are altered in fetuses of diabetic pregnancies and whether this altered MPI and/or E/A ratios influence perinatal outcome.

To determine whether the MPI and E/A ratios are altered in fetuses with intrauterine growth restriction and whether this altered MPI and/or E/A ratios is a prognostic marker.

To determine whether the MPI and E/A ratios are altered in fetuses of pre-eclamptic pregnancies and whether this altered MPI and/or E/A ratios is a prognostic marker.

CHAPTER 1

INTRODUCTION

Fetal echocardiography has been used for non-invasive evaluation of human fetal cardiac anatomy, function and haemodynamics[1,2,3,4,5,6,7,8,9,10] . The myocardial performance index (MPI) or Tei index, a combined index of systolic and diastolic ventricular function has been proposed as a potential useful predictor of global cardiac function and this index is known to be independent for ventricular geometry and heart rate. MPI or the Tei index is defined as the sum of the isovolumetric contraction time (ICT) and isovolumetric relaxation time (IRT) divided by ejection time (ET).[1,2,3]

The equation of the MPI is thus: (ICT + IRT)/ET.

Doppler echocardiographic studies in adult and paediatric patients with heart disease have shown that impairment of ventricular function leads initially to diastolic and then to combined diastolic and systolic dysfunction[11,12]. A measurement that combines assessment of systolic and diastolic function may better reflect global cardiac function than an isolated evaluation of either ejection or relaxation.

It has been reported in adults that because ventricular dysfunction results in

prolongation of both ICT and IRT and the dimunition of the ET, the Tei index can assess myocardial performance; it is increased in in patients with ventricular dysfunction secondary to cardiac diseases such as myocardial infarction[13], dilated cardiomyopathy[1] and amyloidosis[14]. The physiological changes of global ventricular function determined by the Tei index were reported in fetuses in the second and third trimester[15]. Tsutsumi et [15]al also reported in a pilot study that the indices were increased in some high risk pregnancies and neonates. Thus it was theorized that the Tei index or MPI may be able to evaluate fetal myocardial function.

Fetal complications in gestational diabetes or established diabetes without microvascular complications are not related to placental insufficiency but rather fetal hyperinsulinism[16]. Yet most of our conventional antenatal fetal surveillance techniques revolve around placental insufficiency eg umbilical artery resistance indices (RI's), middle cerebral artery resistance indices (RI's), ductus venosus Doppler, umbilical vein Doppler and cardiotographs (CTG's). It is obvious that we cannot transfer Doppler criteria derived from conventional placental insufficiency cases to those in which diabetic metabolism is a major determinant causing augmented soft tissue growth and metabolic demand and larger vascular cross sections. The Doppler measurements of flow velocity in the uterine and fetal circulations have brought us far in identifying placental insufficiency, but for most diabetic patients they are neither appropriate nor sufficient. Delays in left ventricular filling which may reflect changes in myocardial relaxation have been reported[17].

Infants of diabetic mothers are also at risk for hypertrophic cardiomyopathy. It may well be that alterations in cardiac function in fetuses of diabetic mothers reflect an abnormal metabolic milieu. These alterations of cardiac function could be interventricular septal anomalies, increased preload index or a direct myocardial effect. The cardiac dysfunction could in fact be a marker for metabolic acidosis which is the mechanism by which fetuses are put at risk for morbidity and "unexplained" fetal deaths. The myocardial performance index and E/A ratio will be investigated in fetuses of diabetic mothers to establish if there is a link between an abnormal metabolic milieu resulting from the diabetic state and fetal cardiac dysfunction. If this link is confirmed in the study this would in effect change the way we monitor and follow up fetuses in diabetics and could substantially not only reduce the so-called "unexplained " stillbirths but also reduce the significant fetal morbidity associated with this common condition, by guiding clinicians in timing of delivery.

Combined systolic and diastolic dysfunction have been reported in intrauterine growth restriction (IUGR) fetuses[15,18] with a linear correlation with the haemodynamic severity stage[19,20]. Ichizuka et al however have showed no such correlation[21]. This research will attempt to establish a link between the severity of the growth restrictive process and cardiac dysfunction viz. draw a link between the different grades of the IUGR process ie uncompensated, compensated or critical status IUGR and the myocardial performance index. Thus we aim to seek to measure MPI in specifically categorized IUGR fetuses, as noted above, to assess the correlation of myocardial function with severity of the growth restrictive process and to possibly add cardiac Doppler as another significant tool in our armamentarium of antenatal surveillance techniques to predict perinatal morbidity and mortality. The usefulness of this technique if confirmed is that cardiac dysfunction could be a "warning" parameter or precursor parameter to a more serious haemodynamic deterioration that could lead to severe perinatal morbidity or death.

Cardiac dysfunction and mild myocardial damage using troponin T have been demonstrated in neonates of pre-eclamptic mothers in a paper reported by Narin et al[22]. In addition Ichizuka et al reported that the MPI increased under pathological conditions such as an increase in the cardiac afterload secondary to increased placental vascular resistance.[21] Since the contractility of the heart is markedly affected by preload and afterload, we hypothesized that fetal cardiac function might

be impaired in mainly early onset pre-eclamptic mothers where the pathophysiology relates to placental lesions and is in effect a placental mediated disease process resulting in widespread vasoconstriction (as opposed to late-onset pre-eclampsia). Cardiac function using the myocardial performance index in pre-eclamptic patients has been assessed in utero by O.Api et al.[23] This study showed no association between cardiac function as assessed by the MPI and pre-eclampsia. This however may be due to their study population which was performed mainly in late onset pre-eclamptics. It is however the early onset pre-eclamptics that is related to placental maladaptation resulting increased placental vascular resistance and thus increasing fetal cardiac afterload. This part of the study will seek to measure MPI and the E/A ratio in fetuses of pre-eclamptic mothers to assess if these parameters are indeed altered and whether it is a prognostic marker.

This research of fetal cardiac function in high risk obstetric conditions has as one of the main objectives to bring cardiac Doppler assessment into mainstream antenatal surveillance techniques. A technique that quantifies cardiac haemodynamics may prove to be another antenatal surveillance technique that clinicians may use to predict and prevent perinatal mortality. These common high risk obstetric conditions together constitute by far the majority of high risk patients in obstetrics and responsible for significant perinatal morbidity and mortality.

The objective is to establish age-adjusted normograms of the MPI and to determine whether high risk obstetric conditions influence the myocardial performance index and diastolic function. This research will give further insight into the pathophysiology of the fetal circulation in these conditions. The MPI may become a significant marker in helping clinicians determine timing of delivery and in so doing reduce perinatal mortality and morbidity.

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CHAPTER 2

BACKGROUND AND LITERATURE SURVEY

Fetal echocardiography has been used for non-invasive evaluation of human fetal cardiac anatomy, function and haemodynamics[1,2,3,4,5,6,7,8,9,10] . A new Doppler index of combined systolic and diastolic ventricular myocardial performance the Tei index or myocardial performance index (MPI) has been proposed as a potential useful predictor of global cardiac function and this index is known to be independent for ventricular geometry and heart rate. MPI or the Tei index is defined as the sum of the isovolumetric contraction time (ICT) and isovolumetric relaxation time (IRT) divided by ejection time (ET).[1,2,3]

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mothers are also at risk for hypertrophic cardiomyopathy. It may well be that alterations in cardiac function in fetuses of diabetic mothers may reflect an abnormal metabolic milieu resulting in interventricular septal anomalies or increased preload index or a direct myocardial effect with the possibility of metabolic acidosis[19] and thus late in pregnancy puts the fetus at risk for morbidity and "unexplained" fetal deaths. Thus the investigation of MPI's in fetuses of diabetic pregnancies may have great implications in managing these fetuses as the cardiac Doppler, in effect, could be the only parameter to reliably predict compromise and thus could be integrated into the routine fetal surveillance techniques of diabetic pregnancies. The use of this parameter in antenatal surveillance in the diabetic pregnancy may not only reduce the so-called "unexplained" stillbirths in the 3rd trimester but also the significant fetal morbidity associated with this common condition by guiding clinicians in timing of delivery.

Intra-uterine growth restriction (IUGR) is characterised by hemodynamic changes and early onset- IUGR manifests biophysically by fetal growth impairment, possible oligohydramnios and changes in flow velocities in the umbilical artery and/or middle cerebral artery and/or ductus venosus[20,21,22,23]. Several experimental and clinical studies have demonstrated the association of abnormal aortic isthmus (AoI) pattern with adverse outcome[24,25] and later neurodevelopmental status. [26,27] Abnormalities in ductus venosus (DV) flow is known to correlate with fetal acidosis and represents anomalies in forward flow cardiac haemodynamics with deterioration detected

earlier than the biophysical profile[28,29]. AoI and DV are basically extrapolations of a compromised cardiac state . Cardiac flow is greatly influenced by modifications of arterial impedance to flow. Cerebral vasodilatation produces a decrease in left ventricular afterload, whereas increased placental and systemic resistance produce increases in right ventricular afterload. Hypoxaemia may also impair cardiac contractility directly, while changes in blood viscosity due to polycythaemia may alter preload [30] . Consequently growth restricted fetuses show at the level of the atrio-ventricular valves, impaired ventricular filling (lower E/A ratios), [31] lower peak velocities in the aorta and pulmonary arteries [32] , increased aortic and decreased pulmonary time to peak velocity[33] and a relative increase of left cardiac output associated with decreased right cardiac output [34] . These haemodynamic intracardiac changes are compatible with a preferential shift of cardiac output in favour of the left ventricle leading to improved cerebral perfusion. Longitudinal studies of deteriorating growth-restricted fetuses have shown that peak velocity and cardiac output gradually decline , suggesting a progressive worsening in cardiac function.[35] . Similarly there is a symmetrical decrease in ventricular ejection force at the level of both ventricles, despite the dramatically different haemodynamic conditions present in the vascular district of ejection of the two ventricles (ie reduced cerebral resistances for the left ventricle and increased splachnic and placental resistance for the right ventricle)[36] . This supports a pivotal role of the intrinsic myocardial function in the compensatory mechanism of the growth restricted fetus following the establishment of the brain sparing effect. Ventricular ejection force dramatically decreases in a short time interval showing an impairment of ventricular force close to fetal distress. As a consequence cardiac filling is also

impaired. It thus makes more sense to directly investigate cardiac function in IUGR fetuses and the MPI and E/A ratios are just the tools that allow us to do this. Also combined systolic and diastolic dysfunction have been reported in IUGR fetuses with a linear correlation with the haemodynamic severity stage[37,38]. Others[39] have not shown a correlation which may have to do with the type of study population ie there may be a correlation only with severe types of IUGR. The investigation of cardiac haemodynamics in IUGR may play a crucial role in deciding timing of delivery as it may be a precursor to serious adverse events. It may be possible that the MPI may also precede the absent A wave in the DV (which strongly correlates with fetal acidosis and at which stage there is already significant fetal compromise) as this is just a reflection of extreme anomalies in cardiac haemodynamics especially in forward flow cardiac haemodynamics.

Although the exact cause of pre-eclampsia (PET) remains unclear, many theories center on the problems of placental implantation and inadequate trophoblastic invasion of the maternal spiral arterioles[40,41,42] which is thought to give rise to vascular resistance of the uteroplacental circulation[43,44]. The increased vascular placental resistance may affect fetal cardiac function by causing an increase in the fetal cardiac afterload. Fetal cardiac function might be impaired in pre-eclamptic mothers since the contractility of the heart is markedly affected by preload and afterload. Cardiac dysfunction and mild myocardial damage have been reported in a recent paper on the neonates of mildly preeclamptic mothers[45] but there have been

scant studies evaluating fetal cardiac function in severe early-onset preeclampsia or hypertensive crises of pregnancy. Cardiac function using the myocardial performance index in pre-eclamptic patients has been assessed in utero by O.Api et al.[46] This study showed no association between cardiac function as assessed by the MPI and pre-eclampsia. This however may be due to their study population which was performed mainly in late onset pre-eclamptics. It is however the early onset pre-eclamptics that is related to placental maladaptation resulting increased placental vascular resistance and thus increasing fetal cardiac afterload. Fetal cardiac function using the MPI and E/A ratio will be investigated in severe early-onset preeclamptic pregnancies. As the aim of this research will be to study the effect of preeclampsia on the fetal circulation, we will also investigate blood flow in the umbilical artery, middle cerebral artery and ductus venosus and compare in terms of a monitoring model where the MPI fits, in relation to the standard monitoring model in the linear haemodynamic severity stages of pre-eclampsia and to determine outcomes . A correlation will thus be made as to exactly when cardiac dysfunction sets in, in relation to the standard monitoring parameters.

This is an important study as there is a dearth of information evaluating fetal cardiac function in severe pre-eclampsia / hypertensive crises in pregnancy with only information on this parameter mainly coming from twin-to-twin transfusion syndrome (TTTS) pregnancies[39] where it has been reported that myocardial performance might be impaired in recipient fetuses secondary to hypervolaemia or

increased placental vascular resistance. Pre-eclampsia is a condition that often leads to increased placental vascular resistance and it is hypothesized that this may cause a strain on systolic and diastolic function and that global myocardial function could be altered. If this is shown, the MPI can be used as an antenatal surveillance tool, in conjunction with standard monitoring models, in reaching management decisions of the fetus in severe pre-eclampsia. There is also evidence to show especially in TTTS[39] data that myocardial dysfunction tends to precede other Doppler anomalies and if this is applied to pre-eclampsia we could identify fetuses at risk, before significant morbidity occurs. Thus a major objective of this part of the study, if it is shown that cardiac dysfunction indeed occurs in fetuses of severe pre-eclamptic pregnancies, will be to correlate this to other standard monitoring parameters of the fetus and to create a new monitoring model that predicts significant fetal morbidity and thus guide the clinician to appropriate timing of delivery. This original research will further our clinical understanding of the pathophysiology of the enigmatic pre-eclamptic process as part of the wider placental mediated disease phenomenon.

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CHAPTER 3

METHODOLOGY

For the ultrasound examinations General Electric (GE) Voluson E8 and Siemens Antares ultrasound machines will be used.

The myocardial performance index was initially proposed by Tei et al [1] for evaluation of heart function in adults with dilated cardiomyopathy. The MPI is the ratio between the duration of the isovolumetric period (composed of 2 periods – contraction and relaxation ie ICT and IRT) and the duration of the ejection in the cardiac ventricle (ET). Abnormal cardiac function is associated with a prolongation of the isovolumetric period and reduction in ejection time thus resulting in an increase in the MPI. For the original calculation Tei et al proposed the acquisition of 2 waveforms in different locations: initial wave below the atrioventricular valve to record the E/A waveform for calculation of the isovolumetric periods and second in the outflow tracts for the ejection period. Although the MPI has become part of routine clinical assessment in newborns, in fetuses it is still under evaluation. Several authors have calculated the MPI in fetuses using the originally described technique [2,3] but the results show wide variability in the values reported for normal fetuses. To improve the performance of this technique, Friedman et al[4] suggested that the MPI could be evaluated during the same Doppler waveform. This approach is feasible because the aorta emerges very close to the mitral valve; furthermore it allows direct and individual measurement of the ICT and the IRT. However this approach does not solve an important drawback for calculation of the MPI ie absence of clear landmarks delineating the 3 periods for this calculation. A substantial improvement

was achieved by Raboisson et al[5] who initially used the Doppler echo (click) of the opening of the aortic valve as the landmark to better estimate the limits of the ejection period. E. Hernandez-Andrade et al[6] proposed a modified MPI (Mod-MPI) in the left ventricle, which uses the opening and closing clicks of the mitral valve and aortic valve to clearly delineate the three time periods used for the MPI. Isovolumetric contraction time is a term used in cardiac physiology to describe an event occurring in early systole during which the ventricles contract with no corresponding volume change. This short lasting event occurs from the beginning of the mitral valve (MV) closure to the aortic valve (AV) opening but this short period builds up a sufficiently high pressure that overcomes that of the aorta (and pulmonary trunk) upon opening of the semilunar valves thereby allowing correct unidirectional flow of blood. Isovolumetric relaxation time is an interval in the cardiac cycle from the closure of the aortic to the onset of filling by opening of the mitral valve. It is an indicator of diastolic function. Ejection time is time from ejection of blood from the left ventricle beginning with aortic valve opening and ending with aortic valve closure. Ejection time is an indicator of systolic function. The modified MPI significantly improves interobserver reproducibility as compared with the standard MPI calculation and we will use this MPI calculation technique for our studies. For the best results the sweep speed was set at 5cm/sec and the wall motion filter at 300Hz.

The Mod-MPI will be calculated in the fetal left ventricle as originally described by

Hernandez-Andrade et al[6]. A cross sectional image of the fetal thorax at the level of the 4-chamber view with an apical projection of the heart will be obtained. The Doppler sample will be opened to 3mm and placed in the internal leaflet of the mitral valve (MV). In this location owing to its closeness to the aortic valve (AV), the opening and closing AV clicks will be registered. The angle of insonation will always be <30 degrees. E/A waveform will be always displayed as positive flow . The Doppler gain will be lowered as far as possible to clearly visualize the echoes corresponding to the opening and closing clicks of the two valves at the beginning and at the end of the E/A (mitral valve) and aortic waveforms. The three time periods will be estimated as follows :1) ICT from beginning of MV closure to AV opening; 2) ET from AV opening to closure; 3) IRT from AV closure to MV opening. The Mod-MPI = (ICT +IRT) /ET

In addition E-wave (early ventricular filling) and A wave (active atrial filling) peak velocities and the ratio between them (E/A ratio) at the level of the MV as an index of ventricular diastolic function will be performed. [7]

Diagram demonstrating the three time periods: ICT, ET and IRT, using the modified MPI technique

The time cursor is placed at the beginning of each Doppler click.

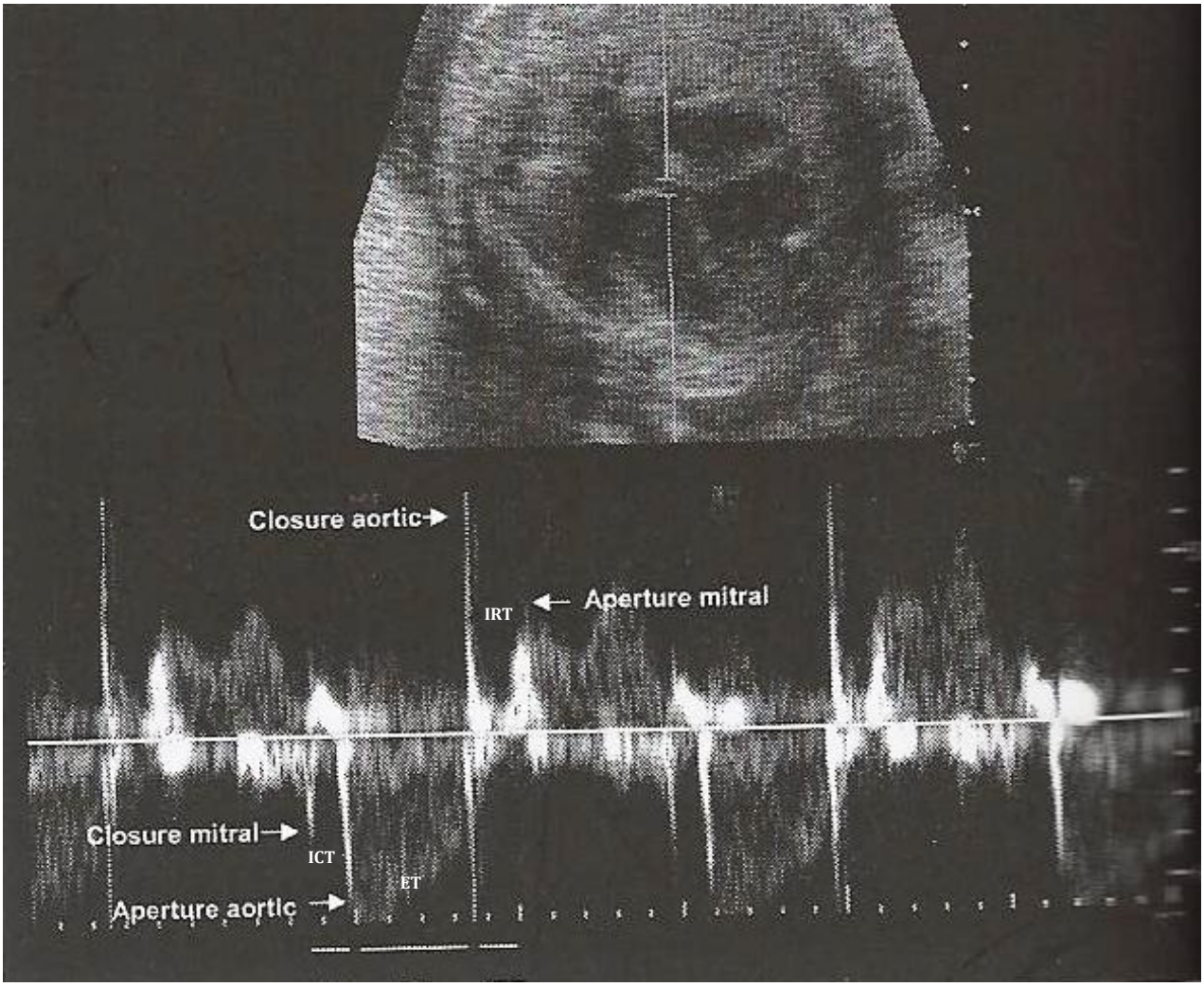

Fig 3.1 Doppler Echocardiography of Fetal Cardiac Cycle

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CHAPTER 4

REFERENCE INTERVALS OF THE MODIFIED

MPI IN PREGNANCY

4.1 Abstract:

Aim

To establish gestational age-adjusted reference intervals of the modified myocardial performance index (Mod-MPI) in pregnancy

Methods

A cross-sectional study using Doppler echocardiography to determine the Mod-MPI was performed on 419 fetuses from 20 to 38 weeks of gestation. Doppler signals of the opening and closing of the mitral and aortic valves were used as landmarks to determine the isovolumetric contraction time (ICT), isovolumetric relaxation time (IRT) and ejection time (ET). The Mod-MPI was modelled using fractional polynomials and the exponential normal model.

Results

The Mod-MPI was relatively constant from 20 to 26 weeks and thereafter steadily decreased with advancing gestational age. ICT and ET remained constant whilst IRT decreased with advancing gestation similar to the Mod-MPI.

Conclusion

Reference intervals of the Mod-MPI evaluating fetal cardiac function have been established. Maturational and developmental alterations in the myocardial performance in utero resulting in better ventricular compliance is most likely responsible for the decreasing trend of the Mod-MPI noted with advancing gestation.

4.2 INTRODUCTION

Fetal cardiac function using echocardiography with Doppler has been increasingly performed in the management of complicated pregnancies [1,2]. A Doppler index of combined systolic and diastolic ventricular myocardial performance, the Tei index or the MPI has been proposed as a potential useful predictor of global cardiac function which is not influenced by ventricular geometry and heart rate[3]. MPI is defined as (ICT + IRT)/ET. The MPI has become established for clinical assessment in adults and newborns[4], but is still under investigation in fetuses. Previous studies done to establish reference intervals for MPI using the originally described technique have had problems in reproducibility mainly due to the method of acquisition and therefore the evolution to the modified MPI [5,6,7,8]. However, there has not been consensus, with studies showing either a decrease, increase or no change in MPI with advancing gestational age[5,7,8,9]. The aim of the present study was to construct normal gestational age related reference values for the modified-MPI (mod-MPI) in the fetus from 20 to 38 weeks gestation and in particular to determine the trend of the Mod-MPI in relation to advancing gestational age.

4.3 METHODS

A cross sectional study was performed on 419 normal fetuses from 20 to 38 weeks of gestation. Exclusions were any complications arising during the pregnancy or birth. The mod-MPI was calculated in the fetal left ventricle. The project was approved by the Bio-ethics committee of the University of KwaZulu Natal.

For the ultrasound and Doppler studies, a Voluson E8 Expert (General Electric Medical Systems, WI, USA) and a Siemens Sonoline Antares (Siemens Medical Systems, Malvern, PA, USA) were used.

The Mod-MPI was calculated in the fetal left ventricle as described by Hernandez-Andrade et al[8]. Briefly, a cross sectional image of the fetal thorax at the level of the 4-chamber view with an apical projection of the heart was obtained. The Doppler sample was opened to 3mm and placed in the internal leaflet of the mitral valve (MV). In this location owing to its closeness to the aortic valve (AV), the opening and closing AV clicks were registered. The angle of insonation was always <30 degrees. The early and late diastolic velocities (E/A waveform) were always displayed as positive flow. The sweep speed was set at 5cm/sec and the Doppler gain lowered as far as possible to clearly visualize the echoes corresponding to the opening and closing clicks of the two valves at the beginning and at the end of the mitral valve and aortic waveforms. The wall motion filter was set at 300Hz. The three time periods were estimated as follows: 1) ICT: from the beginning of MV closure to AV opening; 2) ET: from AV opening to closure; 3) IRT: from AV closure to MV opening. The Mod-MPI = (ICT +IRT) /ET.

Statistical analysis

All analysis was performed using STATA/SE version 12.0 (Stata Corp, College Station, TX, USA). Gestational ages were recorded as completed weeks and to avoid bias

adjusted gestational ages were computed by adding 0.5 weeks to each gestational age as per the recommendation of Royston[10].

Our analysis was performed using the method proposed by Royston and Wright[11]. The exploratory analysis for shape of the mean and standard deviation curves was conducted by fitting Lowess smooth curves. As a starting point, fractional polynomial models were fitted where powers were chosen from (-2, -1, -0.5, 0, 0.5, 1, 2, 3) for the mean and standard deviation curves. Once the most appropriate mean and standard deviation curves were fitted, the age-adjusted mean (μ_T) and standard deviation (σ_T) were computed using the standard methods proposed by Royston[10].

If the Q-Q plot of the z-scores showed strong deviation from normality, measurements were transformed using shifted logarithmic functions. *If there was no normalization of the fitted data after transformation,* we applied more advanced parametric models proposed by Royston and Wright[11].

The exponential-normal transformation involves a skewness parameter γ_T and is presented below :

$$U = \frac{\exp(\gamma_T Z - 1)}{\gamma_T}$$

Where

$$Z = \frac{Y - \mu_T}{\sigma_T}$$

Denoting C_q as the curve corresponding to the 100qth centile of the distribution, and u_q as the 100qth centile of the standard normal distribution $N(0,1)$:

$$C_q = \mu_T + \sigma_T \log\left(1 + \gamma_T u_q\right) / u_q$$

To determine whether a normal or exponential normal model provided a better fit to the data, a likelihood ratio test of $\gamma_T = 0$ was performed by comparing the deviances for the respective models to a $\chi^2(1)$ value. If this test resulted in a significant p-value the exponential normal model was adopted and a linear model was fitted to the skewness parameter.

Centile curves were calculated by back-transformation of the estimated centiles to the original scale. The goodness of fit of the model was assessed by normal Q-Q plots of Z- scores and by examining whether the Z-scores were randomly scattered and showed no trend with gestational age.

Intra-observer and inter-observer variability was assessed using the intra class correlation coefficient (ICC) which was computed using a random effects model.

4.4 RESULTS

A total of 419 fetuses were analysed and there were 19 to 26 fetuses at each gestational age between 20 and 38 weeks. The mean maternal age was 28.6 years.

Mod-MPI

A log transformation was applied to the MPI to reduce skewness and heteroskasticity. The best fitting model for the mean curve was a fractional polynomial illustrated by the equation: $\hat{\beta}_0 + \hat{\beta}_1 T^3 + \hat{\beta}_1 logT * T^3$ and presented in Figure 4.1(a). A linear model best fitted the scaled absolute residuals and is presented in Figure 4.1(b).

The Shapiro Wilk test applied to the corresponding standardized Z-values indicated non-normality ($p < 0.0001$) and Q-Q plot indicated serious departures from normality. Various shifted log and power transformations were applied but none resulted in z-scores meeting the criteria for normality. This indicated that a skewness parameter should be added to the model. The exponential normal model presented a significant improvement on the normal model ($p = 0.023$). Modelling the skewness as a function of age as opposed to a constant in the model further improved model fit ($p = 0.001$) and was adopted as the final model.

The normal Q-Q plot for the Z-values is presented in Figure 4.1c and showed no obvious departure from normality, with the Z-values randomly scattered with gestational age as seen in Figure 4.1(d). The 5^{th}. 50^{th} and 95^{th} centile curves were

estimated and then back transformed to the original scale (Figure 4.1(e) and Table 4.1).

Table 4.1 : Estimated age adjusted centiles for the Mod-MPI

Gestational age (weeks)	5^{th} percentile	50^{th} percentile	95^{th} percentile
20 weeks	0.38	0.41	0.42
21 weeks	0.38	0.40	0.42
22 weeks	0.38	0.40	0.42
23 weeks	0.38	0.40	0.42
24 weeks	0.38	0.40	0.42
25 weeks	0.38	0.40	0.42
26 weeks	0.38	0.40	0.42
27 weeks	0.37	0.40	0.42
28 weeks	0.37	0.39	0.42
29 weeks	0.37	0.39	0.41
30 weeks	0.36	0.38	0.41
31 weeks	0.36	0.38	0.41
32 weeks	0.36	0.38	0.40
33 weeks	0.35	0.37	0.40
34 weeks	0.34	0.36	0.39
35 weeks	0.34	0.36	0.38
36 weeks	0.33	0.35	0.38
37 weeks	0.32	0.34	0.37
38 weeks	0.32	0.33	0.36

IRT

The distribution of the IRT with gestational age in closely resembled that of the Mod-MPI. To reduce skewness and heteroskasticity the IRT values were log transformed. The best fitting model for the mean curve was a fractional polynomial illustrated by the equation: $\hat{\beta}_0 + \hat{\beta}_1 T^3 + \hat{\beta}_1 logT * T^3$ and presented in Fig.4.2a Fractional

polynomial regression was used to determine the most appropriate model for the standard deviation. The powers of the model with the lowest deviance were $T^{-0.5}$ and $\log(T) * T^{-0.5}$ which did not differ significantly from a linear model (p = 0.58), and hence a linear model was adopted for simplicity (Figure 4.2 (b)). The Shapiro Wilk test applied to the corresponding standardized Z values indicated non-normality (p < 0.0001) and Q-Q plot indicated serious departures from normality. The exponential normal model presented a significant improvement on the normal model (p = 0.082). Modelling the skewness as a function of age as opposed to a constant in the model significantly improved model fit (p = 0.005) and was adopted as the final model. The normal Q-Q plot for the Z-values (Figure 4.2(c)) showed no obvious departures from normality, with the Z-values randomly scattered with gestational age as seen in Figure 4.2(d). The 5th. 50th and 95th centile curves were estimated and then back transformed to the original scale seen in Figure 4.2(e)

ET and ICT

The 95th, 50th and 5th percentile of ET and ICT did not vary with gestational age (both p = 1.0).

Intra- and interobserver observer variation

The measurement of MPI showed high levels of intra- and inter observer agreement (ICC 0.97 (0.948; 0.980) and 0.95 (0.91, 0.97) respectively.

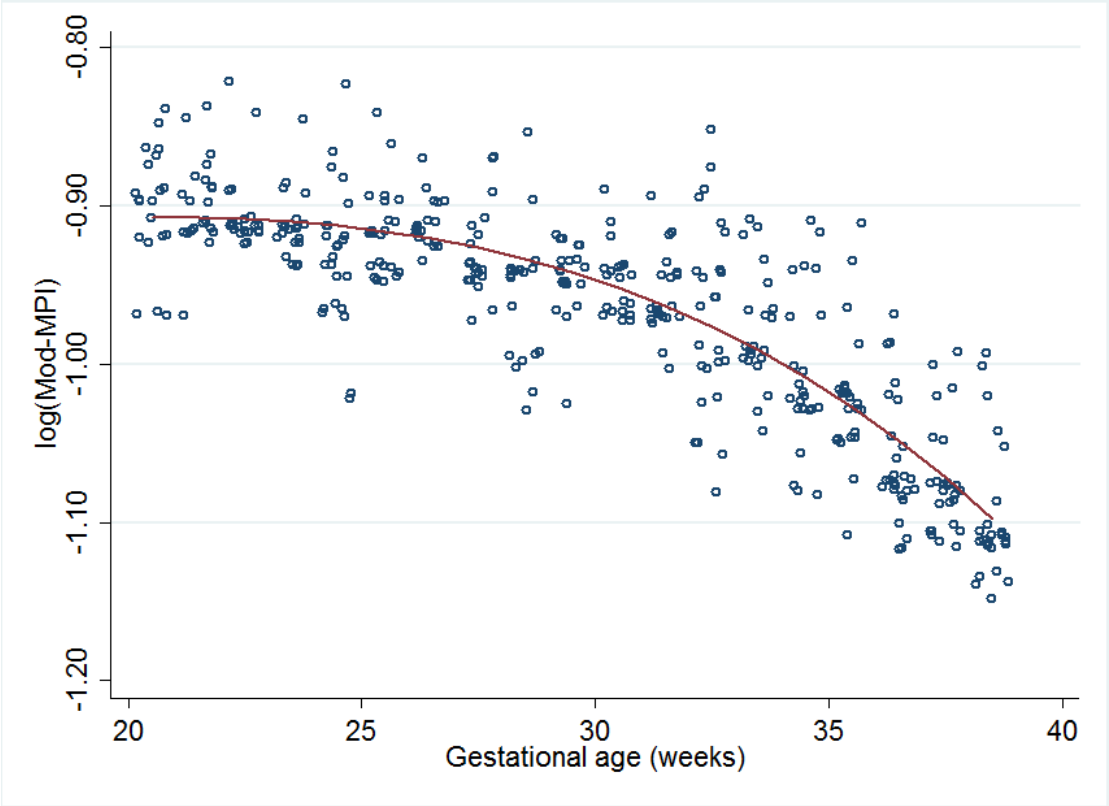

Figure 4.1 a: log Mod-MPI versus age with fractional polynomial fitted to the mean

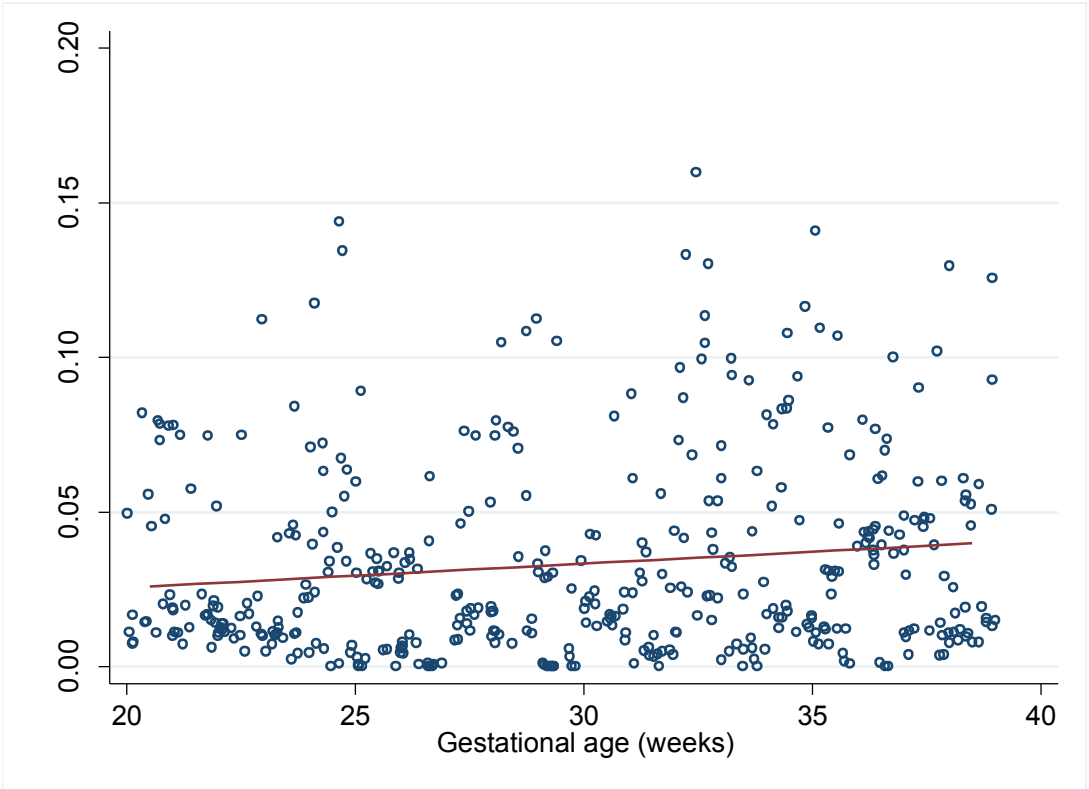

Figure 4.1 b: Scaled absolute residuals with linear model fitted to log Mod-MPI

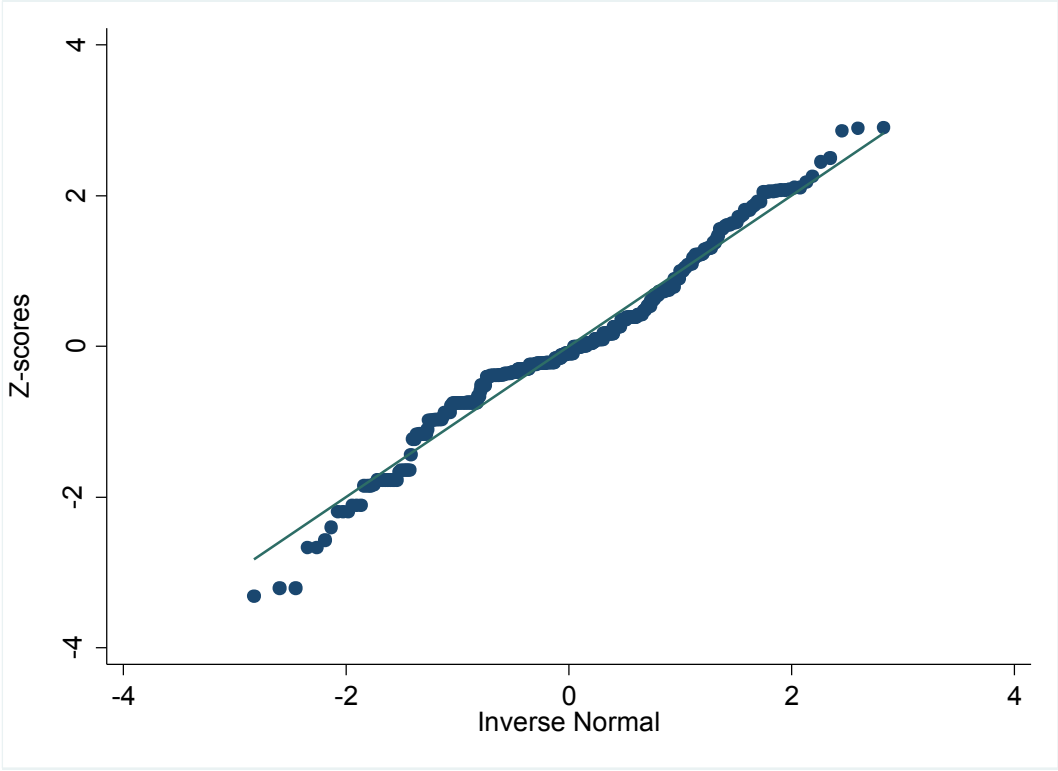

Figure 4.1 c: Normal plot of Z-scores

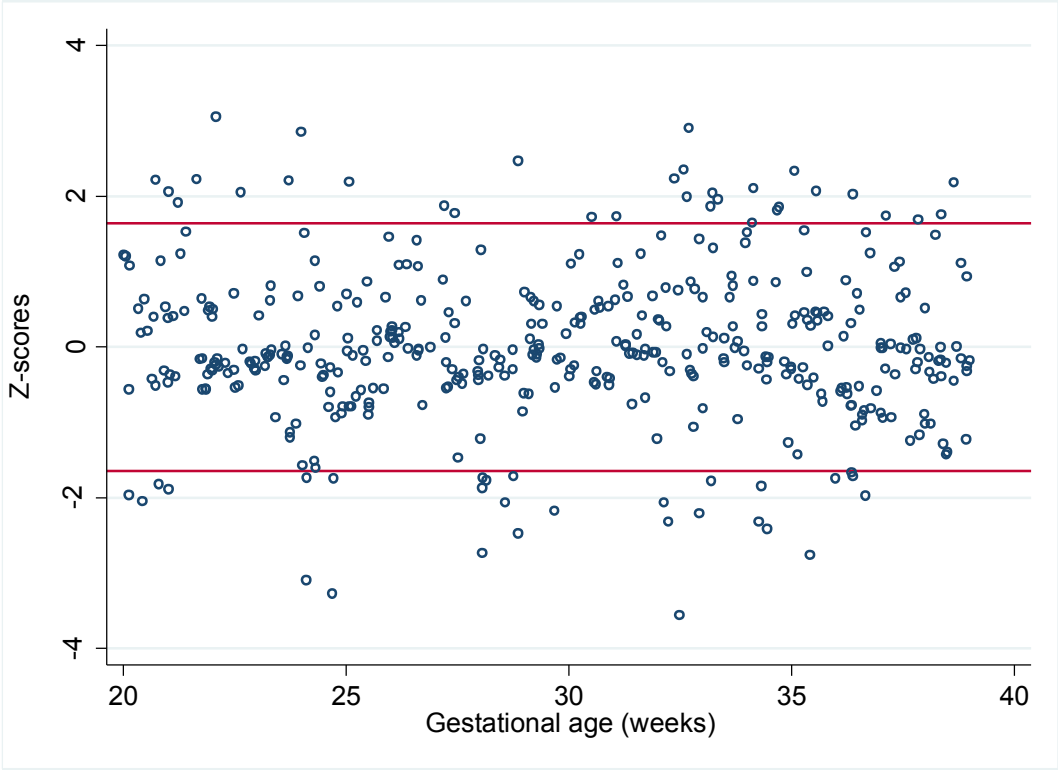

Figure 4.1 d: Z-values versus gestational age

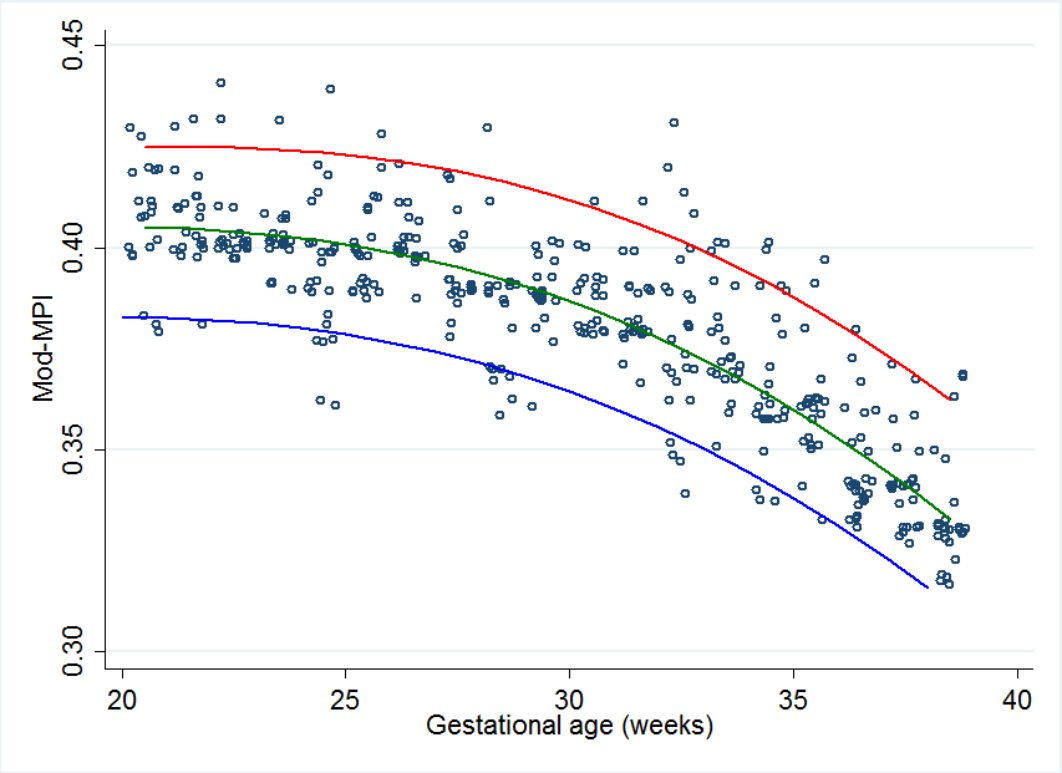

Figure 4.1 e: The 5th, 50th and 95th centile curves of Mod-MPI

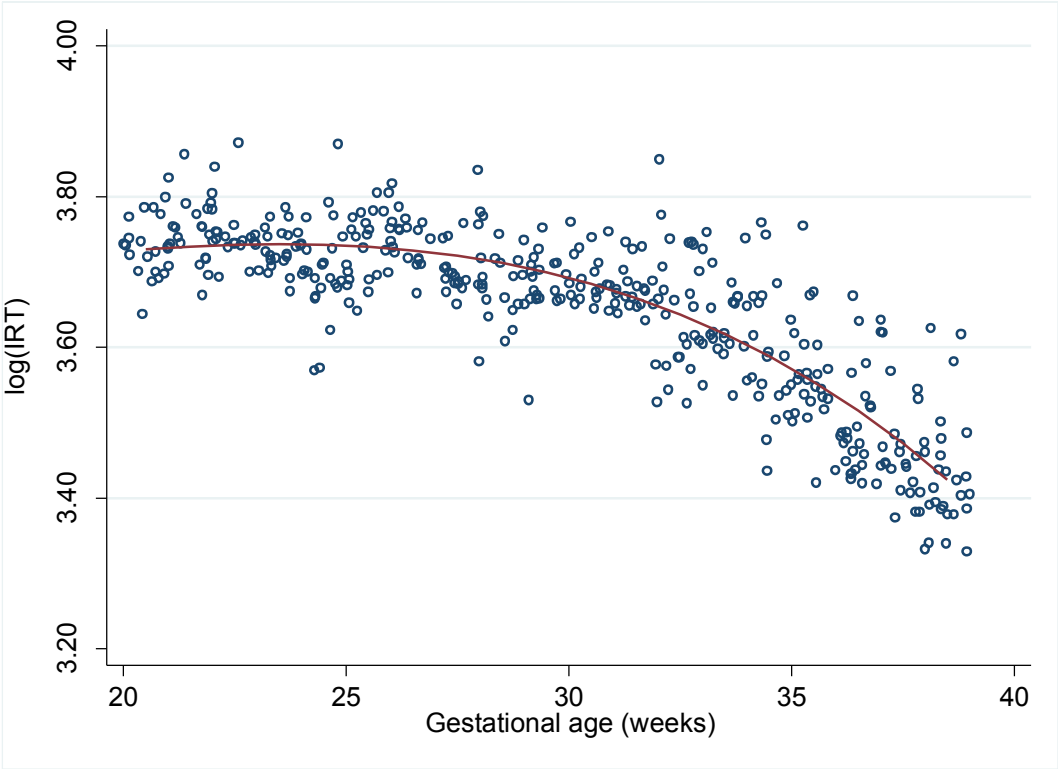

Figure 4.2 a: log(IRT) versus gestational age with fractional polynomial fitted to the mean

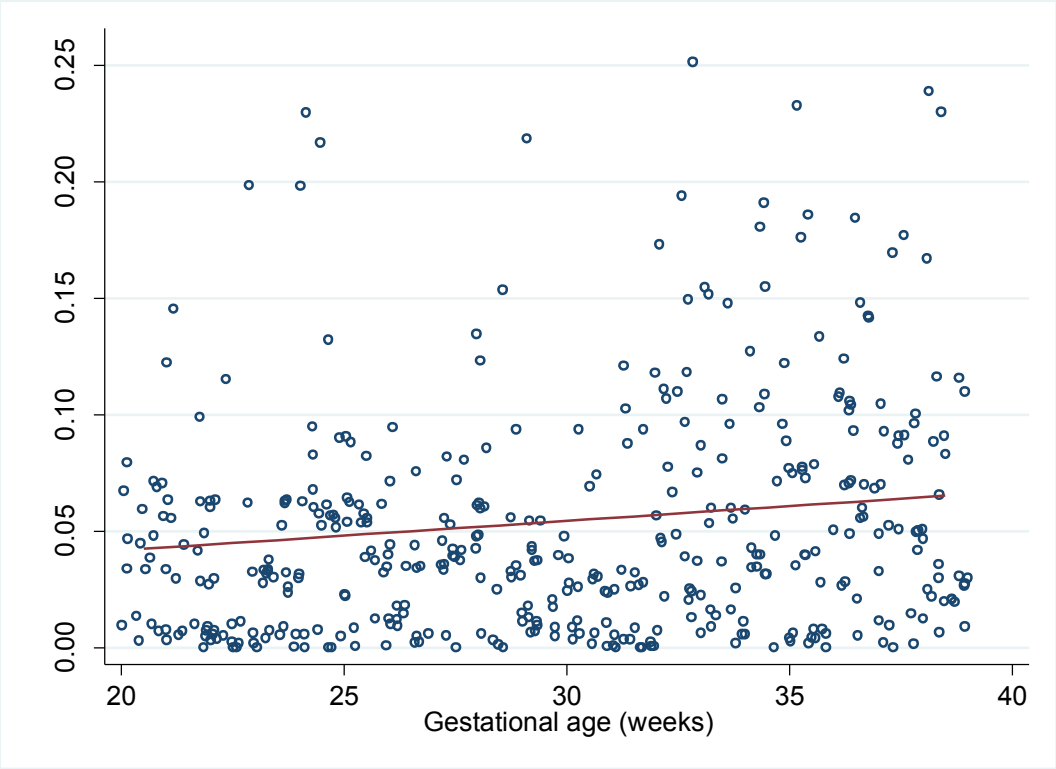

Figure 4.2 b: Scaled absolute residuals with linear model fitted to the log (IRT)

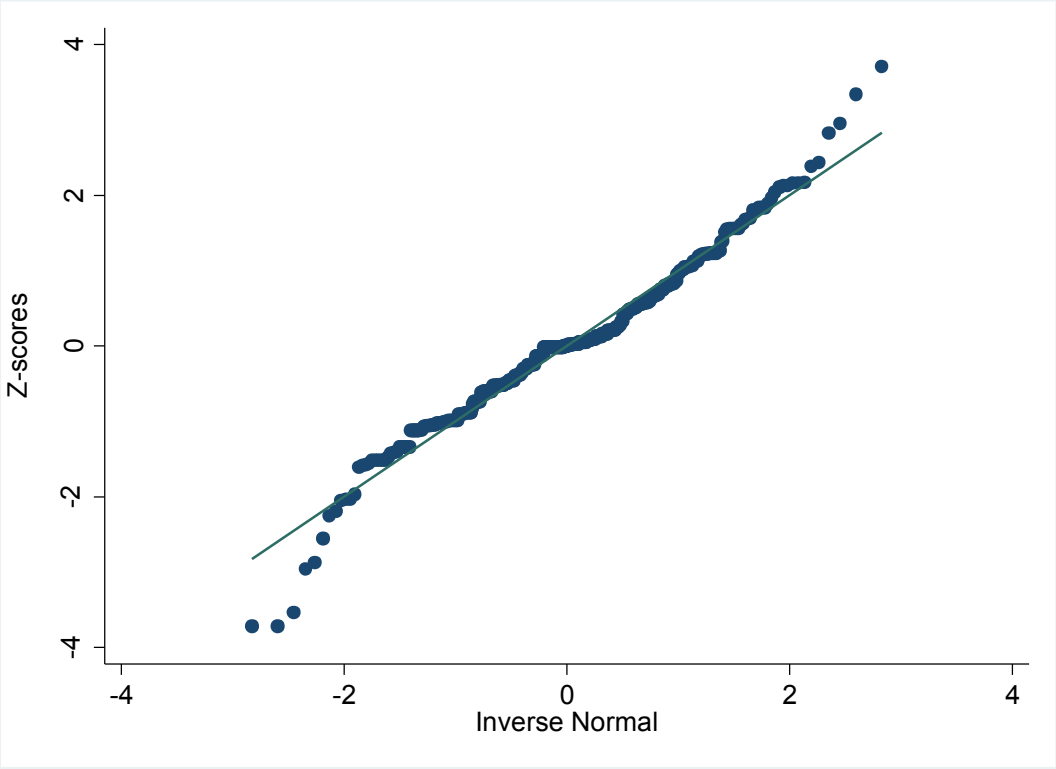

Figure 4.2 c: Normal plot of Z-scores

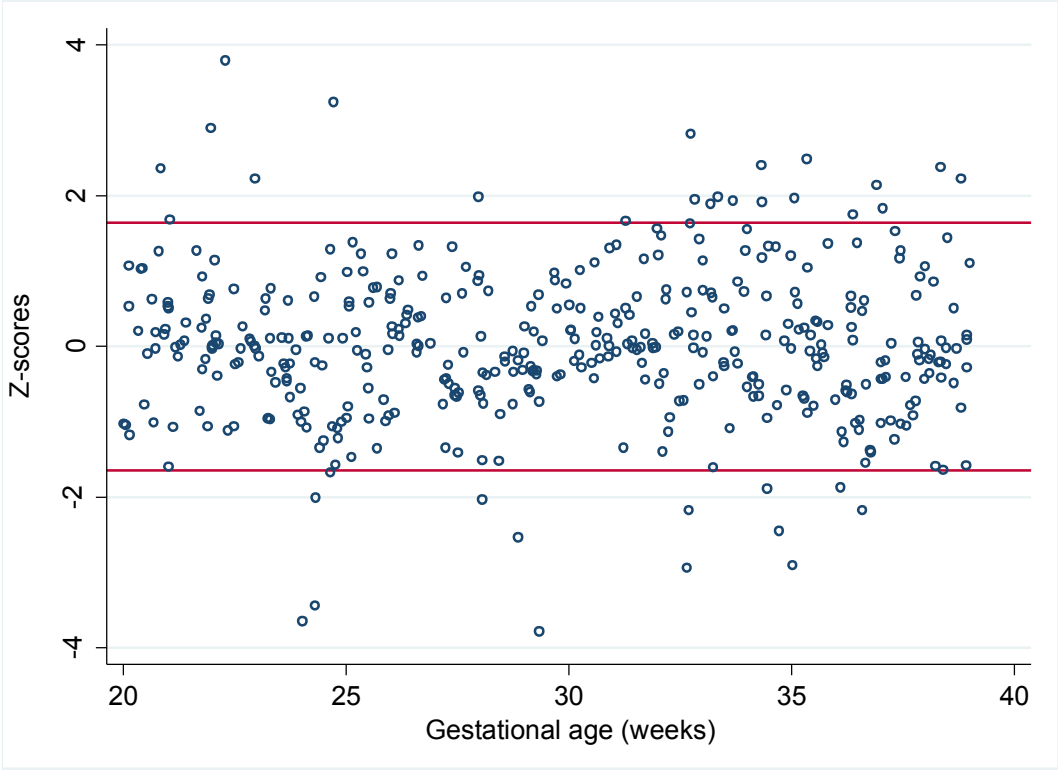

Figure 4.2 d : Z-values versus gestational age

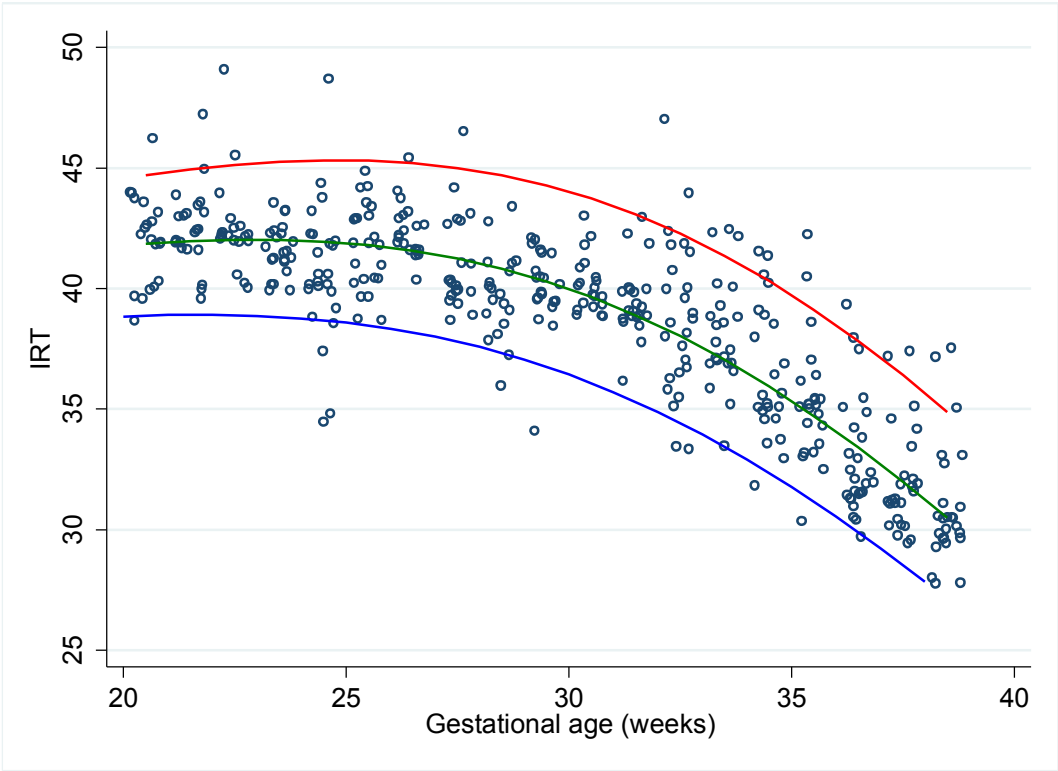

Figure 4.2 e: The 5th, 50th and 95th centile curves of IRT

4.5 DISCUSSION

This study has demonstrated that the mod-MPI of the left fetal heart remained relatively constant from 20 to 26 weeks gestation but decreased steadily thereafter from 27 to 38 weeks gestation. The decrease in MPI was mainly due to a decrease in the IRT as the ICT and ET remained relatively constant. This is in contrast to other studies which showed no variation of MPI with advancing gestational age[7,9] , while another large study showed the mod-MPI to be relatively constant, with a slight increase with advancing gestational age[8]. The first study of MPI in the fetus using the originally described technique by Tei et al[3], demonstrated a decrease in the MPI with advancing gestational age[5]. Tsutsumi et al[5] also reported that the MPI decreased markedly after 34 weeks gestation. However the method of acquisition in the study by Tsutsumi et al[5] using two different waveforms at different times, showed wide variability.

Diastolic flow velocity waveforms show a typical biphasic pattern with an early peak diastolic velocity (E wave) and a second peak during atrial contraction (A wave). In fetuses, E wave is smaller than the A wave and with advancing gestation the E/A ratio increases towards equality[12], and becomes inversed after birth. In normal adults the E wave is always greater than the A wave. The IRT in adults is significantly and negatively correlated with acceleration of the E wave, showing its fundamental relation to the force responsible for early diastolic filling[13]. In other words the IRT and E/A ratio are inversely related[13,14,15,16]. Furthermore IRT has been seen as little more than a brief period between the end of ejection and the start of filling. Its

physiological significance relates to 2 distinct processes of duration and extent of inco-ordinate ventricular wall motion[13]. The duration of IRT depends upon loading conditions. Left ventricular filling pressures act through an effect upon IRT[17]. Thus IRT and early filling pressures are inextricably linked. If we extrapolate this idea to the fetus, the mild reduction in MPI with advancing gestation can be explained: an increasing E wave in the fetus relates to better passive filling of the ventricle resulting in better left ventricular filling pressure which may be due to that important component affecting IRT viz better wall motion coordination. As IRT is inversely related to E/A ratio (extrapolating from adult cardiology), as E increases, the E/A ratio increases and IRT should accordingly decrease, which would result in a mild decrease in Mod-MPI with advancing gestation. A previous study has also noted a trend towards an inverse relation between the E/A ratio and IRT in fetuses[9] . An increase in ET and decrease in ICT was also noted in their study[9] resulting in a constant MPI as opposed to the study by Hernandez-Andrade et al[8] where the ET was shown to decrease, ICT remained constant and IRT increased. In our study the ET and ICT remained constant whilst it was the only the IRT that decreased resulting in the decreasing MPI.

Fetal cardiac physiology undergoes significant changes with advancing gestation. Fetal heart volume increases from a mean of 3.09ml at 20 weeks to 9.18ml at 26 weeks and 24.89ml at 34 weeks[18], left cardiac output increases from 43.45ml/min to 139ml/min at 26 weeks and 284ml/min at 34 weeks and stroke volume increases from 0.3ml to 1.03ml at 26 weeks to 2.67ml at 34 weeks[19]. From 20-26 weeks the

Mod-MPI in our study remained relatively constant at 0.40 (50th percentile) and then decreased steadily from 27 to 38 weeks. This decreasing MPI, especially from 27 weeks gestation maybe as a result of substantial increases in cardiac volume, cardiac output and stroke volume indicating better cardiac function with advancing gestation. The relatively constant MPI from 20 to 26 weeks may be related to the fact that cardiac volumes are still small and not enough to effect substantial changes in function to reflect a decrease in MPI. The dynamic MPI noted in our study especially from the early 3rd trimester is consistent with the marked changes in the fetal heart both anatomically and physiologically with advancing gestation. This is in line with the study by Tsutsumi et al[5] where the MPI decreased acceleratively after 34 weeks gestation. Fetal cardiac maturation which is as a result of increases in the ratio of contractile to non-contractile elements as well as changes in myofilament diameters within the myocardium[20,21], is associated with an improvement in ventricular compliance causing progressively higher peak E waves[12,21] resulting in progressively greater amount of blood flow into the ventricle during the early part of diastole. It is likely that these maturational and developmental changes in myocardial performance in utero acting synergistically results in the decreasing trend of the MPI noted with advancing gestation notably from the early 3rd trimester. This study contributes to a better understanding of fetal cardiac physiology with advancing gestation, underlining the relationships of the various components of the cardiac cycle to ventricular diastole, and ultimately to the myocardial performance index.

The 50th percentile values for the mod-MPI in our study corresponded to 0.4 at 20 weeks and 0.33 at 38 weeks which were in slight variance to the 50th percentile values of the Hernandez-Andrade et al[8] study which corresponded to 0.35 at 20 weeks and 0.37 at the end of pregnancy and also in variance to Van Mieghem et al[9] who reported a mean MPI of 0.36. The 95th percentiles in our study corresponded to 0.43-0.37 (20 -38 weeks), compared to 0.43-0.45 (20-38 weeks) in the study by Hernandez-Andrade et al. and a mean MPI of 0.43 in the study by Van Miegham et al[9].

Construction of the MPI reference values paves the way for its use in the clinical setting and allows us to test its use in prediction of adverse outcome in complicated obstetrics. A number of high risk obstetric conditions in particular pre-eclampsia, intra-uterine growth restriction and diabetes mellitus have a significant impact on the fetal heart[22,23,24] albeit from different pathophysiological pathways that include hypoxia, metabolic acidosis and increased fetal cardiac afterload. The reference values obtained in this study will be tested in the above conditions in future studies to determine if it is in fact a prognostic marker and if so whether different thresholds (rather than the 95th percentile) are predictive of adverse outcome and thus assist in clinical decision making.

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CHAPTER 5:

FETAL CARDIAC FUNCTION IN PREGNANCIES

COMPLICATED BY GESTATIONAL DIABETES

5.1 ABSTRACT

Aim:

To determine whether there are any changes in cardiac function in fetuses of gestational diabetics and whether any of these changes influence perinatal outcome.

Methods:

Twenty nine women with gestational diabetes on insulin therapy in the 3rd trimester of pregnancy attending the Fetal Unit at Inkosi Albert Luthuli Central Hospital in Durban, South Africa were recruited and matched with twenty nine women with normal pregnancies which served as the control group. Using Doppler echocardiography the Mod-MPI and E/A ratios were determined. In addition sonographic data including fetal weights and amniotic fluid indices were determined. The umbilical artery (UA) resistance index (RI), middle cerebral artery (MCA) RI and ductus venosus (DV) pulsatility index (PI), were also determined in both groups. Pregnancy outcomes were recorded in both groups.

Results:

The median Mod-MPI was increased (0.59 vs 0.38; p <0.0001) and the median E/A ratio was decreased (0.65 vs 0.76; p <0.0001) in fetuses of diabetic mothers compared to controls. An MPI > 0.52 had a sensitivity of 100% and specificity of 92% for an abnormal fetal outcome in the diabetic pregnancy. Seventeen of the 29 fetuses in the study group had an adverse outcome with all having an MPI > 0.52 including sixteen admitted to NICU, one stillbirth and one neonatal death. No abnormal outcomes were demonstrated in the control group. Fetal Doppler indices including umbilical artery RI, middle cerebral artery RI and ductus venosus PI were similar in both groups. The fetuses of the diabetic pregnancies were heavier compared to controls at the sonographic assessment (2771g vs 2555g – p <0.005) and at birth (3310g vs 2910g- p<0.0001). The amniotic fluid index (18.1 cm vs 12.9cm – p <0.0001) was also increased in diabetic pregnancies.

Conclusions:

There is significant impairment of cardiac function in fetuses of gestational diabetics which resulted in adverse perinatal outcome. Cut-off values of the Mod-MPI for adverse outcomes have been established. The mod-MPI and E/A ratio has the potential to be integrated into routine fetal surveillance techniques in diabetic pregnancies enabling clinicians in ascertaining the timing of delivery and thus reducing perinatal morbidity and mortality.

5.2 INTRODUCTION:

Fetal echocardiography has been used for non-invasive evaluation of human fetal cardiac anatomy, function and haemodynamics[1,2,3] . A Doppler index of combined systolic and diastolic ventricular myocardial performance, the Tei index or myocardial performance index (MPI) has been proposed as a potential useful predictor of global cardiac function which is not influenced by ventricular geometry and heart rate[1]. MPI or the Tei index is defined as the sum of the isovolumetric contraction time (ICT) and isovolumetric relaxation time (IRT) divided by ejection time (ET).[1,2,3] The equation of the MPI is thus: (ICT + IRT)/ET. To improve reproducibility, the technique of acquisition has evolved to a modified MPI.[4,5,6]

Fetal complications in gestational or pregestational diabetes without microvascular complications are not related to placental insufficiency but rather fetal hyperinsulinism[7]. The best antenatal screening method of pregnancies in diabetic mothers remains elusive. Umbilical artery Doppler velocimetry is widely used to monitor high risk pregnancies because it is considered to be the best available method of fetal surveillance; however it has not been shown to be as effective as a test of fetal wellbeing in diabetic pregnancies[8]. Umbilical artery Doppler velocimetry basically reflects resistance to placental blood flow . The use of ductus venosus Doppler velocimetry can also not be universally recommended for monitoring fetuses of diabetic pregnancy as the specificity and sensitivity is unsatisfactory for routine use.[9]

Doppler measurements of flow velocity in the uterine and fetal circulations have brought us far in identifying placental insufficiency but for most diabetic pregnancies they are neither appropriate or sufficient.

Impaired cardiac function in fetuses of diabetic pregnancies in the second and third trimesters is well documented. Increases of interventricular septal thickness and an associated decrease in the ratio between the peak velocities during early passive ventricular filling and active atrial filling at the level of the atrioventricular valves have been documented[10]. Other studies have also shown development of myocardial dysfunction due to alterations in ventricular compliance[11].

Increased MPI that suggests impairment of global myocardial performance have been reported in small numbers of fetuses of diabetic mothers in mid- to late gestation but their methodology of calculating the MPI in different cardiac cycles may have problems in reproducibility[12,13] . Figuera et al[14] also demonstrated a modest increase in Mod-MPI values in fetuses of diabetic mothers. Their study group however comprised a heterogeneous diabetic population (gestational, pregestational, those on insulin therapy and those on diet). They did not demonstrate any significant differences in mod-MPI antenatally , between newborns with versus without neonatal complications although they do concede that this may be due to the small number of fetuses that presented with complications, which may ultimately have to do with their study population.

This study will investigate cardiac function using the Mod-MPI and E/A ratios in fetuses of gestational diabetics on insulin therapy to determine whether these parameters if altered influence perinatal outcome.

5.3 METHODS:

This was a prospective cross sectional study of the Mod-MPI and E/A ratios in fetuses of diabetic pregnancies conducted at the tertiary referral Fetal Unit at Inkosi Albert Luthuli Central Hospital in Durban, South Africa. Twenty nine women with gestational diabetes on insulin therapy in the 3rd trimester were recruited and matched with 29 women with normal pregnancies which served as the control group. Exclusion criteria were, multiple pregnancies, congenital malformations and/or evidence of placental mediated disease. Ethical approval was obtained from the Biomedical Research Ethics Committee at the University of Kwa-Zulu Natal. . Using Doppler echocardiography the Mod-MPI and E/A ratios were determined. In addition sonographic data including fetal weights and amniotic fluid indices were determined. The umbilical artery RI, middle cerebral artery RI and ductus venosus PI, were also determined in both groups. Pregnancy outcomes were recorded in both groups. An abnormal outcome was recorded if any of the followed occurred: Stillbirth, neonatal death, NICU admission, hypoglycemia, polycythaemia, pulmonary oedema and cardiomyopathy. Cardiac Doppler data was not used by clinicians in the management of the diabetic patients. Delivery of the patients were according to existing standard protocols for diabetic pregnant patients at the institution.

Fetal echocardiography using the E8 Voluson Ultrasound system (GE Medical Systems WI, USA) or Siemens Antares ultrasound system (Siemens Medical Systems Malvern PA, USA) was performed in each woman. The four chamber view,outflow tract views, triple vessel view, longitudinal view of the aortic arch and colour flow mapping were used to screen for cardiac malformations.

The Mod-MPI was calculated in the fetal left ventricle as originally described by Hernandez-Andrade et al[6] . A cross sectional image of the fetal thorax at the level of the 4-chamber view with an apical projection of the heart was obtained. The Doppler sample was opened to 3mm and placed in the internal leaflet of the MV. In this location owing to its closeness to the AV, the opening and closing AV clicks were registered. The angle of insonation was always <30 degrees. E/A waveform was always displayed as positive flow . The Doppler gain was lowered as far as possible to clearly visualize the echoes corresponding to the opening and closing clicks of the two valves at the beginning and at the end of the mitral valve and aortic waveforms. The Doppler sweep velocity was set at 5cm/sec and wall motion filter at 300Hz. The three time periods were estimated as follows : Isovolumetric contraction time (ICT) from beginning of MV closure to AV opening; Ejection time (ET) from AV opening to closure; Isovolumetric relaxation time (IRT) from AV closure to MV opening. The Mod-MPI = (ICT +IRT) /ET.

In addition, E-wave (early ventricular filling) and A wave (active atrial filling) peak velocities and the ratio between them (E/A ratio) at the level of the mitral valve as an index of ventricular diastolic function was performed.

Statistical Methods

Data was collected in MS Excel2004 (Microsoft, redwoods, WA, USA) and analyses were performed using STATA/SE version 12.0 (Stata Corp, College Station, TX, USA). Unpaired t-tests and the Wilcoxon rank sum test were used to compare continuous variables between two groups.

5.4 RESULTS

Twenty nine pregnant women with gestational diabetes mellitus on insulin therapy formed the study group with 29 matched controls. Table 5.1 summarises the demographic, sonographic and cardiac Doppler parameters between the Control and Study groups. The median maternal ages were similar between the groups. The median gestational ages at assessment were the same between the groups. The median fetal weights were 2555g for the study group and 2771g for the control group which was statistically significant at the time of the assessment ($p<0.0045$).

The median birth weights were 2910g for the control group and 3310g for the study group which was also statistically significant ($p<0.0001$). The median AFI corresponded to 12.9cm in the controls compared to 18.10cm in the study group ($p< 0.0001$). E/A ratio was significantly different between groups ($p<0.0001$).

Median Mod-MPI corresponded to 0.38 in the control group and 0.59 in the study group which was statistically significant ($p<0.0001$). This is demonstrated in Fig 5.1 which shows a boxplot of the interquartile ranges of MPI comparing the study group and control groups . Fig. 5.2 demonstrates a scatterplot of Mod-MPI versus gestational age. This graph demonstrates that apart from 4 cases , all cases in the study group had MPI's above 0.43 . The main driving force behind the increased Mod-MPI was the IRT and ET (Fig 5. 3 and Fig 5.5). ICT remained constant between groups (Fig 5.4). Fig5. 6 shows a scatterplot of Mod-MPI versus gestational age with linear predictions from quantile regression superimposed. Mod-MPI decreased with gestational age in both controls and cases. Adjusting for gestational age, the p-value for the effect of group remained statistically significant ($p<0.001$).

The fetal Dopplers reflecting placental resistance were similar in both groups: mean umbilical artery RI : 0.63 and 0.64, mean middle cerebral artery 0.85 and 0.83 and mean ductus venosus PI of 0.56 and 0.54 , study and control groups respectively.

Fig 5.7 demonstrates the distribution of MPI between normal and abnormal outcomes in the study group and correlation to the 95th percentile from the normal ranges study. An abnormal perinatal outcome was reported if one or more of the following complications ensued: stillbirth, neonatal death, NICU admission, tachypnea with pulmonary oedema, hypoglycemia, polycythaemia and cardiomyopathy (Table 5.2). Abnormal outcomes were noted in 17 of the 29 fetuses (all 17 showing an Mod-MPI > 0.52). There were 8 fetuses in the study group who had elevated Mod-MPI's (> 95th percentile) but the Mod-MPI values were < 0.52 and all of these 8 fetuses had normal outcomes (Fig 5.7). Thus there is a link between worsening Mod-MPI values and adverse outcomes. There was a statistically significant difference in Mod-MPI, birth weight and E/A ratios between groups showing normal (n=12) and abnormal outcomes (n=17) in the study group (n=29) [Table 5.3].

At a cut-off MPI value of 0.52, a 100% sensitivity and specificity of 92% for an abnormal outcome was achieved (Table 4). Of note in the study group was that one stillbirth and one early neonatal death was reported and the MPI's for these 2 cases corresponded to 0.70 and 0.67 respectively. Further comment on these 2 cases is given in the discussion.

No abnormal outcomes were noted in the control group.

Table 5.1: Demographic, Sonographic and Cardiac Doppler Data between Control and Diabetic Groups

	Control - Median (IQR)	IDDM - Median (IQR)	p-value
Gestational age (weeks)	35 (34-36)	35 (34-36)	1
Maternal age	32 (30-33)	32 (30- 33)	0.95
AFI (cm)	12.9 (11.9-13.8)	18.10 (16.5 - 23)	<0.0001
EWF (g)	2555 (2410 - 2698)	2771 (2564-2940)	0.0045
Mod-MPI	0.38 (0 .36- 0.39)	0.59 (0.45 -0.62)	<0.0001
IRT (ms)	36 (34- 37)	58 (43-59)	<0.0001
ET (ms)	176(175-178)	157 (150-163)	<0.0001
ICT (ms)	32 (30-33)	33(32-35)	0.0001
EA Ratio	0.76 (0.75-0.78)	0.65 (0.60-0.70)	<0.0001
Birth weight (g)	2910 (2965 – 3017)	3310 (3586-3850)	<0.0001

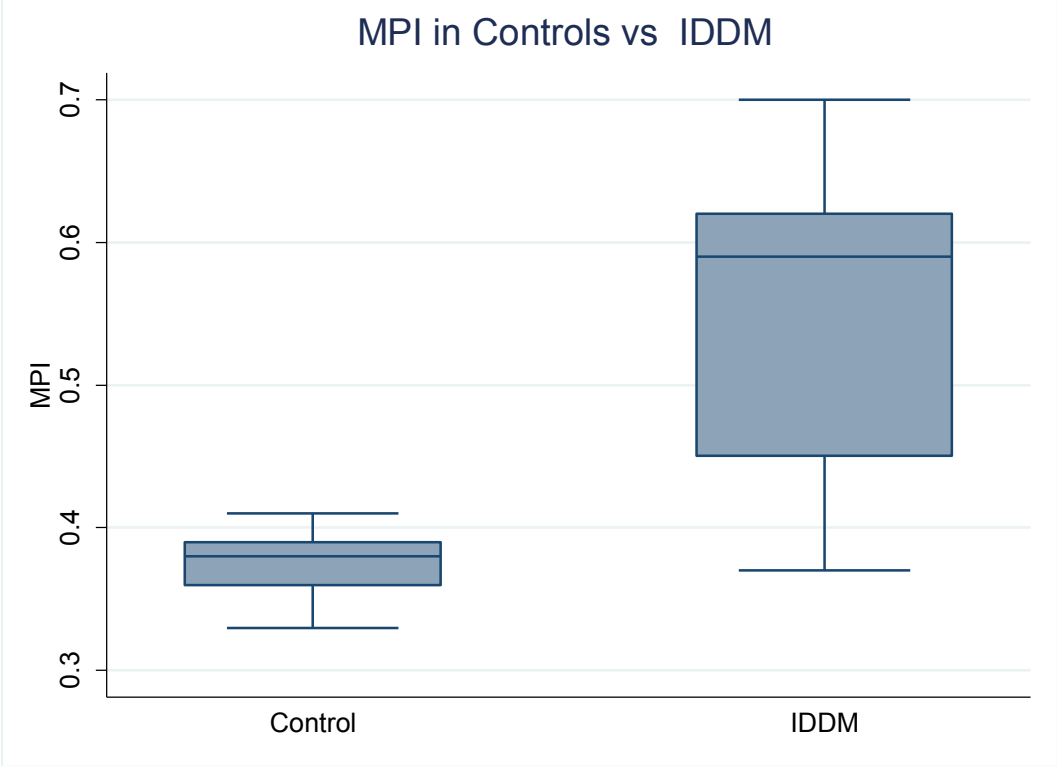

Fig 5.1: Interquartile ranges of MPI in IDDM and control groups

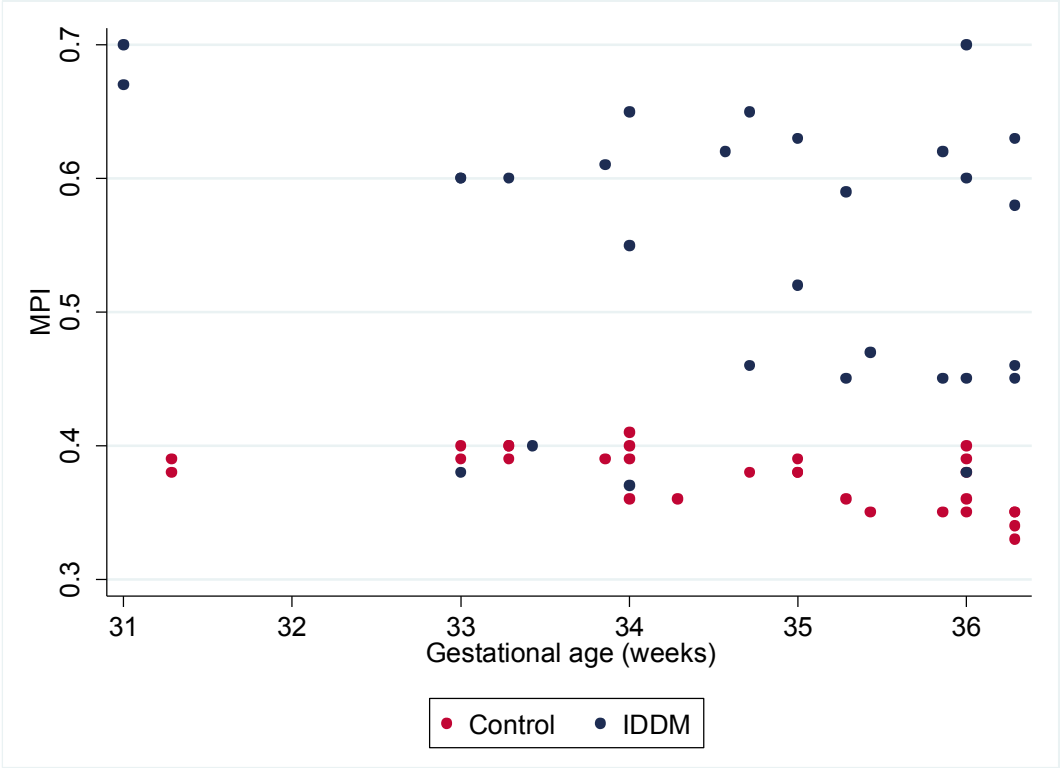

Fig 5.2: Scatterplot of MPI vs Gestational age in IDDM and Control Groups

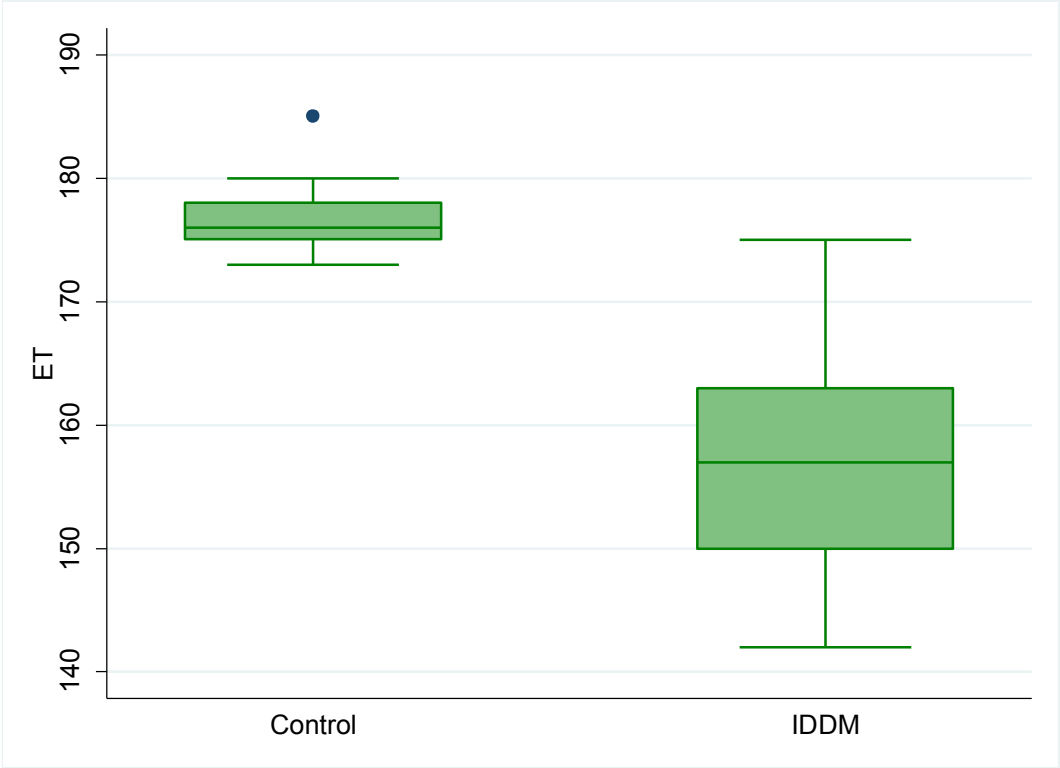

Fig 5.3: Interquartile ranges of ET in IDDM and control groups

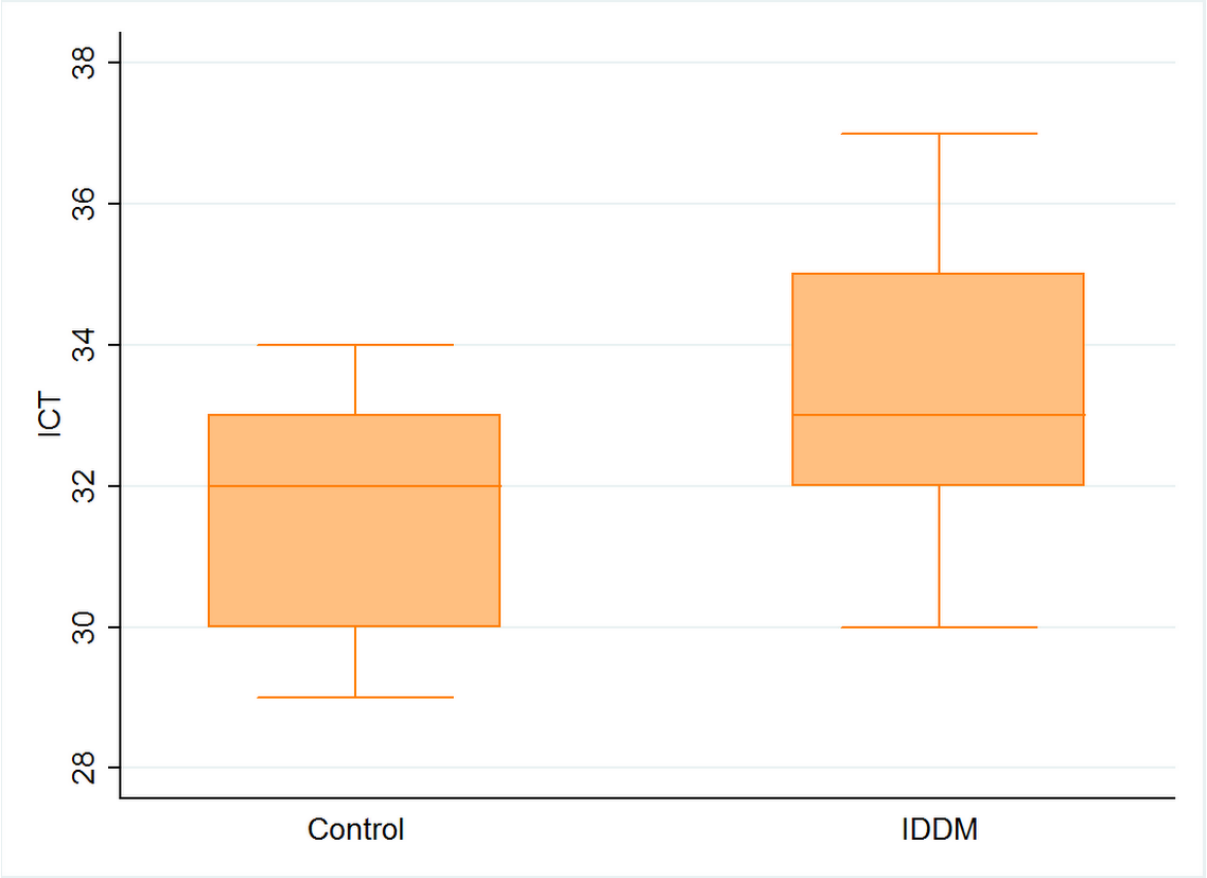

Fig 5.4 : Interquartile ranges of ICT in IDDM and Control groups

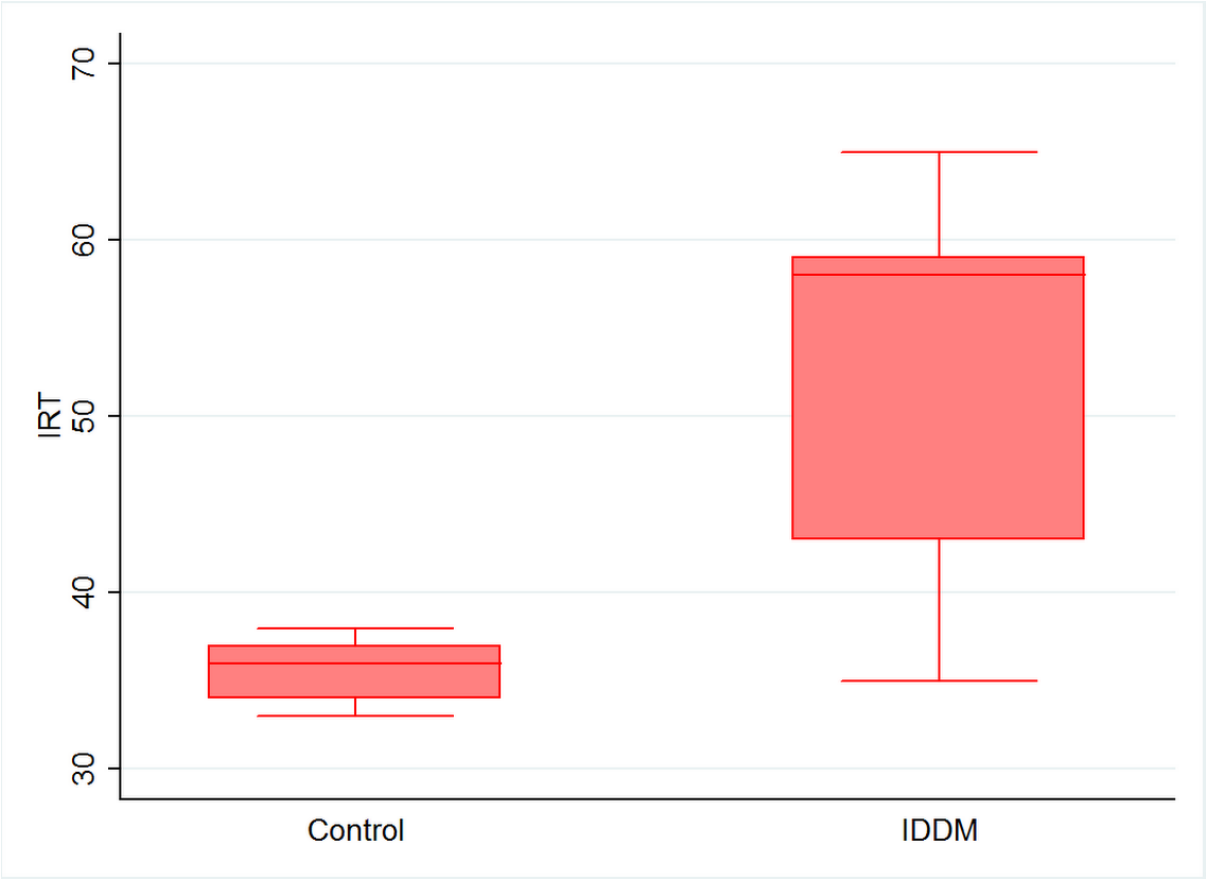

Fig 5.5: Interquartile Ranges of IRT in IDDM control and Control groups

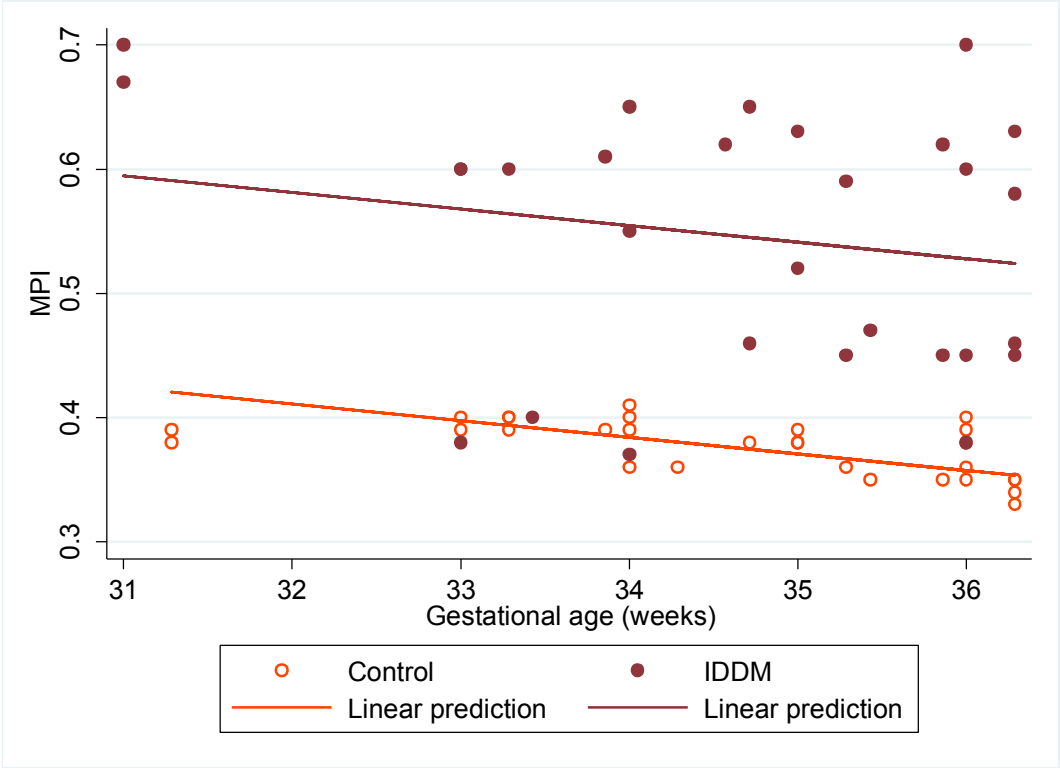

Fig 5.6: Scatterplot of MPI versus gestational age with linear predictions from quantile regression

MPI decreased with gestational age in both controls and cases. Adjusting for gestational age, the p-value for the effect of group remained statistically significant ($p<0.001$).

Table 5.2 : Outcomes in IDDM group and Control groups

Outcomes	Study Group (n=29)	Controls (n=29)
Stillbirth (SB)	1	-
Neonatal Death (NND)	1	-
NICU admission	16	-
Tachypnoea + pulmonary oedema: (PE)	8	-
Hypoglycemia	9	-
Polycythaemia	4	-
Cardiomyopathy	1	-
Normal Outcome	12	29

Table 5.3 : Comparison of variables in the IDDM group between normal and abnormal outcomes

	Normal outcomes (n=12)	Abnormal outcomes (n=17)	p-value
Gestational age (weeks)	35.36 (34.36 -36)	34.57 (33.28- 35.86)	0.1973
Maternal age (years)	31.5 (29.5 – 34)	32 (30 - 32)	0.8581
AFI(cm)	18 (16.4 - 20.5)	19.2 (18 - 23.3)	0.3736
EWF (g)	2789.5 (2571 -2901)	2771 (2564 - 2945)	0.7735
Mod-MPI	0.45 (0.39 - 0.46)	0.62 (0.6 - 0.65)	<0.0001
IRT (ms)	41 (37 - 43.5)	59 (58 - 60)	<0.0001
ET (ms)	163 (162 - 173.5)	150 (145- 155)	0.0001
ICT (ms)	32 (32 - 33)	34 (34 -36)	0.0004
EA Ratio	0.7 (0 .66 - 0.74)	0.6 (0.55 - 0.63)	0.0004
Birth weight (g)	3330 (3195 - 3440)	3825 (3750 - 3920)	0.0006

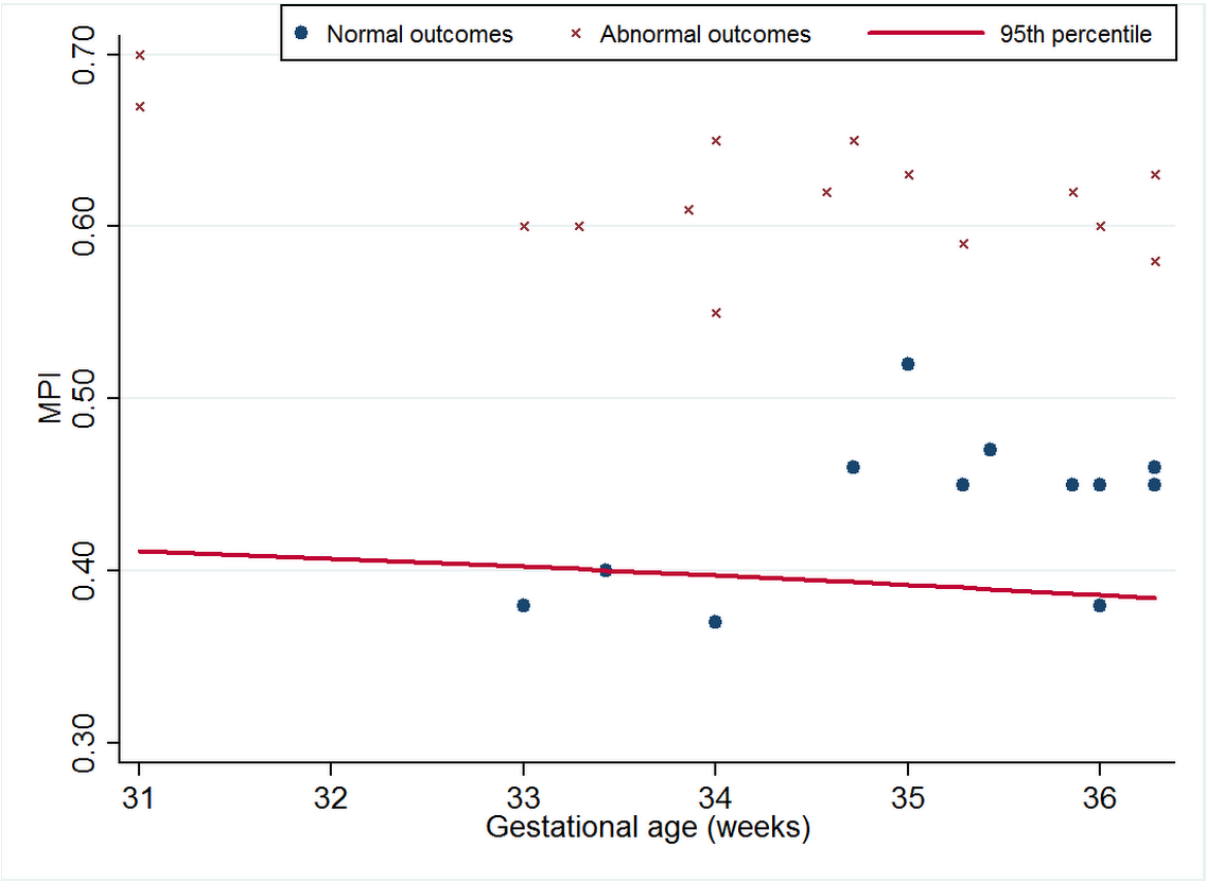

Fig 5.7: Distribution of MPI between normal and abnormal outcomes in the IDDM group and correlation to the 95th percentile from the normal ranges study (Chapter 4).

TABLE 5.4: Sensitivity and Specificity of Mod-MPI cut-offs in prediction of adverse outcome.

Detailed report of Sensitivity and Specificity

Correctly

Cutpoint	Sensitivity	Specificity	Classified	LR+	LR-
(>= .37)	100.00%	0.00%	58.62%	1.0000	
(>= .38)	100.00%	8.33%	62.07%	1.0909	0.0000
(>= .4)	100.00%	25.00%	68.97%	1.3333	0.0000
(>= .45)	100.00%	33.33%	72.41%	1.5000	0.0000
(>= .46)	100.00%	66.67%	86.21%	3.0000	0.0000
(>= .47)	100.00%	83.33%	93.10%	6.0000	0.0000
(>= .52)	100.00%	91.67%	96.55%	12.0000	0.0000
(>= .55)	100.00%	100.00%	100.00%		0.0000
(>= .58)	94.12%	100.00%	96.55%		0.5882
(>= .59)	88.24%	100.00%	93.10%		0.1176

(>= .6)	**58.82%**	**100.00%**	**75.86%**		**0.4118**
(>= .61)	**52.94%**	**100.00%**	**72.41%**		**0.4706**
(>= .62)	**41.18%**	**100.00%**	**65.52%**		**0.5882**
(>= .63)	**29.41%**	**100.00%**	**58.62%**		**0.7059**
(>= .65)	**17.65%**	**100.00%**	**51.72%**		**0.8235**
(>= .67)	**0.00%**	**100.00%**	**41.38%**		**1.0000**
(>= .7)	**100.00%**	**0.00%**	**58.62%**	**1.0000**	
(>.7)	**.%**	**.%**	**.%**		

5.5 DISCUSSION:

This study has shown that the Mod-MPI was significantly increased and the E/A ratios significantly lower in fetuses of diabetic mothers compared to controls. The lower E/A ratio reflects diastolic dysfunction in these fetuses. The increase in the mod-MPI was due to a decrease in ejection time and an increase in the isovolumetric relaxation time. The increase in the isovolumetric relaxation time corroborates the finding of the significantly lower E/A ratio in the diabetic pregnancies indicating diastolic dysfunction. 17 out of 25 fetuses with an elevated Mod-MPI showed abnormal outcomes. Of significance in this study was that abnormal outcomes were related to the severity of an abnormal MPI. A cut-off Mod-MPI value > 0.52 confers a sensitivity of 100% and specificity of 92% for an abnormal outcome. Increased birth weight and low E/A ratios were additional risk factors for an abnormal outcome. The high incidence of transitory tachypnea and/or pulmonary oedema (8 out of 17 infants) in the study group could be the result of diastolic dysfunction as reflected by the low E/A ratios and increased isovolumetric relaxation time in the study group.

There are a number of possible explanations for the above findings. Fetal interventricular septal thickness significantly increases with an associated decrease in the ratio between the peak velocities during early passive ventricular filling and

active atrial filling at the level of the atrioventricular valves.[10] Impaired ventricular compliance has also been reported in fetuses of diabetic pregnancies which could result in diastolic dysfunction[11,15] .This corroborates our finding of diastolic dysfunction in the diabetic pregnancies as evidenced by the decreased E/A ratio and prolongation of the isovolumetric relaxation time. Furthermore fetuses of insulin dependent diabetic pregnancies have an increased preload index in the inferior vena cava which is associated with a lower umbilical arterial blood pH and higher haematocrit at birth, as well as increased neonatal morbidity[16]. These findings suggest that one of the main mechanisms inducing fetal distress in diabetic pregnancies is the development of myocardial dysfunction due to alterations of ventricular compliance in response to an abnormal metabolic milieu and this plays a pivitol role in the genesis of fetal distress and puts the fetus at risk for morbidity and "unexplained"fetal deaths.

Special mention needs to be made of 2 cases, one that ended in a stillbirth and the other in an early neonatal death. In the former case the patient presented at 29 weeks with poorly controlled diabetes, severe polyhydramnios, normal umbilical RI, normal ductus venosus PI and no arterial redistribution but markedly elevated Mod-MPI at 0.70 and abnormal E/A ratio of 0.58. Cardiac Doppler data was not used in the management of the patient. The patient was admitted and closely monitored with umbilical artery RI's and CTG's. The patient remained as an inpatient with close

monitoring until 33 weeks when she developed late decelerations on cardiotocography (CTG); an emergency caesarean section was performed but unfortunately a stillborn was delivered. This despite normal CTG's and UA RI's 24 hours earlier. The 2nd case was seen at 34 weeks which was a mildly macrosomic fetus with a normal umbilical artery RI, no arterial redistribution and normal ductus venosus PI, but markedly elevated Mod- MPI at 0.67 and E/A ratio of 0.6. Cardiac Doppler data was not used in the management of the patient. The patient presented with decreased fetal movements at 36.5 weeks and CTG was found to be suboptimal (2 days prior to admission the umbilical artery RI and CTG's was normal). On this basis the patient was delivered by caesarean section but was extremely asphyxiated at birth and ended in an early neonatal death despite aggressive resuscitation. These 2 cases demonstrate the inability of markers of placental resistance to adequately predict metabolic acidosis whilst the cardiac Doppler parameters of myocardial performance index and E/A ratios appeared to accurately predict fetal compromise in these diabetic pregnancies. It also importantly links the severity of the MPI and E/A ratio to severity of outcome.

Figuera et al[14] also demonstrated increased Mod-MPI in fetuses of diabetic mothers compared to controls but the increase in Mod- MPI in their study (average Mod-MPI of 0.42 in gestational diabetics and 0.45 in pregestational diabetics) was modest as compared to our study. The profile of patients in their study group was a mixture of

patients with impaired glucose tolerance and frank diabetics with only 14 out of 32 patients requiring insulin therapy in the gestational diabetic group, and judging from the small number of fetuses with complications in the study group, it appeared that their study group mostly comprised pregnant diabetics in the milder spectrum of disease. This would explain the milder increases in mod- MPI in their study and would also be in line by the study of Wong et al[17] and Gardiner et al[18] who demonstrated a link between metabolic control during pregnancy and functional fetal heart alterations. The finding in our study that no abnormal outcomes were noted at MPI's below 0.52 is inkeeping with the study by Figuera et al[14] where the mean MPI's in their gestational and pre-gestational diabetics corresponded to 0.42 and 0.45 respectively (modest increase) and they did not find any differences in neonatal complications with their control group.

Fetal complications in gestational diabetes or established diabetes mellitus without microvascular complications are not related to placental insufficiency but rather fetal hyperinsulinism[7] resulting in augmented growth and increased metabolism. This is corroborated in our study by finding no differences in the UA RI, MCA RI and DV PIV in the study and control groups. A powerful and critical finding in diabetic pregnancies is that significant acidaemia and hyperlacticaemia can occur in fetuses in the absence of hypoxaemia[19,20,21]. Unexplained stillbirths of diabetic pregnancies is most likely due to fetal acidaemia as a consequence of increased metabolic rate. A

significant association was also reported between fetal plasma insulin concentration and the degree of fetal acidaemia[7]. Hyperinsulinaemia results in an increased metabolic rate which results in increased glucose oxidation and oxygen consumption. The capacity for oxidative metabolism is reduced in fetuses due to low pyruvate dehydrogenase activity thus increasing the risk for acidosis. This leads to the conclusion that fetal monitoring models have to recognize the pathophysiology outlined above. Standard fetal monitoring models presently used in diabetic pregnancies are inappropriate and insufficient.

This study has documented abnormal outcomes in diabetic pregnancies at Mod-MPI's > 0.52. A link has thus been established between elevated Mod-MPI's and an abnormal metabolic milieu. Furthermore this study has also established a link between severity of the Mod-MPI and abnormal outcomes. This makes the Mod-MPI an attractive monitoring tool of the fetus in the diabetic pregnancy to detect compromise by synchronizing with an abnormal metabolic state. The MPI may be the only non-invasive technique in monitoring fetuses of severe gestational diabetics to detect a significantly abnormal metabolic milieu. We believe that our study significantly contributes to the debate of how to monitor the diabetic pregnancy. This technique we believe has the potential to be integrated into the routine fetal surveillance techniques of diabetic pregnancies, to reduce morbidity and mortality and serve as a guide to clinicians in timing of delivery.

To our knowledge this is the first study to demonstrate a clear relationship between an altered mod-MPI and adverse fetal and neonatal outcome in diabetic pregnancies. The mod-MPI holds great promise as a monitoring tool for fetuses in severe or poorly controlled diabetic pregnancies.

5.6 References

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CHAPTER 6

FETAL CARDIAC FUNCTION IN PREGNANCIES COMPLICATED BY INTRAUTERINE GROWTH RESTRICTION

6.1 ABSTRACT

Aim:

To determine whether fetuses with intrauterine growth restriction have cardiac dysfunction and whether this dysfunction influences perinatal outcome.

Method:

Forty three consecutive pregnant women attending the Fetal Unit at Inkosi Albert Luthuli Central Hospital in Durban, South Africa with IUGR in the 3rd trimester of pregnancy were matched with 43 normal pregnant women. IUGR was diagnosed sonographically by an abdominal circumference (AC) below the 10th percentile for gestational age and with an umbilical artery resistance index (RI) > 2 standard deviations above the mean. The study group was further subdivided on the basis of degree of abnormality of the umbilical artery resistance index(RI), middle cerebral artery resistance index (RI) and ductus venosus pulsatlity index (PI) into different grades of growth restriction viz. uncompensated, compensated and critical status. Doppler echocardiography for cardiac dysfunction was determined by using the Mod-MPI and E/A ratios. The pregnancy outcomes were recorded in both groups. ROC curves were used to evaluate the overall diagnostic accuracy of Mod-MPI in predicting adverse outcome and perinatal mortality.

Results:

The maternal age was similar in both groups. The median AFI was 8.9 vs 12.8cm ($p < 0.0001$) in the IUGR and control groups respectively. The median Mod-MPI was significantly higher in growth-restricted fetuses compared to controls (0.59 vs 0.37- $p < 0.001$). The median Mod-MPI increased with severity of IUGR and was 0.52, 0.6 and 0.7 in the uncompensated, compensated and critical groups respectively. A cut-off Mod-MPI value of 0.54 conferred a sensitivity of 87%, specificity of 75% and a likelihood ratio (LR) of 3.47 for an adverse outcome. The area under the ROC curve for Mod-MPI in prediction of adverse outcome was significant at 0.94. A cut-off Mod-MPI value of 0.67 conferred a sensitivity of 100%, specificity of 81% and LR of 5.28 for perinatal death. The area under the ROC curve for Mod-MPI in prediction of perinatal death was significant at 0.97. The E/A ratios were lower in the growth restricted fetuses (0.62 vs 0.79; $p < 0.0001$). The mean birth weight was 2156 g, 1910g and 920g in the uncompensated, compensated and critical status groups. Adverse pregnancy outcome increased with severity of IUGR from 25% in the uncompensated group, 60% in the compensated group and 79% in the critical group.

Conclusion

There was significant impairment of cardiac function in growth restricted fetuses with the myocardial performance deteriorating with severity of growth restriction. Cut-off Mod-MPI values for abnormal outcomes including perinatal death have been established. The mod-MPI was abnormal before hypoxia or acidosis set in and this can thus be regarded as a “warning” parameter of impending compromise. The Mod-MPI has the potential to be integrated into routine surveillance techniques of the growth restricted fetus. This may assist the clinician to ascertain timeous delivery and thus reduce perinatal morbidity and mortality.

6.2 INTRODUCTION

Fetal echocardiography has been used for non-invasive evaluation of fetal cardiac anatomy, function and haemodynamics[1,2,3] . A new Doppler index of combined systolic and diastolic ventricular myocardial performance, the Tei index or myocardial performance index (MPI), has been proposed as a potential useful predictor of global cardiac function, which is not influenced by ventricular geometry and heart rate[3]. The MPI is defined as the sum of the isovolumetric contraction time (ICT) and isovolumetric relaxation time (IRT) divided by ejection time (ET).[1,2,3] The equation of the MPI is thus: (ICT + IRT)/ET. The technique of acquisition has evolved to a modified MPI (Mod-MPI), which was used in this study[4,5,6].

Fetuses with early onset intrauterine growth restriction (IUGR) are at increased risk for adverse short and long-term outcomes[7-10]. The heart plays a central role in the fetal adaptive mechanisms to placental insufficiency and hypoxia. Elevated fetal levels of atrial and B-type natriuretic peptides, and significant alterations in echocardiographic parameters have been reported in small-for-dates babies[11,12]. These alterations in growth restricted fetuses include impaired ventricular filling (lower E/A ratios)[13] , lower peak velocities in the aorta and pulmonary arteries[14], increased aortic and decreased pulmonary time to peak velocity[15] and a relative increase of left cardiac output associated with decreased right cardiac output [16]. These cardiac haemodynamic changes lead to a preferential shift of cardiac output in favour of the left ventricle thus improving cerebral perfusion. This demonstrates the

pivotal role of the heart in the compensatory mechanisms of the growth restricted fetus.

An increased MPI has been reported in growth restricted fetuses[17,18]. However, the methodology employed by Tsutsumi et al[17] (two different wave- form technique) in obtaining the MPI had a problem in reproducibility and the study by Crispi et al[18] did not report absolute MPI values and ranges to specific adverse pregnancy and neonatal outcomes. In this study we sought to elucidate cardiac function as reflected by the MPI and E/A ratios in the IUGR fetus and compared these parameters to a control group of appropriately grown fetuses. In addition, we also aimed to compare MPI values in each grade (uncompensated, compensated and critical status)of growth restriction. We also aim to determine whether the MPI influences perinatal outcome and thereby be used as a prediction tool in pregnancy management.

6.3 METHODS

The study was approved by the Bioethics Committee of the University of Kwa-Zulu Natal.

Forty three singleton fetuses between 28 and 36 weeks gestation, diagnosed with intrauterine growth restriction on ultrasound (abdominal circumference below the 10^{th} percentile for gestational age and an abnormal umbilical artery resistance index > 2 standard deviations[16]) were recruited to the study. Exclusion criteria were congenital malformations, multiple pregnancies and chromosomal anomalies. Forty three women with normal pregnancies were matched for gestational age and served as the control group. IUGR was categorized into 3 types (uncompensated, compensated and critical status IUGR), reflecting fetal response to placental insufficiency and degree of placental vascular resistance. Uncompensated IUGR was defined by the following: AC < 10^{th} percentile for gestational age, elevated umbilical artery RI with no arterial redistribution and normal venous Doppler. Compensated IUGR had in addition a middle cerebral artery RI below the 5^{th} centile for gestational age reflecting arterial redistribution. Critical status IUGR was defined when there was absent or reversed end diastolic flow in the umbilical artery and/or severe venous Doppler anomalies as reflected in the finding of absent or reversed flow during atrial contraction in the ductus venosus.

Sonographic data included fetal weight for gestational age and amniotic fluid index whilst Doppler data that included Mod-MPI, E/A ratio, umbilical artery resistance index, middle cerebral artery resistance index and ductus venosus Doppler.

Fetal echocardiography was performed using an E8 General Electric Voluson ultrasound system (GE Medical Systems, WI, USA) or the Siemans Antares ultrasound system (Siemens Medical systems, Malvern, PA, USA) were used. The four chamber view, outflow tract views, triple vessel view, longitudinal view of the aortic arch and ductus arch and colour flow mapping were used to screen for cardiac malformations.

The Mod-MPI was calculated in the fetal left ventricle as originally described by Hernandez-Andrade et al[6]. A cross sectional image of the fetal thorax at the level of the 4-chamber view with an apical projection of the heart was obtained. The Doppler sample was opened to 3mm and placed in the internal leaflet of the MV. In this location owing to its closeness to the AV, the opening and closing AV clicks were registered. The angle of insonation was always <30 degrees. E/A waveform were always displayed as positive flow. The Doppler gain was lowered as far as possible to clearly visualize the echoes corresponding to the opening and closing clicks of the two valves at the beginning and at the end of the mitral valve and aortic waveforms. The Doppler sweep velocity was set at 5cm/sec and the wall motion filter at 300Hz. The three time periods were estimated as follows : ICT: from beginning of MV closure to AV opening; ET: from AV opening to closure and IRT: from AV closure to

MV opening. The Mod-MPI = (ICT +IRT) /ET

In addition, E-wave (early ventricular filling) and A wave (active atrial filling) peak velocities and the ratio between them (E/A ratio) at the level of the mitral valve as an index of ventricular diastolic function was performed.

The clinicians were blinded to the cardiac Doppler data. Delivery was indicated according to standard obstetric practice: reversed end diastolic flow in the umbilical artery, reversed or absent end-diastolic flow in the DV or decelerative cardiotocography > 28 weeks gestation.

Statistical analysis

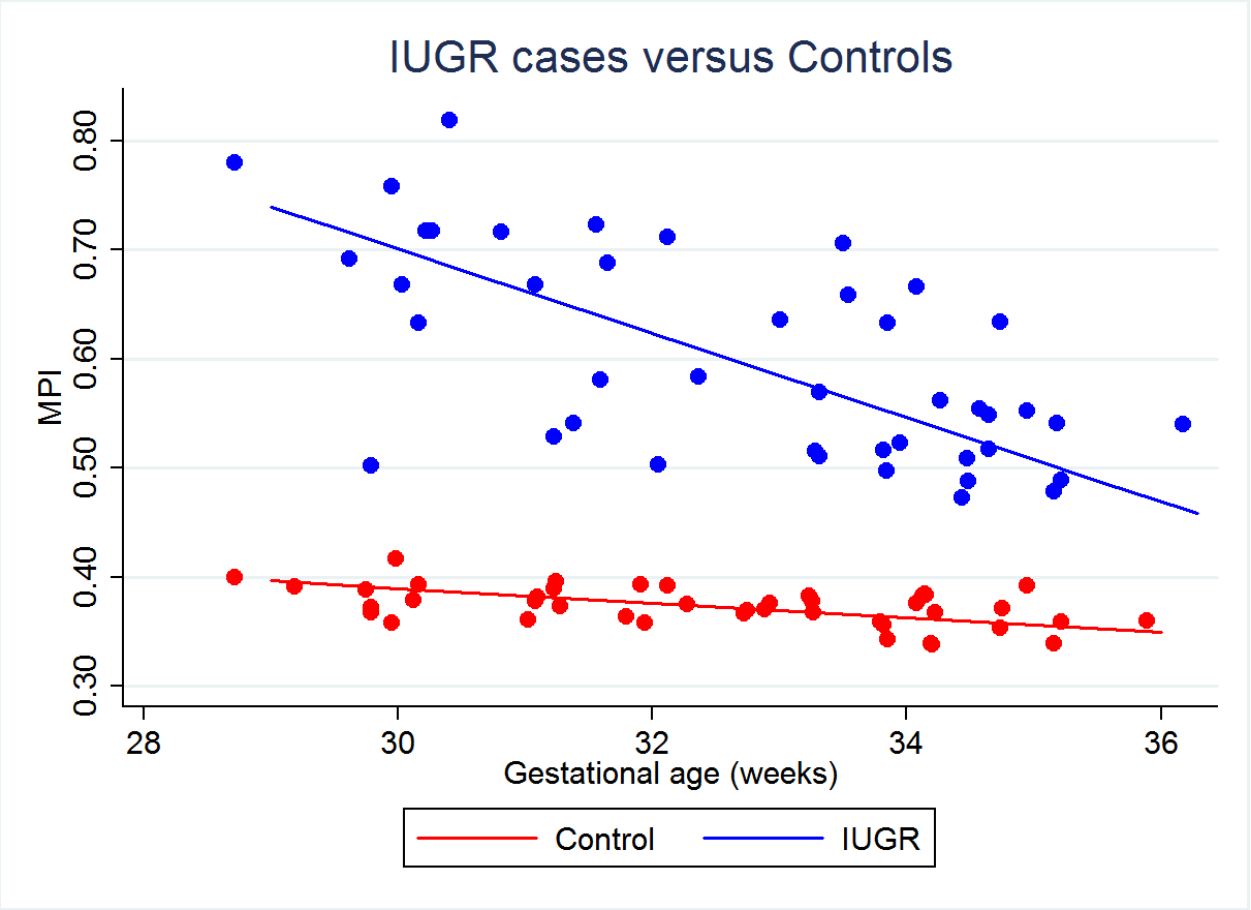
All statistical analysis was performed using STATA/SE version 12.0 (Stata Corp, College Station, Tx, USA). Spearman's rank correlation was computed to assess the correlation between MPI and gestational age within each group. The Shapiro-Wilk ***W*** -test was used to test for normality. All skewed variables are reported as medians with inter-quartile ranges. Multivariable 50^{th} percentile (Median) Quartile regression was used to determine whether there was a significant difference in the median Mod-MPI between growth restricted and normal fetuses (control group) while adjusting for the effect of gestational age. A gestational age and group interaction term was included in the model. We applied the Kruskal Wallis test to

perform the overall comparison between the uncompensated, compensated and critical groups. The Wilcoxon rank sum test was used for pairwise differences.

6.4 RESULTS

The results presented below are based on 86 fetuses. The mean gestational age of the fetuses were 32.58 weeks with a standard deviation of 1.89. The median Mod-MPI was significantly higher in growth-restricted fetuses compared to controls (0.59 vs 0.37- $p < 0.001$) (Table 6.1). There was a decrease in Mod-MPI with gestational age in the 43 normal fetuses (Spearman's correlation coefficient -0.967, $p <0.0001$). Within the growth restricted group there was a negative correlation between the Mod-MPI and gestational age (Spearman's correlation co-efficient -0.595, $p < 0.0001$). The median Mod-MPI, after adjusting for the effect of gestational age, was significantly higher in the growth restricted fetuses ($p <0.001$). There was a significant interaction between group and gestational age. Hence the rate of change in median MPI with increasing gestational age differed in the IUGR and control group. This relationship is illustrated in Figure 6.1.

Figure 6.1: MPI in IUGR and Control groups



The 43 growth restricted fetuses were classified as uncompensated, compensated or critical. Twenty (45.51%) fetuses were classified as uncompensated, 10 as compensated and 13 (30.82%) were critical. The critical group had the highest median Mod-MPI (Table 6.2 and Figure 6.2). The distribution of the Mod-MPI was significantly different between the three groups ($p<0.0001$). We found a statistically significant difference in the Mod-MPI for each of the following pairwise comparisons: Compensated vs Critical, Critical vs Uncompensated and Compensated vs Uncompensated ($p < 0.001$ in all comparisons).

The median E/A ratios, amniotic fluid indices and fetal weights were all significantly different between the Control and IUGR groups (Table 6.1).

Table 6.1: Demographic and Sonographic Data in IUGR and Controls

	Control (n = 43)	IUGR (n = 43)	p-value
	Median (IQR)	Median (IQR)	
Maternal age (mean(SD))	29.62 (3.61)	29.67(3.59)	0.9535
AFI (cm)	12.8 (12.2 - 13.4)	8.95 (7.95 - 10.1)	<0.0001
EWF (g)	2134 (1688 – 2436)	1559.5 (1042 - 1897.5)	<0.0001
E/A ratio	0.79 (0.78-08)	0.63 (0.57-0.67)	<0.0001
Median MPI (IQR)	0.37 (0.36-0.38)	0.59 (0.52-0.69)	<0.001

Table 6.2: Median MPI in IUGR Categories

	Median (IQR)
Uncompensated (n = 20)	0.52 (0.50 -0.52)
Compensated (n = 10)	0.6 (0.6-0.65)
Critical (n = 13)	0.7 (0.69-0.73)

Figure 6.2: Distribution of MPI in each of the IUGR grades

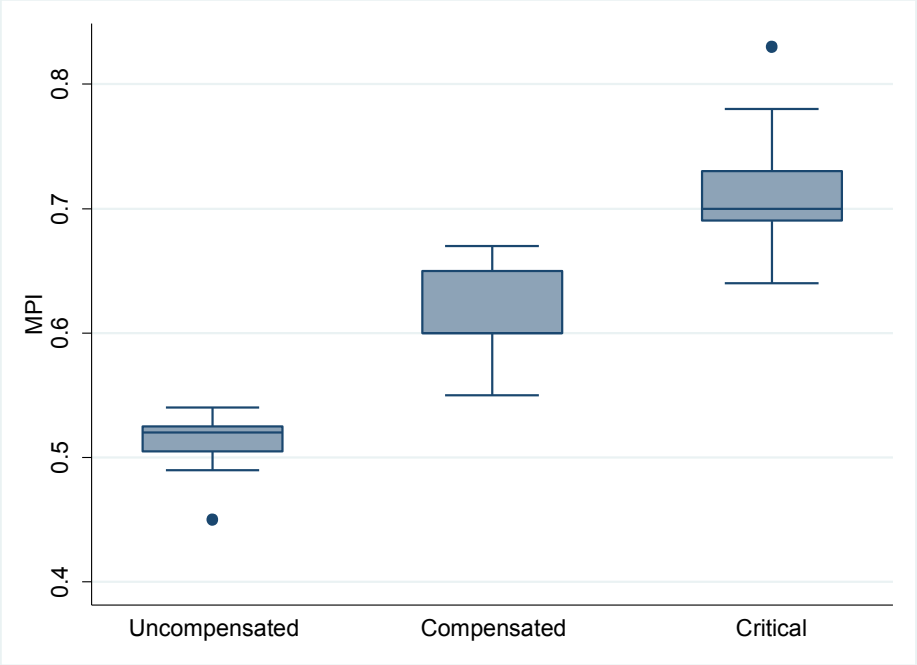
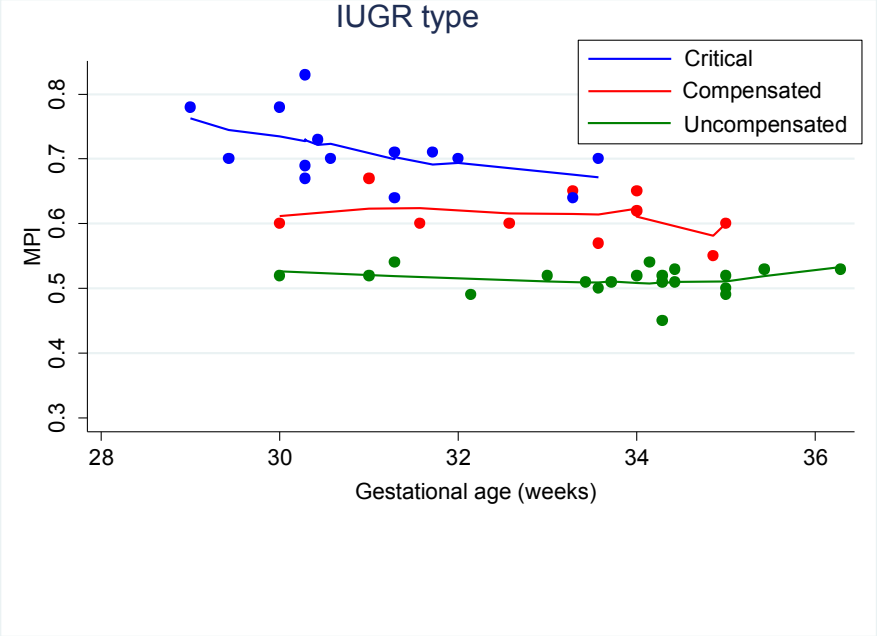


Fig 6.3: IUGR grades vs Mod-MPI and correlation with gestational age

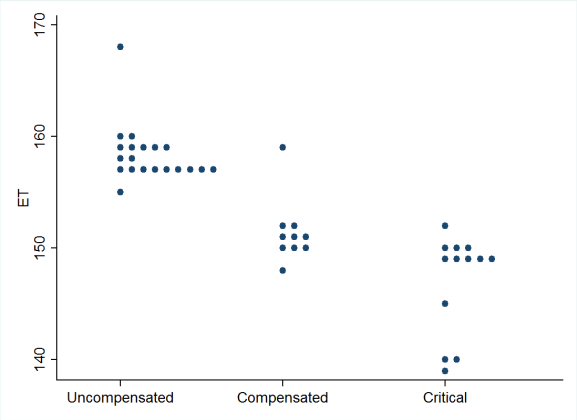


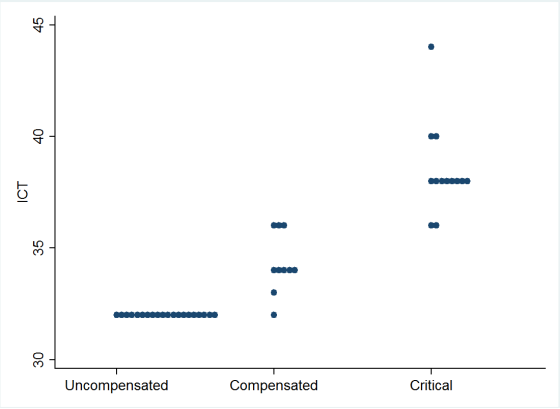
Median MPI in each IUGR grade with fitted Lowess smoother lines versus gestational age.

Table 6.3 : Components of MPI in the different IUGR grades

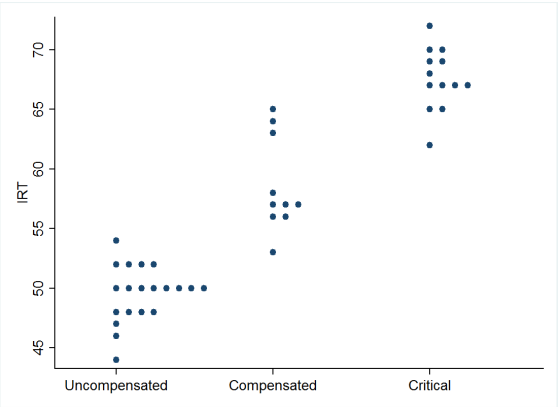
Variable	Uncompensated	Compensated	Critical
Mod MPI (Median, IQR)	0.52 (0.50-0.53)	0.635 (0.60-0.65)	0.70 (0.70-0.73)
ICT (Mean (SD)) ms	32 (0)	34.3 (1.34)	38.46 (2.02)
IRT (Mean (SD))ms	49.55 (2.35)	58.6 (3.97)	67.54 (2.60)
ET (Mean (SD))ms	158.35 (2.60)	151.4 (2.91)	147 (4.45)

Figure 6.4: The ICT, IRT and ET components of the MPI in different grades of IUGR severity





a) ET (ms) vs Grades of IUGR **b) ICT (ms) vs Grades of IUGR**



c) IRT (ms) vs Grades of IUGR

Table 6.4 Pregnancy and Perinatal Outcomes in IUGR categories

Key: IVH=intraventricular haemorrhage, NEC=necrotizing enterocolitis,BPD=bronchopulmonary dysplasia, HIE=hypoxic ischaemic encephalopathy, Vent+ventilation. In the groups below some fetuses exhibited more than one complication.

	UNCOMPENSATED	COMPENSATED	CRITICAL
Number (n)	20	10	14
Gest age (delivery)	37w1d	35w6d	30w2d
Median MPI	0.52	0.6	0.7
Birth Weight (g)	2156	1910	920
%-min APGAR <6	5	5	14
Perinatal Death	-	1	4
IVH	-	-	2
NEC	-	-	1
BPD	-	-	2
HIE	-	1	4
Ventilation	4	3	11
Hypoglycemia	1	1	6
Adverse Outcome	25%	60%	79%

The pregnancy and perinatal data are shown in Table 6.4. The more severe the grade of IUGR, the lower the gestational age at delivery, the lower the birth weight and the higher the need for ventilation. There were no perinatal deaths in the uncompensated group, with one death in the compensated group and 4 in the critical IUGR group.

The control group had normal pregnancy outcomes with the average birthweight being 3110g.

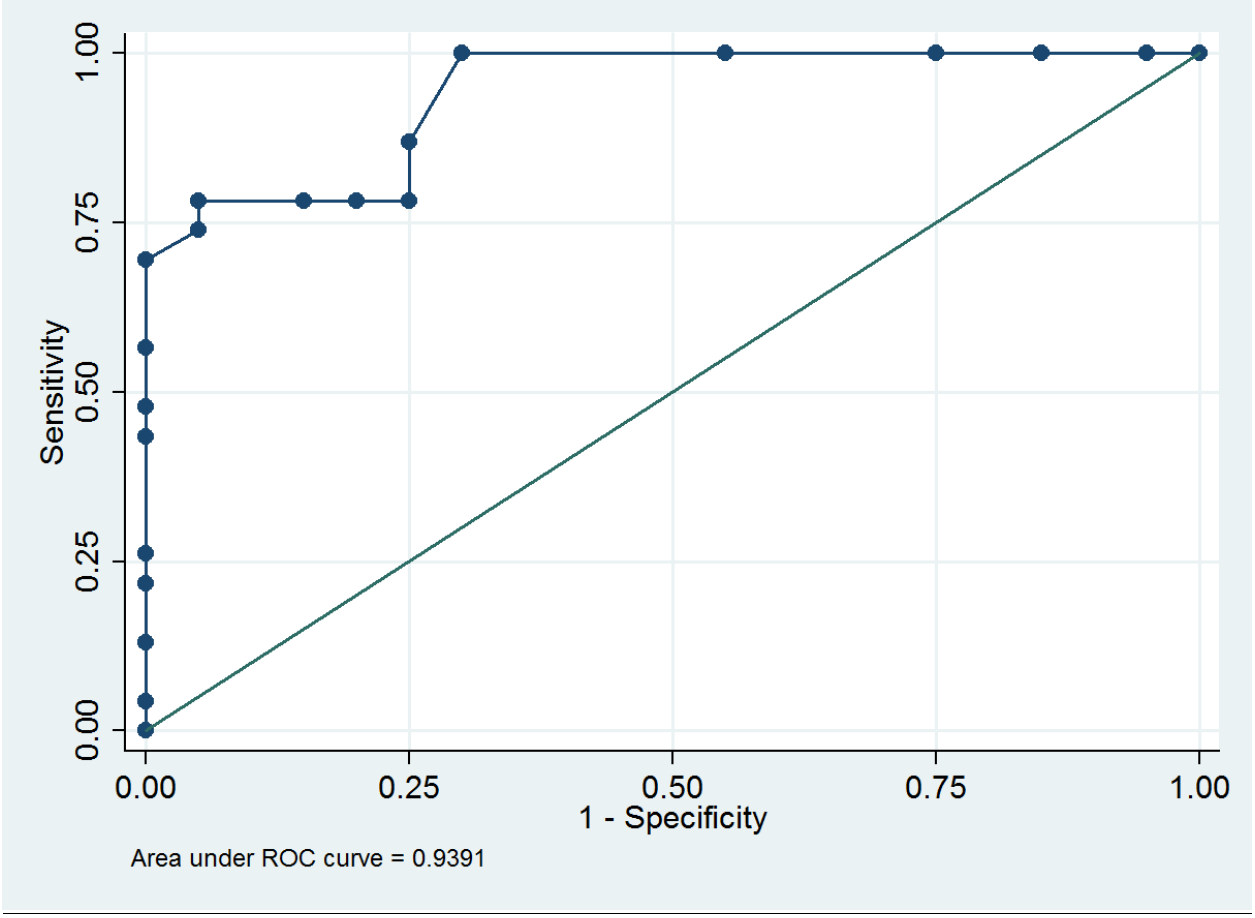


Fig 6.5: ROC curve: Sensitivity and Specificity of MPI in prediction of Adverse Outcome

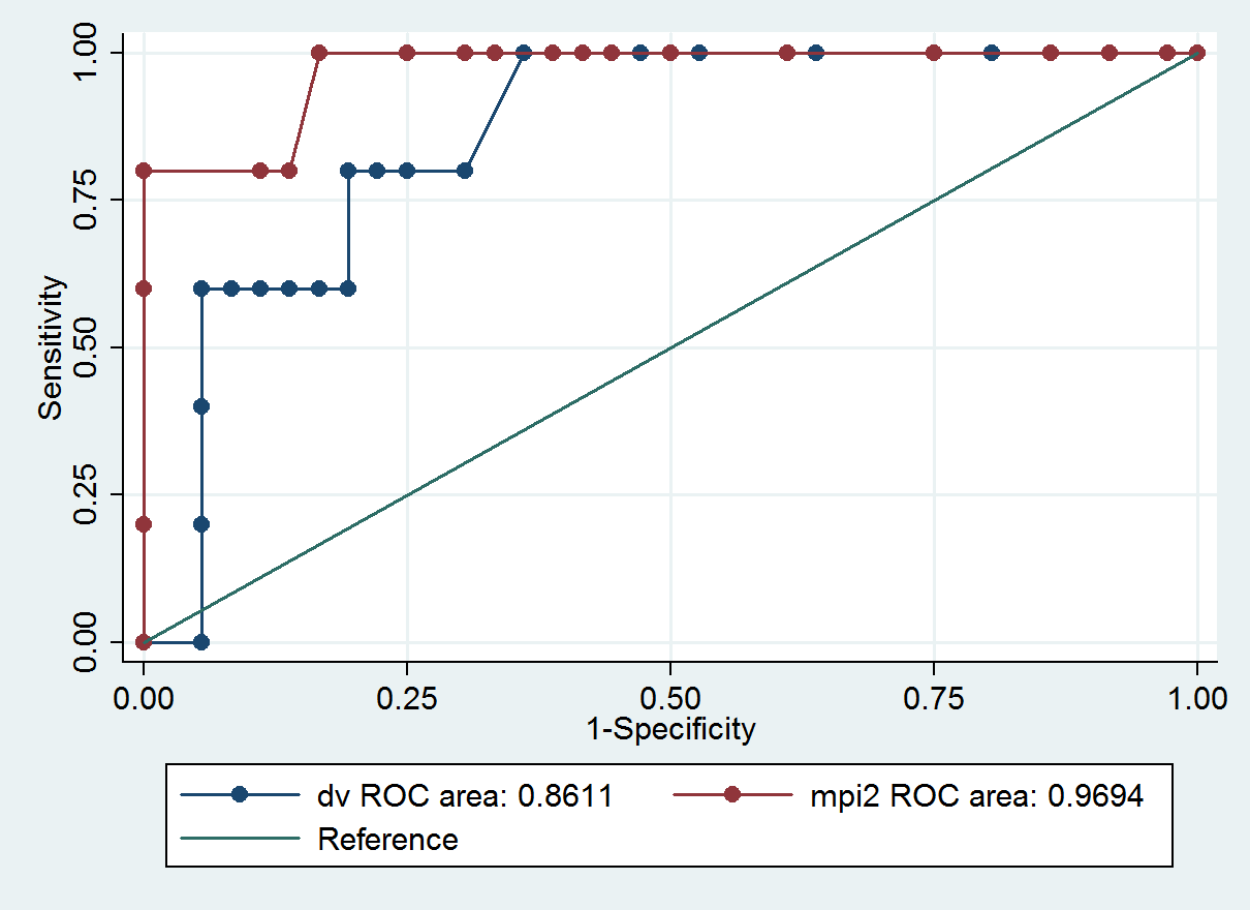


Fig 6.6: ROC curve : Comparing Mod-MPI and DV in prediction of perinatal mortality .

TABLE: 6.5. Sensitivity, Specificity and LR's of Mod-MPI cut-offs for Adverse outcome

Detailed report of Sensitivity and Specificity

Correctly

Cutpoint	Sensitivity	Specificity	Classified	LR+	LR-
(>= .45)	100.00%	0.00%	5.49%	1.0000	
(>= .49)	100.00%	5.00%	55.81%	1.0526	0.0000
(>= .5)	100.00%	15.00%	60.47%	1.1765	0.0000
(>= .51)	100.00%	25.00%	65.12%	1.3333	0.0000
(>= .52)	100.00%	45.00%	74.42%	1.8182	0.0000
(>= .53)	100.00%	70.00%	86.05%	3.3333	0.0000
(>= .54)	86.96%	75.00%	81.40%	3.4783	0.1739
(>= .55)	78.26%	75.00%	76.74%	3.1304	0.2899
(>= .57)	78.26%	80.00%	79.07%	3.9130	0.2717
(>= .6)	78.26%	85.00%	81.40%	5.2174	0.2558
(>= .63)	78.26%	95.00%	86.05%	15.6522	0.2288

(>= .64)	73.91%	95.00%	83.72%	14.7826	0.2746
(>= .65)	69.57%	100.00%	83.72%		0.3043
(>= .67)	56.52%	100.00%	76.74%		0.4348
(>= .69)	47.83%	100.00%	72.09%		0.5217
(>= .7)	43.48%	100.00%	69.77%		0.5652
(>= .71)	26.09%	100.00%	60.47%		0.7391
(>= .73)	21.74%	100.00%	58.14%		0.7826
(>= .78)	13.04%	100.00%	53.49%		0.8696
(>= .83)	4.35%	100.00%	48.84%		0.9565
(>= .83)	0.00%	100.00%	46.51%		1.0000

ROC -ASYMPTOTIC NORMAL-

Obs	Area	Std.err	[95% conf interval]	
43	0.9391	0.0325	0.87541	1.00000

TABLE: 6.6: Sensitivity, Specificity and LR's of Mod-MPI cut-offs in prediction of for Perinatal death

Detailed report of Sensitivity and Specificity

Correctly

Cutpoint	Sensitivity	Specificity	Classified	LR+	LR-
(>= .45)	100.00%	0.00%	13.95%	1.0000	
(>= .49)	100.00%	2.70%	16.28%	1.0278	0.0000
(>= .5)	100.00%	8.11%	20.93%	1.0882	0.0000
(>= .51)	100.00%	13.51%	25.58%	1.1562	0.0000
(>= .52)	100.00%	24.32%	34.88%	1.3214	0.0000
(>= .53)	100.00%	37.84%	46.51%	1.6087	0.0000
(>= .54)	100.00%	48.65%	55.81%	1.9474	0.0000
(>= .55)	100.00%	54.05%	60.47%	2.1765	0.0000
(>= .57)	100.00%	56.76%	62.79%	2.3125	0.0000
(>= .6)	100.00%	59.46%	65.12%	2.4667	0.0000
(>= .63)	100.00%	64.86%	69.77%	2.8462	0.0000
(>= .64)	100.00%	67.57%	72.09%	3.0833	0.0000
(>= .65)	100.00%	72.97%	76.74%	3.7000	0.0000

(>= .67)	100.00%	81.08%	83.72%	5.2857	0.0000
(>= .69)	83.33%	83.78%	83.72%	5.1389	0.1989
(>= .7)	83.33%	86.49%	86.05%	6.1667	0.1927
(>= .71)	83.33%	97.30%	95.35%	30.8334	0.1713
(>= .73)	83.33%	100.00%	97.67%		0.1667
(>= .78)	50.00%	100.00%	93.02%		0.5000
(>= .83)	16.67%	100.00%	88.37%		0.8333
(>= .83)	0.00%	100.00%	86.05%		1.0000

ROC -ASYMPTOTIC NORMAL-

Obs	Area	Std.err	[95% conf interval]	
43	0.9707	0.0310	0.90987	1.00000

6.5 DISCUSSION

This study has shown that IUGR fetuses have a significant impairment of cardiac function as demonstrated by significantly higher Mod-MPI and lower E/A ratios compared to controls on Doppler echocardiography. It has been further shown that MPI values deteriorate with worsening degrees of growth restriction with median MPI values of 0.52, 0.6 and 0.7 in uncompensated, compensated and critical status IUGR. Adverse pregnancy outcome increased with severity of IUGR from 25% in the uncompensated group, 60% in the compensated group and 79% in the critical group. The increase in Mod-MPI was at the expense of all components ie ET, IRT and ICT in the compensated and critical status groups and mainly at the expense of the IRT and ET in the uncompensated group.

Across the IUGR groupings, adverse outcomes were demonstrated at a cut-off Mod-MPI value of >0.52. A cut-off Mod-MPI value of >= 0.54 confers a sensitivity of 87% , specificity of 75% and likelihood ratio of 3.5 for an adverse outcome, with a significant ROC area under the curve of 0.94. A cut-off MPI value of >=0.67 confers a detection rate of 100%, specificity of 81% and likelihood ratio of 5.3 for perinatal death, with a significant ROC area under the curve of 0.97. Both Mod-MPI and DV are significant in prediction of perinatal death. MPI is however a better predictor than DV for perinatal death as evidenced by the Mod-MPI ROC area under the curve of 0.96 compared to the ROC area under the curve of 0.86 for DV.

This study further shows that severe outcomes were linked to deteriorating MPI's. Our study has shown that higher thresholds of the mod-MPI than the 95th percentile were predictive of adverse outcome. Between 28 weeks and 36 weeks the mean 95th percentile varied in our gestational age- adjusted normograms from 0.42 to 0.37 (Chapter 4) whilst in the present study, it has been shown that adverse outcomes were noted at an MPI > 0.52, which is much higher than the 95th percentile. This is important in the clinical setting where trending the absolute levels of MPI would be of value in predicting an adverse clinical scenario rather than using a cut-off value of >95th percentile, which level may not necessarily translate into an adverse outcome.

Crispi et al[18] also demonstrated that MPI values increased with stages of haemodynamic compromise of growth restricted fetuses. However absolute MPI values (and ranges) linked to specific adverse outcomes were not reported in their study-rather only trends of the MPI with haemodynamic compromise were demonstrated. Our study also differed in the definition of the haemodynamic compromise; the study by Crispi et al[18] used stages of haemodynamic compromise relying solely on umbilical artery Doppler anomalies (ie presence, absence or reversed end diastolic flow). This is an important difference because arterial redistribution (as reflected in MCA Doppler anomalies) and venous Doppler anomalies which were used in our study to categorise haemodynamic compromise, constitutes a deteriorating growth restrictive process and the MPI was thus able to be related to different stages of the growth restrictive process. With the use of the above Mod-MPI cut-off values for abnormal outcomes, the Mod-MPI could potentially be used as a monitoring Doppler parameter to track for deteriorating

cardiovascular function and guide the physician in conjunction with standard Doppler parameters for optimal timing of delivery, ie before overt acidosis, myocardial necrosis or perinatal death sets in.

There are many explanations as to the significant increase of the Mod-MPI in growth restricted fetuses. Cardiac flow is greatly influenced by modifications of arterial impedance to flow. Cardiac contractility may be directly impaired by hypoxaemia, while polycythaemia resulting from blood viscosity changes may alter preload [19] . Deteriorating growth-restricted fetuses have shown that peak velocity and cardiac output gradually decline, suggesting a progressive worsening in cardiac function[20]. This could explain deteriorating Mod-MPI's with worsening grades of growth restriction. Prior to fetal distress there is a dramatic decrease in ventricular ejection force and impairment of cardiac filling. This was shown in our study by the decrease in ejection time and increased isovolumetric relaxation times in the critical status IUGR group. Thus the elevated Mod-MPI's and reduced E/A ratios in this study reflect the above cardiac pathophysiological changes.

From a clinical perspective the results of this study provides further insight into the complex cardiac pathophysiology of the intrauterine growth restrictive process. Our study demonstrated that the mod-MPI becomes abnormal much earlier than arterial redistribution (which more or less coincides with hypoxia[21]) or DV anomalies (coincides with onset of acidosis[22]) which is in keeping with the study by Cruz-Martinez et al[23]. The monitoring model in their study however did not report fetuses with middle cerebral artery Doppler anomalies and thus the place of Mod-MPI in

their study was unclear as there was a substantial period between the elevation of the Mod-MPI and DV anomalies. Furthermore there was no trending of MPI values to adverse outcomes which is essential in prediction. Ductus venosus Doppler sonography is regarded as the gold standard for fetal monitoring and timely delivery[24], but also a late sign of fetal compromise which is often associated with fetal acidemia, myocardial necrosis and perinatal death [22,25,26]. Ductus venosus Doppler can thus not be regarded as optimal in establishing timing of delivery as significant morbidity may have already set in. The Mod-MPI which reflects milder stages of hypoxaemia/acidemia may be preferable and could be used in conjunction with standard monitoring models to improve prediction and pre-empt adverse outcomes.

There was significant impairment of cardiac function in growth restricted fetuses with the myocardial performance, as evidenced by increasing Mod-MPI values, deteriorating with severity of growth restriction. Cut-off Mod-MPI values for abnormal outcomes including perinatal death have been established. The mod-MPI was abnormal before hypoxia or acidosis set in and this can thus be regarded as a "warning" parameter of impending compromise. The Mod-MPI has the potential to be integrated into routine surveillance techniques of the growth restricted fetus. This may assist the clinician to ascertain timeous delivery and thus reduce perinatal morbidity and mortality.

One of the potential limitations of the study is that the Mod-MPI requires experience and training to obtain a reliable result. However, this parameter shows good reproducibility when its evaluation is performed using specific settings with valve clicks as landmarks.

To our knowledge this is the first study to establish median Mod-MPI values for different grades of IUGR (using the standard 3- vessel Doppler assessment) and also to establish Mod-MPI cut-off values in the prediction of adverse outcomes. This can potentially serve as a guideline to clinicians to detect significant compromise earlier and assist in timing of delivery.

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CHAPTER 7:

FETAL CARDIAC FUNCTION IN PREGNANCIES COMPLICATED BY SEVERE PRE-ECLAMPSIA

7.1 ABSTRACT

Aim:

To determine whether there are changes in fetal cardiac function in pregnancies complicated by severe pre-eclampsia (PET) and to determine whether these changes influence perinatal outcome.

Methods:

Thirty pregnant women attending the Fetal Unit at Inkosi Albert Luthuli Central Hospital, Durban, South Africa with severe early-onset PET between 27 and 32 weeks were recruited and matched with 30 women having normal pregnancies which served as the control group. The study group was subdivided into 5 groups, with the first 4 groups subdivided on the basis of the degree of abnormality of the umbilical artery resistance index (RI) only: group 1, 0.7<=UA < 0.8; group 2, 0.8<=UA < 0.85; group 3 >= 0.85 and group 4 - absent end diastolic flow in the umbilical artery. Group 5 was based on an umbilical artery RI of > 0.8 together with a middle cerebral artery RI <0.7 reflecting arterial redistribution. Doppler echocardiography using the Mod-MPI and E/A ratios were performed to evaluate cardiac function in all fetuses. The pregnancy outcomes were recorded in both groups. ROC curves were used to evaluate the overall diagnostic accuracy of Mod-MPI in predicting adverse outcome and perinatal mortality.

Results

The maternal age was similar in both groups. Mod-MPI values were increased in the pre-eclamptic group compared to controls (0.62 vs 0.38, $p < 0.001$) and its median value progressively increased with increasing umbilical artery RI's: 0.54 (group 1), 0.62 (Group 2), 0.65 (Group 3) and 0.68 (Group 4). Perinatal complications increased with worsening placental vascular resistance and increasing Mod-MPI, from 44% (group 1 and median Mod-MPI of 0.54) to 60% (group 2 and median Mod-MPI of 0.62) to 80% (group 3 and median Mod-MPI of 0.65) to 83% (group 4 and median Mod-MPI of 0.68). In fetuses with arterial redistribution, the Mod-MPI was also elevated with a median 0.63. For adverse perinatal outcome, a cut-off Mod-MPI value of >0.55 conferred a sensitivity of 100%, specificity of 82% and a LR of 5.5. The area under the ROC curve for Mod-MPI in prediction of an adverse perinatal outcome was significant at 0.94. For perinatal death, a cut-off Mod-MPI value of 0.67 conferred a sensitivity of 100%, specificity of 84% and an LR of 6.25. The area under the ROC curve for Mod-MPI in prediction of perinatal death was significant at 0.95. The E/A ratios were significantly decreased in the pre-eclamptic group compared to controls (0.66 vs 0.79, $p < 0.0001$) indicating diastolic dysfunction in the fetuses of pre-eclamptic women. No adverse outcomes were noted in the control group.

Conclusion

Fetal cardiac function as assessed by the Mod-MPI, is significantly impaired in pregnancies complicated by severe early onset pre-eclampsia. With worsening

degrees of placental mediated disease, as evidenced by deteriorating umbilical artery RI's, the Mod-MPI concomitantly increased. Cut-off MPI values for adverse perinatal outcomes including perinatal death have been established. The Mod- MPI can potentially be integrated into routine fetal surveillance techniques. This may enable clinicians in decision-making regarding timeous delivery and thereby reduce perinatal morbidity and mortality.

7.2 INTRODUCTION

Fetal echocardiography has been used for non-invasive evaluation of fetal cardiac anatomy, function and haemodynamics[1,2,3]. A new Doppler index of combined systolic and diastolic ventricular myocardial performance, the Tei index or myocardial performance index (MPI) which is known to be independent for ventricular geometry and heart rate has been proposed as a potential useful predictor of global cardiac function[3]. MPI is defined as the sum of the isovolumetric contraction time (ICT) and isovolumetric relaxation time (IRT) divided by ejection time (ET)[1,2,3]. The equation of the MPI is thus: (ICT + IRT)/ET. The technique of acquisition has however evolved to a modified MPI which we have used in this study[4,5,6].

The aetiology of preeclampsia is linked to placental maladaptation and in particular inadequate trophoblastic invasion of the spiral arterioles[7,8], which gives rise to vascular resistance of the utero-placental circulation[9] . Early onset pre-eclampsia (PET), intrauterine growth restriction (IUGR), preterm labour, abruptio placentae and stillbirths constitute the great obstetric syndromes which have in common a single pathophysiological event of inadequate transformation or remodelling of the uterine spiral arterioles beginning at about 8-9 weeks gestation[10]. Brosens et al[10] reported that pathophysiologically early-onset preeclampsia was linked to a stage more advanced in the defective placental remodelling process than intrauterine growth restriction in that absent trophoblastic invasion of the spiral arterioles occurred in pre-eclampsia as opposed to partial trophoblastic invasion in growth restriction. The presence of both clinical phenotypes of PET and IUGR in the same fetus represents a

further deterioration of the defective placental spiral arterial remodelling process of absent trophoblastic invasion with obstructive lesions. The increased vascular placental resistance may affect fetal cardiac function by causing an increase in the fetal cardiac afterload.

Ichizuka et al[11] showed that the MPI increased in conditions where cardiac afterload increased secondary to placental vascular resistance. Furthermore, Narin N et al[12] reported cardiac dysfunction and mild myocardial damage in neonates of mildly pre-eclamptic mothers. However, O.Api et al[13] did not show an increase in mod-MPI values in women with pre-eclampsia. This may be due to their study population of mainly late onset pre-eclamptics where the mean gestational age in their severe pre-eclamptic group was 35 weeks. It is only the early-onset pre-eclamptics that is linked to placental mediated disease that results in increased placental vascular resistance[10].

The Mod-MPI has been shown to be increased in growth-restricted fetuses (Chapter 6) as well as in other studies [14,15]. It follows therefore that if preeclampsia represents a more advanced placental pathological state than growth restriction and thus in effect a more serious clinical phenotype, then the Mod-MPI should be altered in fetuses of pre-eclamptic mothers on the pathophysiological basis of increased fetal cardiac afterload.

In this study we sought to elucidate cardiac function as reflected by the Mod-MPI and E/A ratios in fetuses of pre-eclamptic mothers and compared these parameters

to a matched control group of normal normotensive women. In addition we also aimed to compare Mod-MPI values to different groups in the study population of pre-eclamptics, categorized by worsening placental vascular resistance and arterial redistribution. Finally, we also wanted to determine if the Mod-MPI influenced perinatal outcome.

7.3 METHODS

This was a prospective cross-sectional study of the Mod-MPI and E/A ratios in fetuses of severe pre-eclamptic mothers conducted at Inkosi Albert Luthuli Central Hospital in Durban, South Africa. Thirty severe early onset pre-eclamptic mothers between 27 and 32 weeks gestation were recruited and comprised the study group. Thirty normal pregnant women who were matched for gestational age served as controls. All controls at inclusion were normotensive and the fetuses were appropriately grown for gestational age. Severe pre-eclampsia was defined by criteria as set out by the American College of Obstetricians and Gynaecologists[16] ie severe pre-eclampsia was defined as systolic blood pressure >= 160mmHg or diastolic blood pressure >=110mmHg on two occasions at least 6 hours apart in a woman on bed rest, accompanied by proteinuria >=3+ reading on dipstick testing on two random samples at least 6 hours apart. Other features of severe preeclampsia included oliguria (< 500ml of urine in 24 hours), cerebral or visual disturbances, pulmonary oedema, epigastric pain, impaired liver function and thrombocytopaenia. Exclusion criteria were fetuses of pregestational or gestational diabetic mothers, hydropic fetuses, fetuses with rhesus isoimmunisation, fetuses of mothers treated

with a tocolytic agent and multifetal pregnancies. The study was approved by the Biomedical Research Ethics Committtee of the University of Kwa-Zulu Natal.
Data for subjects that were recorded included demographic data of maternal age and parity; sonographic data of fetal weight and amniotic fluid index; cardiac Doppler data of myocardial performance index (MPI) and E/A ratio as well as the umbilical artery resistance index, middle cerebral artery resistance index and ductus venosus Doppler.

The PET women were subdivided into 5 groups with the first 4 groups subdivided on the basis of degree of abnormality of the umbilical artery resistance index (RI) only; group 1 0.7<=UA<0.8 ; group 2 0.8<=UA<0.85; group 3 >0.85 and group 4 having absent end diastolic flow (AEDF) in the umbilical artery. Group 5 was based on an umbilical artery RI > 0.8 together with a middle cerebral artery RI < 0.7 reflecting arterial redistribution. Doppler echocardiography using the Mod-MPI and E/A ratios were performed to evaluate cardiac function in all fetuses. The pregnancy outcomes were recorded in both groups.

Fetal echocardiography using the E8 Voluson General Electric ultrasound system (GE Medical Systems, WI, USA) or Siemens Antares ultrasound system (Siemens Medical Systems, Malvern, PA, USA) was performed in each woman. The four chamber view, outflow tract views, triple vessel view, longitudinal view of the aortic arch and ductal arch, and colour flow mapping were used to screen for cardiac malformations.

The Mod-MPI was calculated in the fetal left ventricle as originally described by

Hernandez-Andrade et al[6]. A cross sectional image of the fetal thorax at the level of the 4-chamber view with an apical projection of the heart was obtained. The Doppler sample was opened to 3mm and placed in the internal leaflet of the mitral valve (MV). In this location owing to its closeness to the aortic valve (AV), the opening and closing AV clicks were registered. The angle of insonation was always <30 degrees. E/A waveform was always displayed as positive flow. The Doppler gain was lowered as far as possible to clearly visualize the echoes corresponding to the opening and closing clicks of the two valves at the beginning and at the end of the E/A (mitral valve) and aortic waveforms. The Doppler sweep velocity was set at 5cm/sec and wall motion filter at 300Hz. The three time periods were estimated as follows : ICT - from beginning of MV closure to AV opening; ET - from AV opening to closure; IRT - from AV closure to MV opening. The Mod-MPI = (ICT +IRT) /ET.

In addition, E-wave (early ventricular filling) and A wave (active atrial filling) peak velocities and the ratio between them (E/A ratio) as an index of ventricular diastolic function was performed.

Delivery was indicated according to standard obstetric guidelines. Fetal indications included reversed end diastolic flow in the umbilical artery, reversed or absent end-diastolic flow in the ductus venosus or decelerations on cardiotocography > 28 weeks gestation.

Statistical methods

All analysis was performed using STATA/SE version 12.0 (Stata Corp,College Station, Tx, USA). Spearman's rank correlation was computed to assess the correlation between Mod-MPI and gestational age within each group. The Shapiro-Wilk *W*- test was used to test for normality. All skewed variables were reported as medians with interquartile ranges. Quantile regression was used to determine whether there was a significant difference in the median MPI between the PET and normal fetuses (control) while adjusting for the effect of gestational age. The Wilcoxon rank sum test was used to test for pairwise differences between the degrees of severity.

7.4 RESULTS

A total of 60 fetuses between gestational ages 27 and 32 weeks were studied. The demographic and sonographic variables are summarized in Table 7.1. The mean fetal weights were significantly lower in the PET group ($p < 0.0001$). There was no difference in the mean AFI between the PET group and the control group.

There was a significant negative correlation between Mod-MPI and gestational age in controls (Spearman' correlation coefficient -0.9368, $p < 0.0001$). Within cases negative correlation with gestational age was also observed, however this was not statistically significant (Spearman's correlation coefficient -0.2602, p- value 0.1650). The Mod-MPI values of the pre-eclamptic group adjusting for gestational age were significantly higher than that of the controls ($p<0.001$). Fig. 7.1 illustrates the relationship between Mod-MPI and gestational age in the pre-eclamptic group and control group. The change in MPI with increasing gestational age did not differ between cases and controls ie no interaction effect. The Mod-MPI values of the pre-eclamptic group were significantly higher than that of the controls ($p<0.001$). The median and interquartile range of the Mod-MPI in PET cases and controls was 0.62(0.54-0.67) and 0.38 (0.38-0.39) and is shown in Table 7.1.

Table 7.1: Demographic and Sonographic Data in PET and Control groups

	Control (n = 30)	PET (n = 30)	p-value
	Mean (SD)	Mean (SD)	
Maternal age (years)	28.91 (3.80)	28 95.36)	0.523
Gestational age (weeks) –(Median (IQR))	30 (30.57-31.28)	29.98 (30.43-32)	0.454
EWF (g)	1629 (1577 - 1813)	1244 (913 - 1654)	0.0001
AFI (cm)	12.83 (1.11)	11.46 (3.29)	0.0697
E/A ratio	0.79 (0.02)	0.66 (0.03)	<0.0001
Median MOD-MPI (IQR)	0.38 (0.38-0.39)	0.62 (0.54-0.67)	<0.001

Figure 7.1: MPI versus Gestational Age in PET and Control Groups

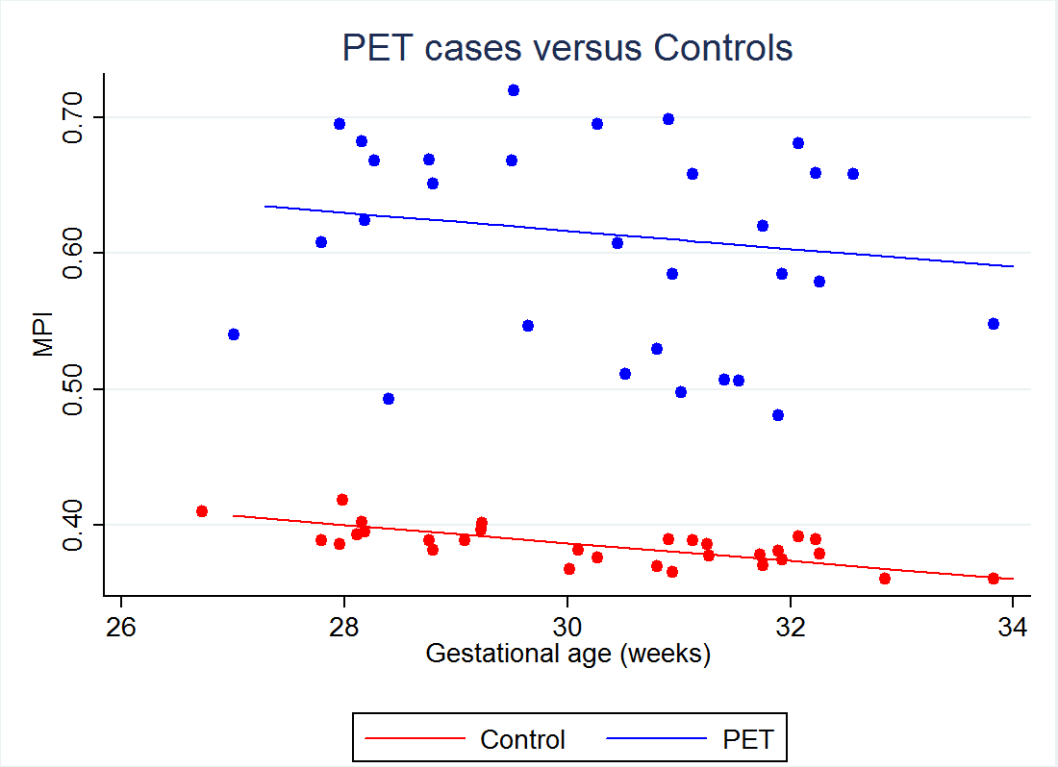

Table 7.2: The IRT, ICT and ET components of the MPI between PET and Control groups

	Control (n = 30)	Cases (n = 30)	p-value
ICT (ms) (Median , IQR)	27 (27 - 28)	35 (34- 38)	<0.001
IRT (ms) (Median , IQR)	39 (39 - 40)	58 (56- 64)	<0.001
ET ms (Median , IQR)	172 (171 - 172)	152 (150-156)	<0.001

ms: metre/second

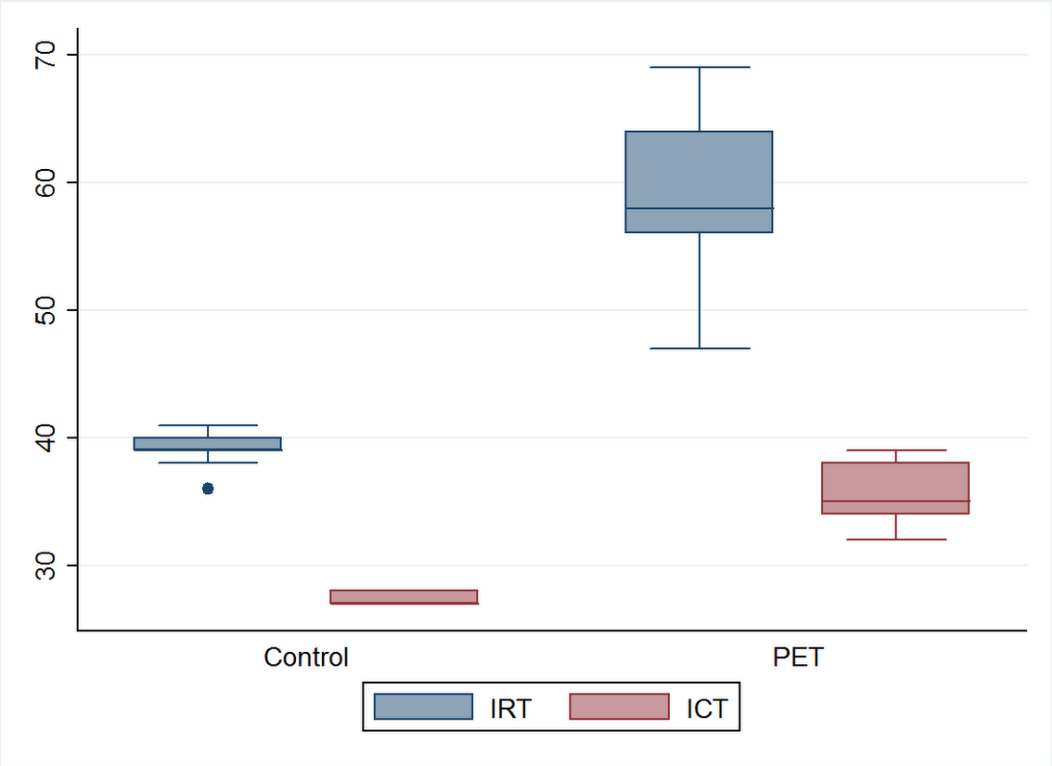

Fig 7.2: The IRT and ICT in the PET and Control groups

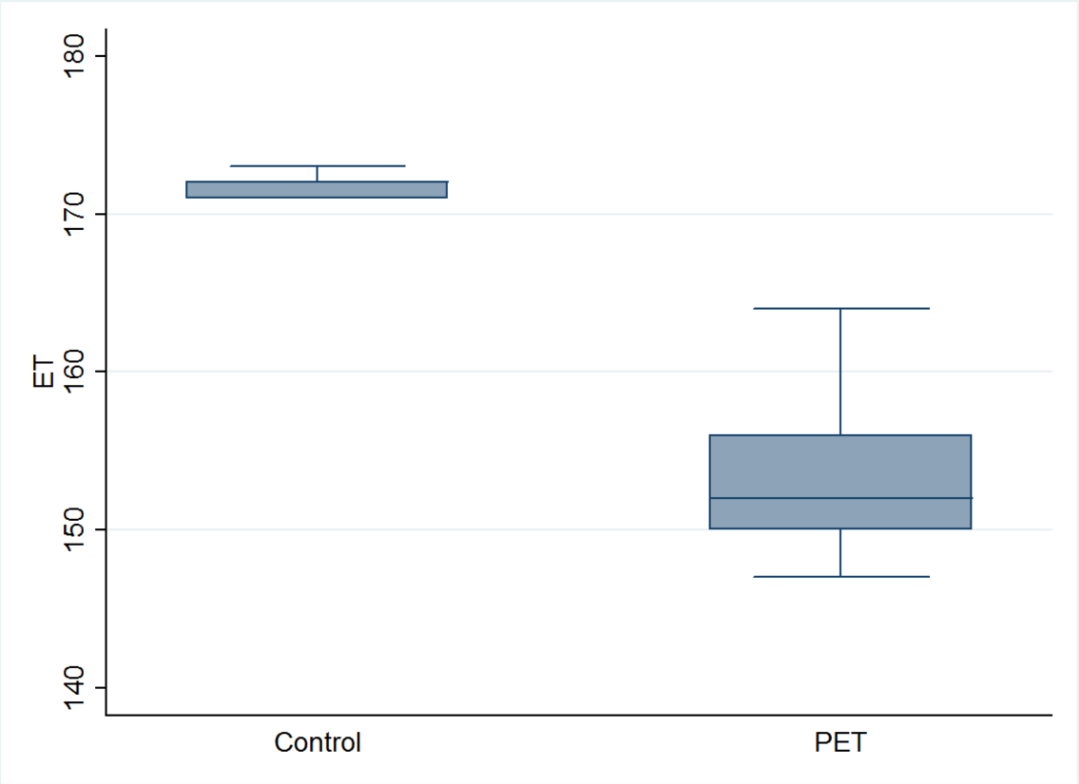

Fig 7.3: The ET in the PET and Control Groups.

The distribution of the PET cases in the 4 categories of deteriorating umbilical artery RI with the median MPI within each category, is displayed in Table 7.3 and Figure 7.4. There was a consistent increase in Mod-MPI's with deteriorating UA RI's. There was a statistically significant difference in the median MPI between group 1 and group2 ($p < 0.013$), group 1 and group 3($p < 0.007$) and group 1 and group 4(p-value < 0.031).

Table 7.3: Mod- MPI in each PET category

Umbilical Artery RI	N	Mod-MPI - Median (IQR)
0.7<=UA<0.8 (group 1)	9	0.54 (0.5-0.58)
0.8<=UA <0.85(group 2)	10	0.62 (0.60-0.62)
≥ 0.85 (group 3)	5	0.65 (0.6-0.67)
AEDF (group 4)	6	0.68 (0.65-0.71)
Total	30	0.62 (0.54-0.67)

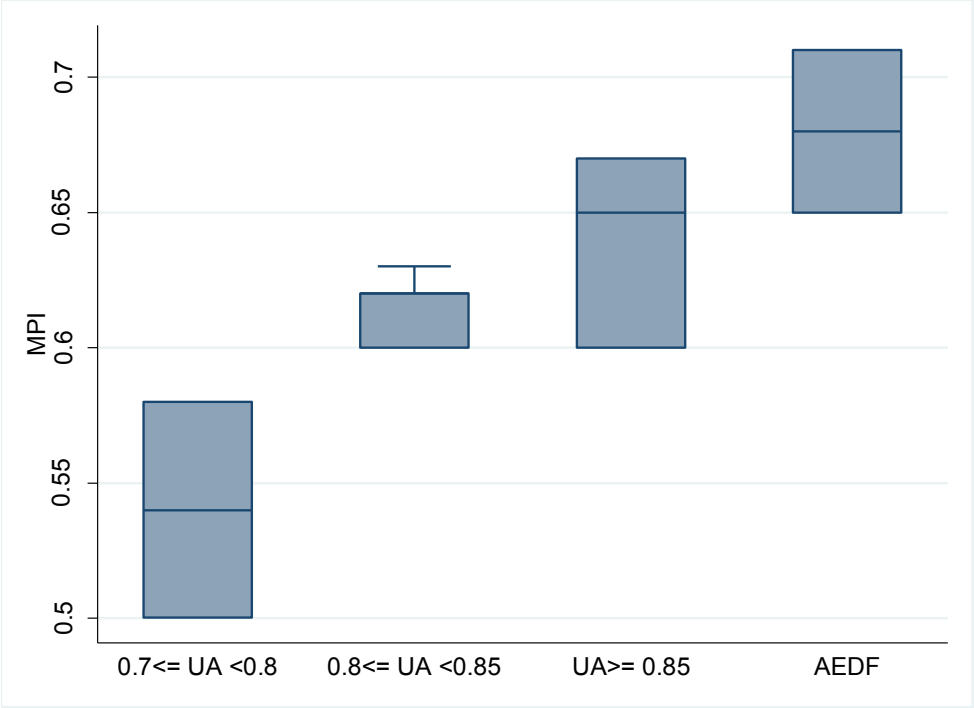

Figure 7.4: MPI values in pre-eclamptic categories

The median Mod- MPI in group 5 (representing the compromised PET group with arterial redistribution) compared to group 1 (with no redistributive effect) is shown in Table 7.4 and figure 7.5 and this was a statistically significant difference ($p<0.0025$).

Table 7.4: Median MPI in groups showing no redistributive effect (Group 1) vs redistributive effect (Group5)

	Group 1 (n=8)	**Group 5 (n=22)**	**p-value**
Mod MPI Median (IQR)	**0.54** (0.50-0.58)	**0.63** (0.60-0.67)	**0.002**

Figure 7.5: Median MPI (with interquartile ranges) in group showing redistributive effect (group5) versus group with no redistributive effect (group 1)

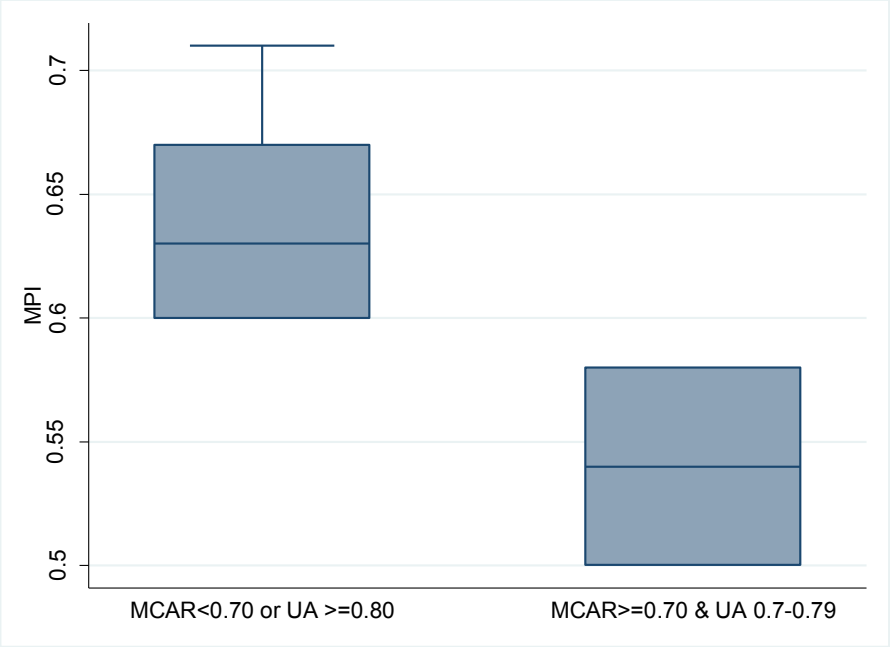

TABLE: 7.5: Pregnancy and Perinatal Outcomes according to Umbilcal Artery RI

	Group 1 0.7<=UA < 0.8 N = 9	Group 2 0.8<=UA <0.85 N = 10	Group 3 RI ≥0.85 N = 5	Group 4 AEDF N = 6
Median MPI	0.54	0.62	0.65	0.68
Birth Weight (g)	1836	1242	1196	950
Gest age (mean)	32w3d	31w3d	30w6d	29w6d
APGARS <6	4	6	4	6
Perinatal death	-	-	2	3
IVH		1	1	1
NEC	-	-	-	-
HIE	-	1	2	1
VENT	3	3	1	2
Hypoglycemia	1	1	-	-
Perinatal complications	44%	60%	80%	83%

Key: IVH: intraventricular haemorrage, NEC: necrotizing enterocolitis, HIE: hypoxic ischaemic encephalopathy, Vent:ventilation. (each fetus may have had more than one complication).

The pregnancy and perinatal data are shown in Table 7.5. Worsening placental vascular resistance as indicated by deteriorating umbilical artery RI's, resulted in a lower gestational age of delivery, lower birth weights and higher perinatal

complications. There were two perinatal deaths in group 3 (UA RI >0.85) and three

perinatal deaths in group 4 (AEDF in UA)

The control group had normal pregnancy outcomes with the average birthweight of 3085g.

Table:7.6 Comparison of MPI, UA RI and Ductus Venosus PIV in Perinatal deaths

Perinatal Deaths	MPI	UA RI	DV PIV
1	0.67	0.87	0.9
2	0.71	AEDF	AEDF
3	0.67	0.86	0.97
4	0.72	AEDF	0.6
5	0.7	AEDF	0.75

Fig7.6: ROC curve: MPI in prediction of adverse outcome in PET

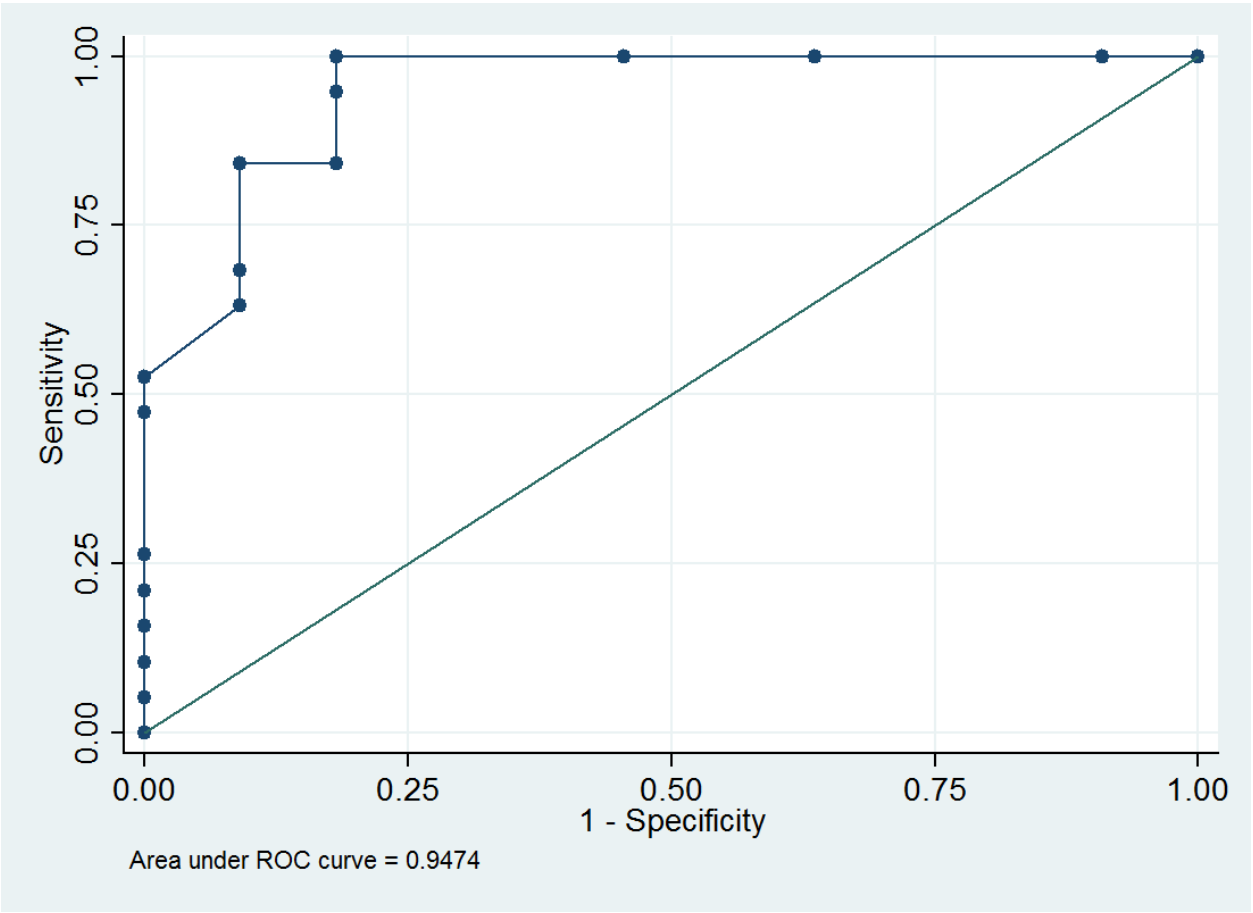

Fig7.7: ROC curve: MPI in prediction of perinatal death in PET

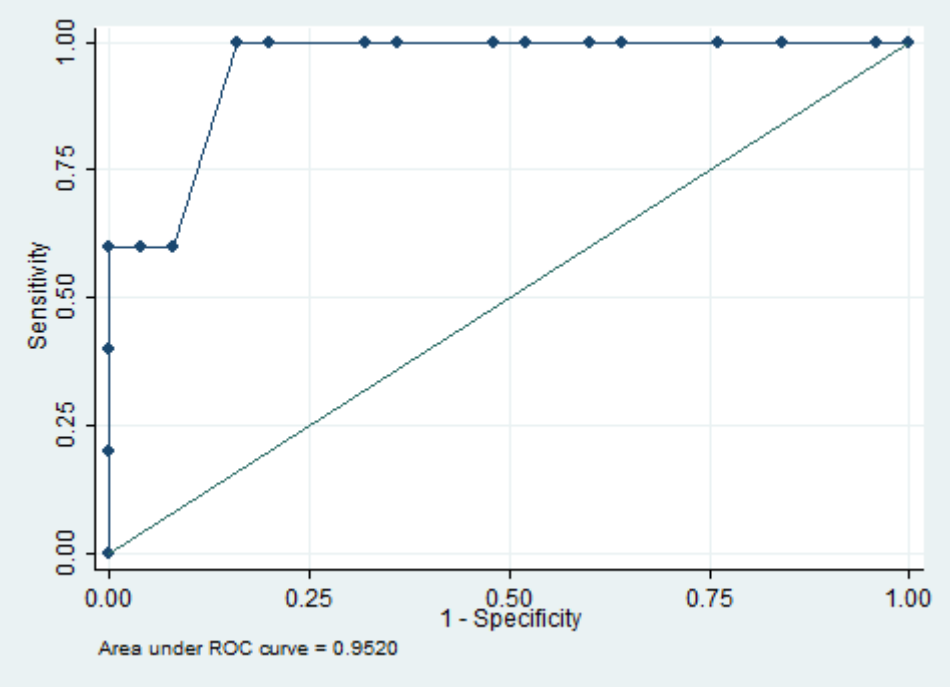

TABLE: 7.7; Sensitivity, specificity and LR's for Mod-MPI cut-offs in prediction of perinatal death in severe PET

Detailed report of Sensitivity and Specificity

Correctly

Cutpoint	Sensitivity	Specificity	Classified	LR+	LR-
(>= .48)	100.00%	0.00%	16.67%	1.0000	
(>= .5)	100.00%	4.00%	20.00%	1.0417	0.0000
(>= .51)	100.00%	16.00%	30.00%	1.1905	0.0000
(>= .54)	100.00%	24.00%	36.67%	1.3158	0.0000
(>= .55)	100.00%	36.00%	46.67%	1.5625	0.0000
(>= .58)	100.00%	40.00%	50.00%	1.6667	0.0000
(>= .6)	100.00%	48.00%	56.67%	1.9231	0.0000
(>= .62)	100.00%	52.00%	60.00%	2.0833	0.0000
(>= .63)	100.00%	64.00%	70.00%	2.7778	0.0000
(>= .65)	100.00%	68.00%	73.33%	3.1250	0.0000
(>= .66)	100.00%	80.00%	83.33%	5.0000	0.0000
(>= .67)	100.00%	84.00%	86.67%	6.2500	0.0000

(>= .68)	60.00%	92.00%	86.67%	7.5000	0.4348
(>= .69)	60.00%	96.00%	90.00%	15.0000	0.4167
(>= .7)	60.00%	100.00%	93.33%		0.4000
(>= .71)	40.00%	100.00%	90.00%		0.6000
(>= .72)	20.00%	100.00%	86.67%		0.8000
(>= .72)	0.00%	100.00%	83.33%		1.0000

ROC -ASYMPTOTIC NORMAL-

Obs	Area	Std.err	[95% conf interval]	
30	0.9520	0.0379	0.87776	1.00000

TABLE: 7.8

Sensitivity, Specificity and Likelihood Ratios for Mod-MPI cut-offs in prediction of adverse outcomes in severe PET

Detailed report of Sensitivity and Specificity

Correctly

Cutpoint	Sensitivity	Specificity	Classified	LR+	LR-
(>= .48)	100.00%	0.00%	63.33%	1.0000	
(>= .5)	100.00%	9.09%	66.67%	1.1000	0.0000
(>= .51)	100.00%	36.36%	76.67%	1.5714	0.0000
(>= .54)	100.00%	54.55%	83.33%	2.2000	0.0000
(>= .55)	100.00%	81.82%	93.33%	5.5000	0.0000
(>= .58)	94.74%	81.82%	90.00%	5.2105	0.0643
(>= .6)	84.21%	81.82%	83.33%	4.6316	0.1930
(>= .62)	84.21%	90.91%	86.67%	9.2632	0.1737
(>= .63)	68.42%	90.91%	76.67%	7.5263	0.3474
(>= .65)	63.16%	90.91%	73.33%	6.9474	0.4053
(>= .66)	52.63%	100.00%	70.00%		0.4737

(>= .67)	47.37%	100.00%	66.67%		0.5263
(>= .68)	26.32%	100.00%	53.33%		0.7368
(>= .69)	21.05%	100.00%	50.00%		0.7895
(>= .7)	15.79%	100.00%	46.67%		0.8421
(>= .71)	10.53%	100.00%	43.33%		0.8947
(>= .72)	5.26%	100.00%	40.00%		0.9474
(>= .72)	0.00%	100.00%	36.67%		1.0000

ROC -ASYMPTOTIC NORMAL-

Obs	Area	Std.err	[95% conf interval]	
30	0.9474	0.0425	0.86407	1.00000

7.5 DISCUSSION

This study has shown that fetuses in mothers with severe PET have cardiac dysfunction as manifested by increased Mod-MPI values and decreased E/A ratios. The lowered E/A ratios indicate diastolic dysfunction in the fetuses of severe pre-eclamptic mothers. The increase in the Mod-MPI was due to all components of the Mod-MPI; both the IRT and ICT increased and ET decreased. Furthermore, the degree of increase of Mod-MPI in pre-eclampsia was related to the degree of the placental mediated disease in that at mildly elevated umbilical artery resistance indices the increase was less profound than when there were very high umbilical artery resistances (worsening placental vascular resistance) or absent end diastolic flow in the umbilical artery. Perinatal complications increased with worsening placental vascular resistance and increasing Mod-MPI, from 44% (group 1 and median Mod-MPI of 0.54) to 60% (group 2 and median Mod-MPI of 0.62) to 80% (group 3 and median Mod-MPI of 0.65) to 83% (group 4 and median Mod-MPI of 0.68).

Abnormal perinatal outcomes were only noted when Mod- MPI was > 0.55. Across the groupings of worsening placental mediated disease, a cut-off Mod-MPI value of >=0.55 conferred a sensitivity of 100%, specificity of 82% and likelihood ratio of 5.5 for an adverse perinatal outcome. The ROC area under curve for Mod- MPI predicting an adverse perinatal outcome was highly significant at 0.94. A cut-off Mod-MPI of 0.67 conferred a sensitivity of 100%, specificity of 84% and a likelihood

ratio of 6.25 for perinatal mortality. The ROC area under the curve for MPI predicting perinatal death was also highly significant at 0.95. The severity of perinatal outcomes appeared linked to deteriorating Mod-MPI levels.

The results emanating from the comparison of the four groups is in keeping with the notion that very high umbilical artery RI's or AEDF, reflect very high placental vascular resistances which impact on the extent of fetal cardiac afterload resulting in deteriorating myocardial performance as manifested by increasing Mod-MPI values. There was also a statistically significant difference in Mod-MPI's between the group showing arterial redistribution (group 5) and group 1 where there was no redistributive effect. Arterial redistribution more or less coincides with onset of hypoxia[17]. This is consistent with the findings from our IUGR study (chapter 6) where there was also a statistically significant difference in Mod-MPI's between the compensated growth restricted group (showing arterial redistribution) and the uncompensated group (no arterial redistribution). Thus in pre-eclampsia, with worsening placental vascular resistance, fetal cardiac function is progressively compromised.

This study is in variance to that by O.Api et al[13] where no increase in the Mod-MPI values in the pre-eclamptic mothers was reported. In their study, they did not differentiate between early-onset pre-eclampsia, which is associated with placental

lesions, and late-onset pre-eclampsia where the placental disease association is less profound. It also appears that most of the patients in the O. Api et al study, were late-onset pre-eclamptics, judging from the mean gestational age of 35 weeks in their severe pre-eclamptic group. It is the early onset pre-eclampsia which is linked to absent transformation of the spiral arterioles[10] that results in the increased placental vascular resistance that affects fetal cardiac function by causing an increase in fetal cardiac afterload. Thus the finding of an increased Mod-MPI is consistent with the pathophysiology of early onset PET and not late onset PET.

Pathophysiologically PET is a stage more advanced in the defective placental remodelling process than IUGR. The combination of both PET and IUGR clinical phenotypes in the same fetus represents absent transformation of the spiral arterioles with obstructive lesions[10].

Adequate placentation and placental development are crucial steps for normal pregnancy, and angiogenesis and vascular transformation are important for normal placental development. The exact pathophysiology of pre-eclampsia remains elusive despite extensive research[18] . A two-stage disorder model is commonly accepted- reduced placental perfusion and shallow trophoblastic invasion leading to abnormal placentation which in turn leads to clinical disorders in later pregancy[19,20]. The abnormal placental remodelling process and reduced placental perfusion alluded to, implies an imbalance of angiogenic growth factors including decreased placental growth factor (PlGF), vascular endothelial growth factor (VEGF) and increased soluble fms-like tyrosine kinase (sFlt-1)[21-25]. These anti-angiogenic substances are able to block the effects of VEGF and PlGF by inhibiting interactions with its

receptors, resulting in placental vessel injury and placental vasoconstriction, leading to increased placental vascular resistance and increased fetal cardiac afterload. The fetal cardiac dysfunction shown in this study by the elevated Mod-MPI's can thus be regarded as reflective of this pro-antiangiogenic process. Schlembach et al showed a strong correlation between maternal and fetal angiogenic growth factor serum levels and Doppler ultrasound indices of uterine and umbilical arteries[26] .

Fetal cardiac function as assessed by the Mod-MPI, in pregnancies complicated by severe early onset pre-eclampsia is significantly impaired. With worsening degrees of placental mediated disease, as evidenced by deteriorating umbilical artery RI's, the Mod-MPI concomitantly increased. The unique property of the Mod-MPI is that it becomes abnormal before severe compromise. A substantial increase in the Mod-MPI precedes the scenario where there is hypoxia or severe fetal cardiovascular deterioration. In this regard, cut-off Mod-MPI values for prediction of adverse perinatal outcome and perinatal death have been established. This in effect means that the Mod- MPI can potentially be integrated into routine antenatal surveillance techniques. This may enable clinicians in decision-making regarding timeous delivery and thereby reducing perinatal morbidity and mortality.

To our knowledge, this is the first study in severe pre-eclampsia showing that fetal cardiac function as assessed by the Mod-MPI progressively deteriorates with worsening placental vascular resistance in and is associated with increasing perinatal complications.

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CHAPTER 8

CONCLUSION

The aim of this thesis was to construct normal gestational age-adjusted reference values of a fetal cardiac parameter viz. the modified myocardial performance index (Mod-MPI) using real time 2 dimensional and Doppler ultrasonic techniques. The fetal Mod-MPI and diastolic function (early diastolic velocity/late diastolic velocity – E/A ratios) were then evaluated in high risk obstetric conditions. Specifically we determined whether the Mod-MPI and E/A ratios were altered in fetuses of diabetic, intrauterine growth restriction and pre-eclamptic pregnancies and whether these altered parameters influenced perinatal outcome.

We found that the Mod-MPI decreased with advancing gestational age. Maturational and developmental alterations in the myocardial performance in utero resulting in better ventricular compliance is most likely responsible for the decreasing trend of the Mod-MPI noted with advancing gestation.

Construction of the Mod-MPI reference values paves the way for its use in the clinical setting by identifying the fetus at risk of morbidity and mortality and thus enabling clinicians in making interventions timeously. A number of high risk obstetric conditions in particular pre-eclampsia, intra-uterine growth restriction and diabetes have a significant impact on the fetal heart, albeit from different pathophysiological pathways that include hypoxia, metabolic acidosis and increased

fetal cardiac afterload. We tested these reference values in the above conditions and found them valuable as a tool guiding clinical decision-making. In addition, we have determined the cut-off thresholds (rather than the 95th percentile) for adverse perinatal outcomes in diabetes, IUGR and PET

Mod-MPI may be the only non-invasive technique in monitoring fetuses in gestational diabetes in order to detect a significantly abnormal metabolic milieu. This technique, we believe has the potential to be integrated into routine fetal surveillance techniques of diabetic pregnancies, to reduce perinatal morbidity and mortality, and serve as a guide to clinicians in timing of delivery. To our knowledge, this is the first work that has demonstrated a clear relationship between an altered Mod-MPI and adverse fetal and neonatal outcome in diabetic pregnancies.

We have shown that Mod-MPI and E/A ratios in IUGR fetuses are altered and we have established cut-off values that may dictate intervention. The unique property of the mod-MPI is that it becomes abnormal before hypoxia or acidosis sets in, and as such, this parameter can be used as a monitoring tool for assessing deteriorating cardiovascular function in IUGR fetuses, and thereby guide the physician to optimal timing of delivery before overt acidosis, myocardial necrosis or perinatal death sets in.

In fetuses of pre-eclamptic mothers, evaluation of fetal cardiac function using the mod-MPI and E/A ratios together with the evaluation of umbilical artery Doppler flow has been shown as a modern approach in the management of PET pregnancies. To our knowledge, this is the first work in pre-eclampsia demonstrating the value of categorizing the resistance to blood flow in the fetus with the degree of cardiac dysfunction, as illustrated by using the Mod-MPI.

These studies of fetal cardiac dysfunction in high risk obstetric conditions have provided evidence in bringing cardiac Doppler investigations into the mainstream of antenatal surveillance techniques.

Appendix A

University Approval

Review of Dr IE Bhorat proposal for PhD

15/08/2012

This is an excellent proposal for a very important and potentially ground-breaking study. It is suitable for PhD.

One small comment – the candidate should ensure that data on likely confounders of the case controlled study is collected and controlled for in the analysis.

Appendix B

Ethical Approval

UNIVERSITY OF
KWAZULU-NATAL
INYUVESI
YAKWAZULU-NATALI
RESEARCH OFFICE
Biomedical Research Ethics Administration
Westville Campus, Govan Mbeki Building
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16 November 2012

Dr IE Bhorat
Department of Obstetrics and Gynaecology
Nelson R Mandela School of Medicine
University of KwaZulu-Natal

PROTOCOL: Fetal Cardiac Haemodynamics in Normal and Complicated Pregnancies.
REF: BE228/12

We wish to advise you that your correspondence dated 27 September 2012 in response to BREC letter dated 17 September 2012 for the above study has been noted by the sub-committee of the Biomedical Research Ethics Committee. IALCH approval noted.
Please note that the study remains provisionally approved subject only to KZN Department of Health permission as required by IALCH medical manager (item 2).

Yours sincerely

Mrs A Marimuthu
Senior Administrator: Biomedical Research Ethics

Appendix C

Hospital Approval

health
Department:
Health
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Reference: BE 228/12
Enquiries: Dr M E L Joshua

21 September 2012

Dr IE Bhorat
Department of Obstetrics and Gynaecology
UKZN

Dear Dr Bhorat

RE: PERMISSION TO CONDUCT RESEARCH AT IALCH

I have pleasure in informing you that permission has been granted to you by the Medical Manager to conduct research on: **Fetal Cardiac Haemodynamics in Normal and Complicated Pregnancies.**

Kindly take note of the following information before you continue:

1. Please ensure that you adhere to all the policies, procedures, protocols and guidelines of the Department of Health with regards to this research.
2. This research will only commence once this office has received confirmation from the Provincial Health Research Committee in the KZN Department of Health.
3. Kindly ensure that this office is informed before you commence your research.
4. The hospital will not provide any resources for this research.
5. You will be expected to provide feedback once your research is complete to the Medical Manager.

Yours faithfully

.....
Dr M E L Joshua
Medical Manager

Appendix D

Department of Health Approval

health
Department:
Health
PROVINCE OF KWAZULU-NATAL

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Reference : HRKM142 /12
Enquiries: Mrs G Khumalo
Telephone : 033 – 395 3189

02/10/2012

Dear Dr I E Bhorat

Subject: Approval of a Research Proposal

1. The research proposal titled **'Fetal cardiac haemodynamics in normal and complicated pregnancies'** was reviewed by the KwaZulu-Natal Department of Health.

The proposal is hereby **approved** for research to be undertaken at Inkosi Albert Luthuli Central Hospital.

2. You are requested to take note of the following:
   a. Make the necessary arrangement with the identified facility before commencing with your research project.
   b. Provide an interim progress report and final report (electronic and hard copies) when your research is complete.

3. Your final report must be posted to **HEALTH RESEARCH AND KNOWLEDGE MANAGEMENT, 10-102, PRIVATE BAG X9051, PIETERMARITZBURG, 3200** and e-mail an electronic copy to hrkm@kznhealth.gov.za

For any additional information please contact Mrs G Khumalo on 033-395 3189.

Yours Sincerely

Clutge

Dr E Lutge
Chairperson, Health Research Committee
KwaZulu-Natal Department of Health
Date: 04/10/2012