THE INCIDENCE AND CLINICAL CHARACTERISTICS OF PLACENTAL INSUFFICIENCY AMONG HIGH-RISK PREGNANCIES WITH NORMAL UMBILICAL ARTERY RESISTANCE INDEX AFTER 32 WEEKS GESTATION: A CROSS-SECTIONAL STUDY

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DECLARATION

By submitting this thesis electronically, I declare that the entirety of the work contained therein is my own, original work, that I am the authorship owner thereof (unless to the extent explicitly otherwise stated) and that I have not previously in its entirety or in part submitted it for obtaining any qualification.

Date: December 2015

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Abstract

__Introduction:__ Intrauterine fetal growth restriction (FGR) due to placental insufficiency (PI) is an important cause of perinatal morbidity and mortality. There is also evidence that FGR is associated with neurodevelopmental delay, as well as the development of insulin resistance, obesity, hypertension and diabetes mellitus type 2 as an adult. It is therefore of the utmost importance to develop surveillance strategies and management protocols to reduce the incidence of FGR or, failing that, improving their outcome. Traditionally fetal wellbeing in suspected SGA was assessed by umbilical artery Doppler (UAD) resistance index (RI) or pulsatility index (PI) and if found to be within the normal range, it was seen as a reassuring sign that no significant placental disease is present. However, studies have shown that the pathophysiology of early- and late onset FGR are different and that late onset placental insufficiency (LOPI) may be present even in the presence of a normal umbilical artery Doppler result. The aim of this prospective study was to determine the incidence of LOPI in high risk women with a normal UA RI and assess which clinical variables are associated with this**.**

__Method__: The study was a prospective, descriptive study conducted from 11 February 2013 till 21 October 2013 at Tygerberg Hospital (TBH), a secondary and tertiary referral centre in the Western Cape Province, South Africa, responsible for the Eastern half of the Cape Town Metropole and surrounding areas. The study population consisted of all women referred by the clinical (nursing or medical) staff to the Fetal Evaluation Clinic (FEC) or ultrasound unit at TBH for UA RI assessment according the current Western Cape Ultrasound policy. Exclusion criteria included known fetal anomalies, multiple pregnancies and proven pre-eclampsia. Recruited patients received an ultrasound examination by senior staff and the ultrasound data were captured in Astraia$^©$ database. Based on the ultrasound data the women were divided into 4 subgroups for comparison**.**

__Results__: A total of 228 patients were recruited. Eight were excluded from the study for various reasons (incomplete consent (2), no ultrasound data (3), too early GA after redating (2), known LOPI at time of recruitment (1)). In 10 cases fetal anomalies were noted on ultrasound and these were also excluded – 6 of these had evidence of late onset placental insufficiency and 4 were small for gestational age. This left 210 study participants for the final analysis, with 76 classified as likely LOPI (36.2%) and 134 in the non LOPI group (63.8%). The likely LOPI group was equally divided with 38 (18%) patients each in the average for gestational age (AGA) and small for gestational age (SGA) groups. In the normal placenta group the majority of patients (112 (53%)) were AGA with 22 (11%) being SGA. There were no clinically significant differences between the groups when the baseline characteristics, Doppler and non-Doppler findings were compared**.**

__Conclusion:__ LOPI is a condition that affects a significant proportion of our population. This does not only have consequences for the short term pregnancy outcome, but also for the long term outcomes, with regards to neurodevelopment and the development of metabolic diseases. In settings where pregnancy dating is far less accurate than in developed countries and where customised growth charts are not available, it may not be appropriate to base management algorithms on the expected fetal weight (EFW) centile as inaccurate clinical or relatively late ultrasound dating (after 20 weeks) may not have allowed the EFW to drop below the 10th centile for the assumed (and perhaps underestimated) gestation. This study shows that relying on a distinction between AGA and SGA would seriously underestimate the magnitude of the problem of placental pathology and also illustrates the poor sensitivity of traditional clinical risk factors and grey scale ultrasound findings in identifying the

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pregnancies at risk of LOPI-associated complications. Further studies are needed to assess feasibility and impact of the proposed policy change.

Opsomming

Inleiding: Intrauterine fetale groei beperking (FGR) as gevolg van plasentale ontoereikendheid (PI) is 'n belangrike oorsaak van perinatale morbiditeit en mortaliteit. Daar is ook bewyse dat FGR geassosieer word met neurokognitiewe abnormaliteite, sowel as die ontwikkeling van insulienweerstandigheid, vetsug, hoë bloeddruk en diabetes mellitus tipe 2 as 'n volwassene. Dit is dus van die uiterste belang om toesig strategieë en behandeling protokolle te ontwikkel om die voorkoms van FGR te verminder, of indien nie,`n verbetering in die uitkoms bewerkstellig. Tradisioneel is fetale welstand beoordeel deur umbilikale arterie Doppler (UAD) weerstands indeks (RI) of pulsatiliteits indeks (PI).Indien dit binne normale perke bevind word , is dit gesien as 'n gerusstellende teken dat geen beduidende plasentale siekte teenwoordig is. Studies hetegter getoon dat die patofisiologie van vroeë- en laat aanvang FGR wel verskil en dat laat aanvang plasentale ontoereikendheid (LOPI) teenwoordig kan wees selfs in die teenwoordigheid van 'n normale UAD. Die doel van hierdie studie was om die voorkoms van LOPI in 'n groep hoë risiko vroue met `n normale UA RI te bepaal en te evalueer watter kliniese veranderlikes daarmee verband hou.

Metode: Die studie was 'n prospektiewe, beskrywende studie wat vanaf 11 Februarie 2013 tot 21 Oktober 2013 by die Tygerberg Hospitaal (TBH), 'n sekondêre en tersiêre verwysing sentrum in die Wes-Kaap Provinsie, Suid-Afrika, wat verantwoordelik is vir die Oostelike helfte van die Kaapstad Metropool en omliggende gebiede. Die studie kohort het bestaan uit al die verwysings deur kliniese (verpleging of mediese) personeel na die Fetale Evaluering Kliniek(FEC) of ultraklankeenheid by TBH vir UA RI assessering volgens die huidige Wes-Kaap verloskunde ultraklank beleid . Uitsluitingskriteria het pasiënte met bekende fetale abnormaliteite, meervoudige swangerskappe en pasiënte bekend met pre-eklampsie ingesluit. Gewerfde pasiënte het`n ultraklank ondersoek deur senior personeel in die sonar department ontvang . Die ultraklank data is opgeneem in die Astraia© databasis. Gebaseer op die ultraklank data is die pasiënte in 4 subgroepe verdeel vir vergelyking.

Uitslae: 'n Totaal van 228 pasiënte is gewerf. Agt pasiente is as ontoepaslik beskou en is nie in die studie ingesluit nie. 'n Verdere 10 pasiënte het fetale kongenitale abnormaliteite gehad en was ook uitgesluit- 6 het bewys van laat aankoms plasentaleontoereikenheid gehad en 4 was klein vir hulle swangerskapsduurte.Dit het 210 studie deelnemers vir die finale analise oorgelaat, met 76 geklassifiseerd as waarskynlik LOPI (36,2%) en 134 in die nie LOPI groep(63,8%). Die waarskynlike LOPI groep het gelyke getalle gehad in elke groepmet 38 (18%) pasiënte elk in die gemiddelde gestasie-ouderdom(AGA) en klein vir gestasie-ouderdom (SGA) groepe. In die normale plasenta groep is die meerderheid van die pasiënte (112 (53%)) AGA met 22 (11%) SGA. Daar was geen kliniese betekenisvolle verskille tussen die groepe toe die basislyn eienskappe, Doppler en nie-Doppler bevindings vergelyk is.

Gevolgtrekking: LOPI is 'n toestand wat 'n betekenisvolle deel van ons bevolking affekteer. Dit beteken nie net gevolge op die kort termyn vir die swangerskap nie, maar ook in met betrekking tot neurokognitiewe ontwikkeling en die ontwikkeling van metaboliese siektes. In `n kliniese omgewing waar swangeskapsdatering dikwels nie akkuraat is, en waar daar nie persoonlike groeikaarte beskikbaar is nie, is dit dus baie maklik om die geskatte fetale massa en sonar meetings verkeerd te interpreteer en sodoende SGA en LOPI te mis. Hierdie studie toon dat die vertroue op 'n onderskeid tussen AGA en SGA die omvang van die probleem ernstig sou onderskat . Dit illustreer ook die swak sensitiwiteit van tradisionele kliniese risiko faktore en swart en wit ultraklank bevindinge in die

identifisering van die swangerskappe wat in gevaar is vir die risiko van LOPI-verwante komplikasies .Verdere studies is nodig om die haalbaarheid en die impak van die voorgestelde beleids verandering te evalueer.

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List of abbreviations

AC – abdominal circumference
AFI – amniotic fluid index
AGA – appropriate for gestational age
BPD – biparietal diameter
CHT – chronic hypertension
CPR – cerebroplacental ratio
DM – diabetes mellitus
EFW – estimated fetal weight
EOPI-early onset placental insufficiency
EUS – early ultrasound
FEC- fetal evaluation clinic
FGR – fetal growth restriction
FL – femur length
GA – gestational age
GHT – gestational hypertension
HC – head circumference
HCG- human chorionic gonadotropin
HPT – hypertension
IUFD – intrauterine fetal death
LMP – last menstrual period
LOPI – late onset placental insufficiency
LUS – late ultrasound
MCA – middle cerebral artery
MoM – multiples of the median
PAPP-A- pregnancy-associated plasma protein A
PI – pulsatility index
PSV – peak systolic velocity
RCOG- Royal College of Obstetricians and Gynaecologists
RI – resistance index
SFH – symphysis-fundus height
SGA – small for gestational age
SLE – systemic lupus erythematosus
TBH – Tygerberg Hospital
UA – umbilical artery
Ut A – uterine artery
WHO- world health organisation

Introduction

The development of the placenta is a highly regulated process that is essential in normal growth and development of the fetus, as well as the maintenance of the healthy pregnancy. The placenta has many roles – it prevents rejection of the fetal allograph, facilitates respiratory gas exchange and transport of nutrients and eliminates fetal waste products. It also secretes peptide and steroid hormones. The majority of the blood flow to the uterus is through the uterine arteries. Trophoblastic invasion of the spiral arteries within the myometrium and decidua as well as an increase in maternal blood volume results in an increase in uterine blood flow. When normal throphoblastic invasion and modification of the spiral arteries are interrupted the resultant increase in resistance within the uterine arteries lead to a decrease in placental perfusion. This leads to a relative hypoxia and/or ischemia that can be detrimental to fetal development and growth.

Intrauterine fetal growth restriction (FGR) due to placental insufficiency is an important cause of stillbirths. The estimated number of worldwide stillbirths in 2009 was 2.64 million, (uncertainty range 2.14 to 3.82 million) with two thirds of stillbirths worldwide occurring in South-east Asia and Africa (1).

There is also evidence that FGR is associated with neurodevelopmental delay, as well as the development of insulin resistance, obesity, hypertension and diabetes mellitus type 2 as an adult (2, 3). Globally the incidence of these metabolic disorders is increasing and they place a significant burden on healthcare systems. According to the World Health Organisation (WHO) global status report (4)there were 56 million deaths worldwide in 2012. Of these 38 million (± 57%) were due to non-communicable diseases with cardiovascular disease contributing to 46.2% and Diabetes mellitus contributing to 4%. Three quarters of the deaths due to non-communicable disease occurred in low- and middle income countries with a worldwide increase in deaths from non-communicable disease from 31 million in 2000. In the latest publication on the mortality and cause of death in South Africa, 2013 from Stats SA, 32% of the deaths were due to cardiovascular disease (9.9%), diabetes mellitus (9.8%), hypertension (7.5%) and ischemic heart disease (4.8%) (5). Likewise the time and costs needed to care for a child with neurocognitive disabilities contribute to a significant burden on healthcare as well as individual families and communities (6).

It is therefore of the utmost importance to develop surveillance strategies and management protocols to reduce the incidence of FGR or, failing that, improving their outcome. The first challenge is to identify pregnancies at risk for or complicated by FGR. Not all small fetuses are FGR, as 10% of normal pregnancies will result in constitutionally small for gestational age (SGA) fetuses. Ultrasound is an important tool to differentiate causes of SGA, not only by accurately dating pregnancies, but by excluding aneuploid or euploid syndromes and anomalies responsible for the small size, where intervention by early delivery is not beneficial.

The reverse is also true; not all FGR fetuses are SGA (3). It is therefore not effective to rely only on fetal size as an indicator for at risk pregnancies.

Traditionally fetal wellbeing in a suspected SGA fetus was assessed by umbilical artery Doppler (UAD) resistance index (RI) or pulsatility index (PI) and if found to be within the normal range, it was seen as a reassuring sign that no significant placental disease is present. However, studies have shown that the pathophysiology of early- and late onset FGR are different and that late onset placental

insufficiency (LOPI) may be present even in the presence of a normal umbilical artery Doppler result (5).

The current Western Cape Ultrasound policy completely relies on the interpretation of the UA RI to distinguish between healthy, well-nourished fetuses and fetuses with FGR (6). In a study by Theron et al (7) the authors concluded that symphysis-fundal height (SFH) measurements followed by UAD RI in cases with poor SF growth were sufficient to detect IUGR babies at risk of complications, and that all fetuses with possible placental insufficiency are thus identified. The policy does not make provision for any further Doppler or ultrasound assessment in cases where the UA RI is within the normal range, as such a finding is seen as confirmation that placental insufficiency is not present and that the fetus is not at increased risk for distress or intra uterine fetal demise (IUFD). While this may be appropriate for early onset placental insufficiency (EOPI), the current policy makes no distinction based on the gestational age (GA) at the time of the investigation. With new insights into the progression and outcome of LOPI, this policy may need to be revised. This is relevant since the new fetal evaluation clinics (FEC) in the region are now manned by sonographers with the necessary skill and equipment to perform more extensive Doppler assessment of the fetoplacental circulation in addition to the UA RI. A change in policy would therefore be feasible if the incidence of LOPI amongst cases currently labelled as "normal" is high enough to justify this.

The aim of this prospective study was to determine the prevalence of LOPI in low risk women with normal UA RI and to describe the associated clinical variables.

Literature review

Normal fetal growth is determined by various factors such as the genetically predetermined growth potential as well as fetal, maternal and external factors. The failure to grow normally can likewise have a varied aetiology including for example chronic hypertension (CHT), pre-eclampsia, autoimmune disease, smoking and placental abnormalities (8).

Pathophysiology of intrauterine growth restriction

Placental insufficiency already starts with placental development. Trophoblast invasion into the media of the maternal spiral arteries facilitates a decrease in downstream blood flow impedance and maximizes blood supply to the intervillous spaces. Villous sprouting and differentiation is integral to the decrease in blood flow resistance in the fetal umbilical artery, the increase of the area for nutrient and waste exchange as well as a decrease in the diffusion distance, especially for oxygen (9).

Early placental vasculogenesis and angiogenesis are controlled by various substances, such as placental growth factor, angiopoietins, placental protein A, endoglins and vascular endothelial growth factor (5, 10). The relative insensitivity of the maternal circulation to these vasoactive substances result in a relative increase in maternal cardiac output, as well as a decrease in peripheral vascular resistance and blood pressure from as early as 8 weeks gestation. Successful trophoblast invasion results in the loss of diastolic notching of the uterine arteries by the end of the first trimester, and resistance decreases till the end of the pregnancy (11).

In the umbilical artery the presence of end diastolic forward flow is established by the end of the first trimester, and the umbilical artery blood flow resistance continues on a downwards trend till the end of the pregnancy.

Three organs are responsible for maintaining fetal growth and wellbeing: the heart, which maintains the circulation; the liver which provides all the blood components, proteins and blood cells (by physiologic extramedullary hematopoiesis); and the placenta which is responsible for all exchange functions, oxygen supply and nutrition. (12)

Should there be any inadequacy in the maternal supply line, it will be revealed by the detection of placental areas that have ceased to function. A parenchyma loss pattern is usually recognised on macroscopic examination of the placenta by the presence of focal lesion, most commonly begin infarcts of varying size and age. On microscopic examination accelerated compensatory maturation of the chorionic villi in the remaining functional areas of the placenta could be seen. Maturation is the main mechanism by which the placenta meets growing fetal demand in the last 2 months of pregnancy. A study by Stallmach et al showed that severe maturation defect increased the risk of fetal death 70-fold and the risk of recurrent stillbirth tenfold.(12, 13) Grannum classification has been used for ultrasound placental grading. Grade III placental calcification is characterised by the significant formation of indentations or ring-like structures within the placenta is often found in term pregnancies and is of no significance. However, the presence of calcification before 36 weeks gestation may represent an abnormal placenta. Abnormal appearance of the placenta at the second trimester ultrasound scan (e.g. placental calcification or lakes) was found to correlate with placental infarction and uteroplacental dysfunction. Preterm placental calcification (the presence of calcification before 36 weeks) is a major risk factor for adverse maternal and neonatal outcomes

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including preterm delivery, low birth weight, and neonatal death in both low-risk and high-risk pregnancy populations. (32)

The fetus has 3 major shunts to facilitate nutrient and oxygen distribution (5). The first shunt is the ductus venosus where 70-80% of the nutrient and oxygen rich blood gets shunted towards the liver, with about 60% of the blood in the liver shunted to the left liver lobe. The remaining blood is directed towards the right atrium and foramen ovale. Via the foramen ovale the majority of the nutrient rich blood is directed to the left ventricle, from where it reaches the myocardium and cerebral circulation. The nutrient depleted blood from the venae cava mainly goes through the right ventricle to the pulmonary vasculature and then the descending aorta. In the ductus arteriosus the blood streams from both ventricles coalesce. Should there be a decrease in the left ventricular after load (such as with mid-cerebral artery [MCA] dilatation) or an increase in right ventricular after load (increase in placental resistance to blood flow) there will be preferential blood flow to the brain and the myocardium. This effect is due to auto-regulation in the brain to ensure optimum oxygen and nutrient delivery in times of relative shortage.

The fetus responds to placental dysfunction with early compensatory and late decompensatory mechanisms. This occurs mainly in three phases. The first phase is subclinical and characterized by venous redistribution. A decrease in blood flow in the umbilical vein with a decreased proportion of the fetal cardiac output that is distributed to the placenta are some of the vascular signs that precede the development of clinical growth restriction. A decrease in the resistance in the ductus venosus leads to increased shunting of nutrient rich blood to the left side of the heart, as well as intrahepatic shunting of blood away from the right liver lobe. This causes a down regulation of the glucose-insulin-insulin like growth factor growth axis with resultant decreased glycogen storage in the liver (insulin like growth factors are proteins with high similarity to insulin. They are part of a complex system that cells use to communicate with their physiologic environment). This leads to a smaller liver size that in turns manifests as a decrease in the abdominal circumference (14).

After the "pre-clinical" phase there is a phase of early symptoms of arterial redistribution and delayed behavioral development. The early sub-clinical increase in the placental blood flow resistance with a resultant decrease in the cerebral blood flow resistance results in a decrease in the cerebro-placental ratio (CPR: MCA PI/UA PI). When ± 1/3 of villous vasculature is obliterated due to placental pathology the umbilical artery Doppler indices increase, the fetal blood pressure increases and the oxygen transfer decreases, resulting in a decrease of the MCA Doppler indices, or so called redistribution. In chronic fetal hypoxia there is a decrease in the resistance to blood flow in the cerebral arteries due to vasodilatation in the auto regulation process. In the hypoxic fetus there is hemodynamic adaptation with preferential perfusion to the fetal brain, heart and adrenals. This is a compensatory adaptive mechanism that centralizes circulation to maintain perfusion to the essential organs. This process is sometimes referred to as brain sparing. In this phase there is a relative increase in fetal heart rate baseline and a decrease in the variability, as well as a delay in heart rate reactivity and behavioral states. These signs are frequently sub-clinical, but can be useful in detection and monitoring of early growth restriction (5, 15).

When there is ≥50% villous obliteration of the placenta the umbilical artery end-diastolic flow becomes absent and then reversed. The fetus is then at a high risk for fetal hypoxia and acidemia. These are already late signs of fetal response to placental insufficiency. The increase in placental

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vascular resistance results in an increase in the right ventricular after load, which in turn results in the shunting of more blood over the foramen ovale towards the left ventricle. In the aortic isthmus there is initially a decrease in the diastolic forward flow, that will become absent and eventually reversed as the disease progresses. This is proportional to the increase in fetoplacental blood flow resistance. These changes result in the redistribution of nutrient rich, but importantly also nutrient poor blood to the myocardium and cerebral circulation. Once absent or reversed end diastolic flow is present, abnormalities in venous flow patterns become evident. The ductus venosus dilates to facilitate the cardiac diversion of blood, but it also allows retrograde transmission of atrial pressure-volume changes. Once the cardiac output drops and the central venous pressure rises there is decreased forward cardiac output that results in an increase of the venous Doppler indices, seen as an absent a-wave and eventually a-wave reversal in the ductus venosus with progressive pulsatility (14, 16).

As the arterial and venous Doppler indices deteriorate, there is a progressive loss of the biophysical parameters. First there is a decrease in fetal heart rate reactivity, followed by the loss of breathing, gross body movements and tone. The change in the amniotic fluid index is independent from the biophysical deterioration and is more closely related to the cardiovascular deterioration. When nutritional deficiency is sufficiently severe, or has persisted for a long enough period, the growth rate of all the fetal measurements slows down and the sonographic estimated fetal weight falls below the 10th centile (5, 17, 18).

In early growth restriction (<34 weeks GA) late cardiovascular manifestations of placental insufficiency become more likely when the UA EDF velocity is reversed (REDV). The typical pattern of deterioration progresses from increasing abnormalities in UA and venous Doppler parameters to abnormal biophysical profiles. In this setting the diminishing supply of glucose forces the brain and heart to metabolise lactate and ketones as the primary energy source. As the placental function worsens the supply of lactate and ketones also becomes impaired. Their deficiency has been linked independently to neurodevelopmental disorders. The deterioration of the UA Doppler parameters correlates closely with the overall speed of deterioration of the FGR and can be used as a monitoring device to assist with management decisions. The fetus with growth restriction is more susceptible to sudden changes in the uterine-placental flow with a higher risk of hypoxia, acidosis, meconium passage in utero and intrapartum death. In the TRUFFLE study it was found that 8% of babies died after a diagnosis of fetal growth restriction was made with a third of these occurring in the antenatal period (19).

In contrast, in late onset growth restriction (>34 weeks GA) the placental dysfunction tends to be less severe, and the cardiovascular abnormalities rarely extend beyond the cerebral vasculature. It is typically characterised by milder placental dysfunction and may often not produce an elevation in the UAD RI. The only sign of placental dysfunction and insufficiency may be Doppler changes in the MCA with an increase in diastolic flow velocity, the so-called "brain sparing effect" as mentioned earlier. This is followed by cerebral redistribution of blood from the frontal lobe towards the basal ganglia with an increased vulnerability of the frontal lobe areas. In the neonate this manifests as socio-interactive and attention deficits, while later in life performance attention, communication, problem solving, emotion and social function might be impaired (2, 16, 20).

Screening and diagnosis

The first challenge is in recognising all cases of growth restriction. In routine clinical practice as many as three quarters of fetuses at risk for FGR are not diagnosed before delivery. The rate of detection is

as low as 15% in low risk pregnancies where there is a lower threshold of suspicion(15).There is an added complication in that the term SGA and FGR are commonly used interchangeably. The term SGA refers to a weight for gestation below a given threshold (typically the 10th centile for the population), with no distinction between fetuses that are small due to physiological or constitutional causes or fetuses that are small due to placental pathology (FGR). Conventional population growth charts do not take maternal characteristics into consideration with the overall result that maternal physiological variables like booking weight, height, parity, ethnicity etc. are mostly ignored in clinical practice, while it is well known that they do affect fetal growth significantly. A survey done by Gardosi et al (12) showed that when physiological variables are not taken into account about a quarter of diagnoses of SGA is false-positives. The reverse is also true that many SGA fetuses are missed if conventional population based growth charts are used instead of customised growth charts. In studies of birth weight databases, SGA based on a customised growth chart is more strongly associated with abnormal antenatal Doppler findings, fetal distress and emergency caesarean section, admission to neonatal wards as well as stillbirths and neonatal deaths.

The validation of the principles of growth potential has allowed FGR to be introduced as an additional category when classifying stillbirths. Traditional classification systems for perinatal mortality such as the Wigglesworth or 'Obstetric/Aberdeen' system did not have a category for SGA or FGR (21). A category of 'fetal growth restriction' has been included in a new stillbirth classification system called ReCoDe (relevant condition at death). After this system was introduced, the proportion previously considered "unexplained stillbirth" dropped to 15%, down from 65-70% when the Wigglesworth classification was used. Examination of cases through confidential enquiry panels has shown that, of term stillbirths weighing less than the 10th centile of a customised weight chart, 84% were considered to be potentially avoidable (21).

According to the Western Cape provincial delivery database there were 29547 deliveries in the Tygerberg Hospital general specialist drainage area (Metro East including Grabouw) in 2012. Customised antenatal growth charts cannot be used for all pregnant women since that would involve routine and serial ultrasound examinations, as well as access to electronic devices such as computers and the development of growth norms for all ethnic groups in the area.

A more efficient approach is screening to identify "high risk" pregnancies that will benefit from closer surveillance. The maternal medical and obstetric history as well as physical examination is important and relatively easy to obtain. A history of a previous FGR baby puts the current pregnancy at a 50% increased risk for severe FGR. A history of stillbirths before 32 weeks gestation also has a strong association with FGR. Women with diabetes are not only at risk for macrosomia, but also for FGR with 15% of women with Type 2 Diabetes diagnosed with a pregnancy with FGR. They also have an increased risk of developing pre-eclampsia, an extra risk factor for FGR, with 15-20% of pregnancies of women with diabetes mellitus (DM) type 1 without nephropathy and as much as 50% of pregnancies of women with DM type 1 with nephropathy developing pre-eclampsia (15). Hypertensive disorders in pregnancy increase the incidence of FGR 2-3 fold. Many other maternal conditions such as cyanotic cardiopathies, restrictive lung disease, severe renal conditions, auto-immune diseases, inherited or acquired thrombophilias, hyperchromocysteinaemia and severe anaemia are also associated with FGR (19). Obesity has historically been considered a protective factor for FGR, but findings show that obesity increases the risk for FGR by 50% (15). Multiple pregnancies also pose a risk for FGR, but as

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they are managed according to well established protocols that are in place to identify complications such as FGR, they will not be discussed in detail.

Biochemical screening for FGR in the first trimester may consist of pregnancy-associated plasma protein A (PAPP-A) and human chorionic gonadotropin (HCG).Unexplained low values are associated with an increased risk for placental diseases such as FGR or pre-eclampsia. In the second trimester, an unexplained elevation of the serum alpha-fetoprotein, HCG or inhibin-A are also associated with the development of placental disease (15). In general though, the association is more marked for pre-eclampsia and early-onset FGR than for LOPI. Despite the associations with placental disease, the performance in terms of sensitivity/specificity and predictive values of these markers individually or combined currently does not support their use in the screening for late FGR (15).

Uterine artery evaluation in the first or second trimester has been proposed for predicting early onset FGR (22). Vergani *et al* showed that in cases of ultrasonic diagnosis of FGR ≥34 weeks gestation, abnormal Doppler waveforms in the uterine arteries were associated with a 4-fold increased risk of neonatal admission, as well as earlier delivery, greater risk of caesarean section and of lower birth weights than FGR fetuses with normal uterine artery Doppler indices According to the RCOG Green-top Guideline no 31 (23)all women should be assessed for risk factors for FGR at booking and women who are evaluated as high risk should be offered uterine artery Doppler at 20-24 weeks (23). An abnormal uterine artery Doppler at 20-24 weeks have a moderate predictive value in the high risk population and those patients should be referred for more intense surveillance. Antiplatelet agents may be effective in preventing FGR in women who are at high risk for pre-eclampsia. Although the effect size is small Aspirin should be started before 16 weeks gestation for women who are high risk for pre-eclampsia.

In the third trimester the use of serial fundal height measurement and the plotting on customised growth charts are recommended by the RCOG Green-top Guideline no 3. As a serial measurement the emphasis with fundal height measurement is on the slope of the curve. Referral guidelines for further investigation by ultrasound biometry and Doppler include a single fundal height measurement that falls below the 10th centile, and serial measurements that plateau or cross centiles. The challenge is to standardise this tool to improve its reliability and effectiveness. A recently updated meta-analysis showed that routine late pregnancy ultrasound in a low-risk population does not confer any benefit to the mother or the baby, and might lead to a small increase in caesarean section rates (15).

For pregnancies at risk, serial assessment of estimated fetal weight (EFW) or abdominal circumference (AC) is the best predictor of FGR. EFW is an easy and straightforward way in which to screen for intrauterine growth restriction. It is tempting to compare EFW with the distribution of birth weight, but the use of birth weight curves might miss the diagnosis of IUGR. IUGR is over-represented in premature deliveries, the use of birth weight curves might lead to a missed diagnosis of IUGR. There is an important discrepancy between birth weight and EFW at the same GA in fetuses who will eventually deliver at term. Previous reports suggest that preterm infants are somewhat smaller than fetuses of the same gestational age while still in utero. EFW and birth weight charts tend to merge by the end of pregnancy. At term, the EFW provides a good estimate of birth weight. Therefore, serial biometry is the gold standard for assessing pregnancies that are high risk, either on basis of past history or due to complications that arose in the current pregnancy, but interpretation thereof requires accurate dating (24). Eight biophysical features are commonly observed in high risk

pregnancies. Four reflect the acute wellbeing of the fetus: fetal movement, fetal tone, fetal breathing movements and CTG. The other four reflect the chronic state of the fetus: UAD, placental architecture, AFI and EFW (25).

The mortality rate of FGR is largely influenced by GA and birth weight at delivery; this poses a dilemma as iatrogenic earlier delivery is associated with a higher mortality rate but also a higher rate of illness in infancy and sudden neonatal deaths, whereas delayed delivery increases the risk of stillbirth. This dilemma is more pronounced before 28 weeks gestation when each day gained in utero increases the survival and intact survival by 1-2%. In the majority of early-onset FGR abnormal UAD are documented and these correlate with the severity of placental disease. While in EOPI the management challenge is a balancing act between severe iatrogenic prematurity and fetal metabolic deterioration, the current challenge in LOPI is the failure to recognise the condition in the first place or the failure to time delivery appropriately due to the false reassurance of the normal UA Doppler indices.

Late onset FGR (> 34 weeks) often goes undetected due to the mild Doppler abnormalities and subtle biophysical changes. Isolated brain sparing with a normal UAD is characteristic of this group. This poses a significant clinical problem, as late onset FGR contributes to >50% of stillbirths at term in international literature (1, 5, 26). A local study done in 2010 cited the number of stillbirths related to IUGR at 14.7%, but no differentiation was made between early- and late-onset growth restriction. Unexplained intrauterine deaths constituted 7.4% of total deaths (27).

Infants born after being exposed to an intrauterine milieu of nutritional insufficiency are also at higher risk of developing insulin resistance, diabetes mellitus type 2, obesity, hypertension and atherosclerosis later in life (3). This phenomenon is explained by the "Barker phenomenon", also sometimes called the "thrifty phenotype" (28). The general idea is that in a poor nutritional environment the development of the unborn child can be altered so that it will be able to adapt to an extra uterine environment where nutritional resources are scarce. However, when this child then is raised in an environment where there are sufficient nutritional resources, this response can backfire and lead to the development of chronic disease later in life.

Methods

The study was a prospective, descriptive study conducted from 11 February 2013 till 21 October 2013 at Tygerberg Hospital (TBH), a secondary and tertiary referral centre in the Western Cape Province, South Africa, responsible for the Eastern half of the Cape Town Metropole for secondary referrals and for tertiary referrals from the Winelands West and West coast rural areas. The study population consisted of all women referred by the clinical (nursing or medical) staff to the Fetal Evaluation Clinic (FEC) or ultrasound unit at TBH for UA RI assessment according the current Western Cape Ultrasound policy(6). Indications for referral included poor growth as indicated by a symphysis-fundus height (SFH) <10th centile of the local reference range, no SFH growth in 4-6 weeks, hypertension in pregnancy, previous unexplained mid-trimester or third-trimester fetal loss and diabetes. (Last three all at 24 weeks or as soon as possible thereafter). Although the patients may have had other risk factors only the current indication for referral was taken into account.

Women with an abnormal UA RI were referred to the medical team responsible for further management as per current provincial protocol. Women with a normal UA RI (<95th centile of the local reference range[15]) and who were assessed as having reached a GA of at least 32 weeks by best estimate, barring any exclusion criteria, were eligible for the study. Exclusion criteria included known fetal anomalies, multiple pregnancies and proven pre-eclampsia.

Eligible women were counselled and written consent was obtained in English, Afrikaans or Xhosa. Basic information regarding the patient`s demographics, previous medical and obstetric history as well current pregnancy were collected on recruitment. The gestational age was determined according to the guideline in the current Western Cape Ultrasound policy. Gestational age was calculated using the last menstrual period (LMP), booking SFH and previous ultrasound. Certain menstrual history was defined as certain of the exact date of the first day of the LMP, normal amount and duration of vaginal bleeding, regular cycle of 25-31 days with no bleeding since the LMP and no hormonal contraception within 3 months prior to LMP.GA was considered accurate if calculated using certain LMP compatible with early ultrasound (EUS) or late ultrasound (LUS), or ultrasound alone if done before 24 weeks GA.

Recruited patients received an ultrasound examination by senior staff and the ultrasound data were captured in the Astraia[©] database. Biparietal diameter (BPD), head circumference (HC), abdominal circumference (AC), femur length (FL) using the charts of Chitty(29), amniotic fluid index (AFI), placental anatomy, UA RI, UA PI, uterine artery (Ut A) PI and presence of early diastolic notching, MCA PI and peak systolic velocity (PSV) were recorded. All results were made available to the clinical team responsible for further management of the pregnancy. If the assumed GA at referral was implausible based on the current ultrasound findings and all available information, the pregnancy was re-dated to obtain the final GA to be used for the analysis. Redating was not performed if an earlier ultrasound was available or if the difference between the assumed GA and the ultrasound estimate was less than 2 weeks (3 weeks if based on early SFH, preceding the scan by more than 10 weeks).

Based on the ultrasound data the women were divided into 4 subgroups for comparison:

Women in whom all Doppler values were within the normal range were regarded as not having placental insufficiency (non-LOPI).

If the EFW was>P10 for the final GA on the Salomon centile chart (24)they were labelled as non- LOPI average for GA (AGA).

If the EFW was <P10 for the final GA on the Salomon centile chart they were labelled as non-LOPI small for GA (SGA)

Women in whom either the UA PI or mean UtA PI were > P95 or the cerebroplacental ratio or MCA PI <P5 were regarded as likely having placental insufficiency (likely-LOPI).

If the EFW was > P10 for the final GA on the Salomon centile chart they were labelled as likely-LOPI AGA

If the EFW were < P10 for the final GA on the Salomon centile chart they were labelled as likely- LOPI SGA

STATISTICA version 10 was used to analyse the data. Depending on the distribution of the data, with means or medians with standard deviations or centiles as appropriate, non-LOPI and likely-LOPI cases were compared regarding abovementioned variables by Student`s t-test for normally distributed variables, non-parametric tests for not-normally distributed data and Chi-square for categorical data (or Fisher`s test where the numbers were too small) to identify any non-Doppler predictors of likely-LOPI cases.

Consent to perform the study was obtained from the University of Stellenbosch Health and Research Ethics committee. Ethics reference number S12/09/238

Results

A total of 228 patients were recruited. Eight were excluded from the study for various reasons (incomplete consent (2), no ultrasound data (3), too early GA after redating (2), known LOPI at time of recruitment (1)). In 10 cases fetal anomalies were noted on ultrasound and these were also excluded – 6 of these had evidence of LOPI and 4 were SGA. Abnormalities noted included:

nuchal oedema and liver calcifications
clenched fists
cardiac abnormality
unbalanced AVSD
nuchal oedema
nuchal oedema and pericardial effusion
ventriculomegaly
increased prenasal thickness, short femurs and brachycephaly
hydronephrosis
congenital syphilis

This left 210 study participants for the final analysis, with 76 classified as likely LOPI (36.2%) and 134 in the normal placenta group (63.8%). in the likely LOPI group there were equal numbers of patients- 38 (18% of total study group) patients each in the AGA and SGA groups. In the non-LOPI group the majority of patients (112 [53%]) were AGA with 22 (11%) being SGA.

In Table 1 the study cohort is described in terms of baseline characteristics and demographic data Almost 84% of patients had an ultrasound done by time of enrolment, with 78.4% of these being done before 24 weeks gestation. This led to a GA that was considered reliable in 69.5% of patients.

Table 1: Demographic data and baseline characteristics of study cohort

	N of patients (%) of total	Mean ± SD Median (P10-P90)
N	210	
Age (years)		27.4±6.6
Gravidity:		3 (1-5)
Parity: Nullipara	49 (23.3%)	1(0-3)
Miscarriage	36(17.1%)	0 (0-1)
Body mass index (kg/m$^{2)}$) >30-<35 ≥35	31 (14.8%) 44 (21%)	28.4±8.3
N with prior ultrasound GA at first ultrasound # <14 w <20w <24w	176 (83.8%) 38/176 (21.6%) 83/176 (41.2%) 138/176 (78.4%)	20.2±6.9
GA considered reliable	146 (69.5%)*	
# Of patients who had an ultrasound prior to referral GA – gestational age * GA was considered accurate if calculated using certain LMP compatible with early ultrasound (EUS) or late ultrasound (LUS), or ultrasound alone if done before 24 weeks GA.		

In Table 2 the various risk factors for placental insufficiency are shown for the 4 groups. The majority of patients had either no relevant obstetric history, or no underlying medical condition and 81 (38.6%) had neither. The previous obstetric history and the current underlying medical conditions did not differ across the 4 groups and between Likely-LOPI and non-LOPI cases ($p>0.05$)

The largest number of patients were referred either for suspected poor fetal growth as measured by SFH (83 or 40%), or a history of previous IUD/Abruption (67 or 32%) and the proportion of the different indications did not differ significantly between the 4 groups apart from significantly more referrals for poor SFH growth in non-LOPI SGA ($p<0.05$). Of the patients who were referred for poor SF growth none had current medical conditions, and only 5 had previous obstetrics history (1 previous IUGR, 2 recurrent miscarriages and 2 previous gestational hypertension).

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Table 2: Clinical risk factors for placental insufficiency

	Likely LOPI AGA	Likely LOPI SGA	Normal placenta AGA	Normal placenta SGA
N	38	38	112	22
Relevant previous obstetric history				
Nil	15(39.5%)	23(60.5%)	68(60.7%)	14(63.6%)
Recurrent miscarriages	1 (2.6%)	0	2 (1.8%)	1 (4.6%)
Abruption IUD	1(2.6%)	0	2(1.8%)	0
IUD	14(36.8%)	10(26.3%)	28(25.0%)	6(27.3%)
FGR	0	2(5.3%)	0	0
HPT with IUD	2(5.3%)	0	4(7.1%)	0
GHT/Pre-eclampsia	5(13.2%)	3(7.9%)	8(7.1%)	1(4.6%)
Underlying medical condition				
Nil	29(76.3%)	31(81.6%)	85(75.9%)	21(95.5%)
CHT	7(18.4%)	7(18.42%)	17(15.2%)	0
CHT + DM	0	0	7(6.3%)	0
SLE	1(2.6%)	0	3(2.7%)	0
GHT	0	0	0	1(4.6%)
Renal	1(2.6%)	0	0	0
SFH pattern at referral				
N [$]	9 (23.7%)	16 (42.1%)	42 (37.5%)	13 (59%)
Normal	0	0	1 (2.4%)	0
Plateau	0	0	7 (16.7%)	0
Drop since last visit	2 (22.2%)	1 (6.25%)	4 (9.5%)	1 (7.7%)
Drop < P10	7 (77.8%)	15 (93.8%)	30 (71.4%)	12 (92.3%
$- number of patients who had SFH measurements done prior to referral. IUD – intrauterine death, FGR – fetal growth restriction, HPT- hypertension, GHT- gestational hypertension, CHT – chronic hypertension, DM – diabetes mellitus, SLE- systemic lupus erythematosus				

In line with our subgroup-definitions significant differences in Doppler results were anticipated as depicted in Table 3. As expected, the mid-cerebral artery PI and the CPR were different between the likely LOPI and normal placental groups, as this was used as part of the diagnostic criteria. However, the UA RI did not differ much between the four groups. LOPI was less common if the RI was below P50 compared to above P50 (37/128 (33%) vs. 39/82 (48%) p=0.006).

Table 3: Doppler findings

	Likely LOPI AGA	Likely LOPI SGA	Normal placenta AGA	Normal placenta SGA
N	38	38	112	22
Mean uterine PI				
N	38(100%)	38(100%)	107(95.5%)	21(95.5%)
Mean ±SD	1.05±0.27	1.14±0.38	0.72±0.14	0.73±0.14
Bilateral notch	6(15.8%)	10(26.3%)	0	4(19%)
Any notch	14(36.8%)	19(50%)	2(1.9%)	12(57.1%)
P<50	3(7.9%)	3(7.9%)	56(52.3%)	8(38.1%)
P50-95	13(34.2%)	12(31.6%)	51(47.7%)	13(61.9%)
>P95	22(57.9%)	23 (60.5%)	0	0
UA RI				
N	38(100%)	38(100%)	112(100%)	22(100%)
Mean±SD	0.65±0.07	0.66±0.09	0.60±0.06	0.61±0.06
Median (P10-90)	0.65 (0.57–0.72)	0.67(0.56-0.76)	0.60 (0.56-0.67)	0.62(0.51-0.67)
P<50	10(26.3%)	9(23.7%)	58(51.8%)	9(40.9%)
P50-95	9(23.7%)	8(21.1%)	36(32.1%)	8(36.4%)
P75-95	17(44.7%)	8(21.1%)	18(16.1%)	5(22.7%)
>P95	2(5.3%)	13(34.2%)	0	0
UA PI				
N	38(100%)	38(100%)	112(100%)	22(100%)
Mean±SD	1.04±0.17	1.11±0.25	0.90±0.14	0.93±0.13
Median (P10-90)	1.03 (0.8–1.3)	1.13(0.76-1.37)	0.89(0.75-1.09)	0.94(0.69-1.09)
<50	6(15.8%)	7(18.4%)	54(48.2%)	7(31.8%)
P50-95	23(60.5%)	16(42.1%)	58(51.8%)	15(68.2%)
>P95	9(23.7%)	15(39.5%)	0	0
MCA PI				
N	38(100%)	37(97.4%)	111(99.1%)	21(95.5%)
Mean ±SD	1.73±0.44	1.56±0.45	1.90±0.38	1.85±0.28
Median (P10-90)	1.7 (1.15-2.45)	1.49(1.03-2.17)	1.87 (1.40-2.40)	1.82(1.53-2.20)
P>50	18(47.4%)	11(29.7%)	59(53.2%)	13(61.9%)
P5-50	13(34.2%)	16(43.2%)	52(46.8%)	8(38.1%)
<P5	7(18.4%)	10(27%)	0	0
Vmax				
Valid N	29(76.3%)	29(76.3%)	96(85.7%)	19(86.4%)
mean±SD	61.2±10.6	64.0±12.7	59.0±10.3	58.2±9.7
Median (P10-90)	62.7 (46-75.5)	62.0 (54.0-74.0)	59.5(45.8-72.6)	58.0 (43.0-71.9)
>1.5 Mom	2(6.9%)	3(10.3%)	2(2.1%)	2(10.5%)
CPR				
N	38(100%)	37(97.4%)	111(99.1%)	21(95.5%)
Mean±SD	1.69±0.43	1.47±0.48	2.11±0.36	2.02±0.39
Median (P10-90)	1.69 (1.19-2.18)	1.45(0.84-2.12)	2.06(1.68-2.63)	2.0(1.59-2.56)
P>50	7(18.4%)	4(10.8%)	54(48.6%)	5(23.8%)
P2.5-50	17(44.7%)	15(40.5%)	58(52.3%)	16(76.2%)
<P2.5	14(36.8%)	18(48.6%)	0	0

The groups were compared regarding non-Doppler findings (Table 4). Ultrasound-based re-dating reclassified 16 non-LOPI SGA cases as AGA. Only 3 cases (all LOPI-SGA) had a pathological HC/AC ratio indicating asymmetric growth. Placental maturation was appropriate for the gestation in all but 5 cases, 3 of which had likely LOPI. The AFI was lower in LOPI (p=0.009) and especially in LOPI-SGA (p<0.000). Reduced liquor (AFI < 8cm) was more common in LOPI (p=0.04) especially in LOPI-SGA (p=0.002) but oligohydramnios was rare. LOPI was more common when liquor was reduced compared to normal (11/38 (28.9%) vs. 27/192 (14.2%) p=0.04).

In total 183/210 patients had normal liquor, normal placenta and normal HC/AC ratio (60 of all LOPI (79%) vs. 123 of non-LOPI [92%]). There was a significant difference in EFW between the AGA and SGA groups, but not between subgroups of likely LOPI and non-LOPI. Using the Salomon EFW reference range significantly increased the number of cases identified as SGA compared to the birth weight reference range of Theron *et al* (30) (increase by 26 cases, incl. 17 of likely LOPI).

Table 4: Non-Doppler findings

	Likely LOPI AGA	Likely LOPI SGA	Normal placenta AGA	Normal placenta SGA
N	38	38	112	22
Redating indicated	3 (7. 9%)	0	16 (14.3%)	0
HC/AC ratio abnormal	0	3 (7.9%)	0	0
N with Placental assessment	33 (86.8%)	30 (78.9%)	104 (92.9%)	21 (95.5%)
Grade III maturation	5 (15.2%)	7 (23.3%)	14 (13.5%)	0
Abnormal maturation	0	3 (10%)	0	2 (9.5%)
N with AFI (cm)	37 (97.4%)	38 (100%)	111 (99.1%)	21 (95.5%)
Mean AFI±SD	13.9±4.5	11.7±4.7	14.7±4.2	14.7±3.2
Median (P10-P90)	14.1 (8.9-19.2)	11.6 (5.7-17.3)	14.3 (9.7-21.1)	14.2 (10.2-17.9)
<8 cm	2 (5.4%)	7 (18.4%)	8 (7.2%)	0
<5 cm	0	2 (5.3%)	0	0
Final GA (weeks) Mean±SD	34.6±2.8	35.1±2.5	34.5±2.7	34.8±2.1
Median (P10-P90)	34.5 (31.9-37.9)	34.6 (32-38.7)	34.8 (32.0-37.7)	34.1 (32.3-38.3)
EFW (grams) Mean±SD	2309.2±468.4	1942.3±335.0	2363.2±526.7	1953.5±378.8
Median (P10-P90)	2335(1818-2847)	1931(1533-2439)	2414(1731-2987)	1863(1605-2578)
EFW category according to local reference (31)				
>P50	12 (31.6%)	1 (2.6%)	48 (42.9%)	0
P10-50	26 (68.4%)	17 (44.7%)	64 (57.1%)	9 (40.9%)
P3-10	0	9 (23.7%)	0	11 (50. %)
<P3	0	11 (28.9%)	0	2 (9.1%)
SGA for assumed GA TBH (31)	2 (5.3%)	20(52.6 %)	15 (13.4%)	13 (59%)
SGA for final GA TBH	0	21 (55.3%)	0	13 (59%)

SGA for assumed GA Salomon	0	38 (100%)	0	22 (100%)

Discussion

Our study aimed to look at the incidence as well as the characteristics of placental insufficiency after 32 weeks gestational age, in pregnancies that had a normal UA RI at the FEC. As per the current provincial protocol, an UA RI <P75 requires no follow-up, an UA RI P75-95 needs a repeat umbilical artery Doppler in 2 weeks, and an UA RI>P95 will get weekly follow-up and referral to the high risk clinic. This however does not make provision for the possibility that the UA RI may in fact be normal in the presence of other ultrasound and Doppler abnormalities that are indicative of placental insufficiency.

In this study 76 out of the 210 patients (36.2%) were categorised as having a pregnancy likely complicated by LOPI. Half of these fetuses were small for gestational age, while the rest had appropriate weight for the estimated gestational age. The finding that more than a third of patients with a normal UA RI had features of LOPI on more extensive investigation is quite worrying. It effectively means that we are currently missing the diagnosis of possible LOPI in a not insignificant number of pregnancies. While it is true that 129 of the referred patients required secondary/tertiary level of care due to their obstetric or medical history, 81 patients had no such risk factors and would have been discharged from the secondary platform, only to have routine low-frequency antenatal care and delivery at a primary level health care facility, without the infrastructure for electronic fetal monitoring during labour (with CTG) or speedy access to emergency caesarean section in case fetal distress develops, in spite of 25 of them having evidence of LOPI. We currently do not know how many of these pregnancies were complicated by IUFD or fetal distress necessitating emergency abdominal or assisted vaginal deliveries but it is well established in the literature that they are certainly at increased for such complications.

While the solution seems obvious - to offer all patients with risk factors for placental insufficiency after 32 weeks a full fetal evaluation, including Dopplers of the entire fetoplacental circulation– this is not feasible in the current set-up as they need referral to a fetal medicine unit. Even if these patients could be managed in a FEC on the primary healthcare platform, the numbers will be too overwhelming to manage. Using the 2010 FEC statistics, it was estimated that only about 200 extra patients would need to be accommodated over a 12 month period, but in less than eight months we identified 228 eligible patients and it was at times impossible to accommodate them in addition to the normal clinical workload of the ultrasound unit. Even though the argument can be made that only 83 patients were referred for poor SF growth and that the rest should be in the secondary level system already, these patients are usually only seen at the FEC. The purpose of the study was therefore to try and find any characteristics that may identify pregnancies most likely to have LOPI in order to select these patients for full ultrasound and Doppler evaluation.

We expected having problems with dating the pregnancies, as experience showed that many of our patients book too late for routine dating scans, which are used locally up to a GA of 24 weeks and not offered afterwards. It was surprising that almost 83% of our study patients had been scanned, but this high percentage may partially be explained by the high risk nature of this cohort. Only 138 of the scans however were before 24 weeks and considered "early" and 41% of these "early" dating scans (55/138) were actually beyond 20 weeks when ultrasound is significantly less reliable than before "Reliable"

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dating (as accepted in the local circumstances) was actually only obtained in 69% of the study sample and was in a substantial number of cases based on a relatively late scan (between 20 and 24 weeks). This illustrates the limitation of using the EFW percentile as a method to detect FGR in our local population as the relatively late dating may not have allowed the EFW to drop below the 10 centile for the assumed (and perhaps underestimated) gestation. It was also noted that only 57% of our patients had a SFH measurement before their first scan (only 32% of the SFH were measured before 24 weeks). This could suggest that we are foregoing the basics in healthcare in favour of technology. While technology is very useful, it should never be used instead of a good history taking and clinical exam, but rather together with it and this should be discussed with the staff serving at the booking clinics at all levels of care.

Almost 40 % of patients (83/210) were referred for SFH and had no other risk factors. Of these patients 31.3% (26/83) were assessed as having LOPI. That means 31% of a group who would be discharged to follow-up at a primary level should the UAD be normal, can be missed with the current protocol. Of the rest of the patients who either had a historical risk factor or a current medical condition that would make them high risk not one single factor in history or current medical condition could be identified that would help in predicting LOPI in these patients.

It is clear that an umbilical artery RI of <P95 is not a helpful in diagnosing suspected placental insufficiency after 32 weeks, although LOPI was less common if the RI was below P50 compared to above. There were also no useful differences between the groups with regards to abnormal HC/AC ratios, abnormal placental maturation or oligohydramnios, but LOPI was more common when liquor was reduced compared to normal. This shows that commonly looked for grey scale ultrasound signs lack the sensitivity and specificity to reliable detect LOPI at advanced gestations, when placental disease is usually less severe than with early onset disease.

The Doppler findings from the more extensive assessment of this study indicate that the worst Doppler changes (higher uterine and umbilical artery PI, lowest MCA PI and CPR) are observed in LOPI-SGA cases but these were not substantially different from LOPI-AGA cases. This again illustrates the difficulty of basing a diagnosis of placental insufficiency (and selection policy for surveillance) on the EFW percentile.

So while we know that between 30 and 40% of the patients referred for various risk factors for placental disease will have a pregnancy complicated by LOPI in spite of a normal UA RI, this study shows that we are not able to distinguish between these high risk patients and the low risk patients who do not need further work-up, based on history, clinical presentation or grey scale ultrasound findings only.

The only reasonable conclusion from this study is therefore that patients who require an UAD assessment after 32 weeks, for whatever (valid) reason, need to have a Doppler assessment of the MCA and uterine arteries in addition. If any of those Dopplers are abnormal, the patient should be regarded as at risk of complications of LOPI including IUFD, fetal distress before or during labour, perinatal morbidity and adverse long term neurodevelopmental outcome. These patients should be offered more specialised management and follow up at specialist level and it is not appropriate that they are further managed at the lowest level of care. If AFI and HC/AC and all Dopplers are normal however, the patient can remain at the current level of care and this can probably suffice if the fetus

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is AGA. If the fetus is SGA it is suggested that the investigations are repeated two weeks later as the situation may change over time.

In this way the number of patients needing management at level regional or tertiary facilities will be kept to a minimum, while pregnancies with evidence of LOPI and at risk of late onset FGR and its complications will be identified and offered more intense surveillance.

The strength of this study is that we now have data about LOPI that is relevant to our local population, where dating is often relatively late and inaccurate.

A limitation of this study is the sample size, as a larger sample size could possibly have revealed more statistically significant differences between the groups. From the available data however it is quite unlikely that a larger sample size would have revealed differences of sufficient magnitude as to be useful in a clinical screening algorithm.

A serious limitation is the lack of outcome data as a comparison of the long- and short term outcomes of the different groups would be a useful to correlate ultrasound findings with outcome. The study has not addressed the possible barriers to implementation of the suggested policy change. Our health care resources are limited in terms of personnel, out- and inpatient facilities as well as equipment and the specialised and highly specialised antenatal and intrapartum services of this region are already overburdened and may struggle to accommodate more patients while still delivering quality healthcare. The reality is that we are in a middle income country and that while our incidence of LOPI may be similar to developed countries, we may not necessarily be able to intervene in such a way as to limit the negative outcomes associated with LOPI. It needs to be assessed whether the adverse outcomes that can potentially be averted, ultimately justify the extra resources needed to identify and manage these patients.

This study served as a powerful confirmation that the problem of LOPI is indeed very real in our population, and that ways to identify high risk pregnancies, while limiting the impact on an already overburdened healthcare system, should be developed.

Conclusion

Late onset placental insufficiency is a condition that affects a significant proportion of our population. This does not only have consequences for the short term pregnancy outcome, but also for the long term outcomes, with regards to neurodevelopment and the development of metabolic diseases.

In settings where pregnancy dating is far less accurate than in developed countries and where customised growth charts are not available, it may not be appropriate to base management algorithms on the EFW centile as inaccurate clinical or relatively late ultrasound dating (after 20 weeks) may not have allowed the EFW to drop below the 10 centile for the assumed (and perhaps underestimated) gestation. This study shows that relying on a distinction between AGA and SGA would seriously underestimate the magnitude of the problem of placental pathology and also illustrates the poor sensitivity of traditional clinical risk factors and grey scale ultrasound findings in identifying the pregnancies at risk of LOPI-associated complications.

Further studies are needed to assess feasibility and impact of the proposed policy change.

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