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).

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”

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

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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