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Sonographic markers of increased fetal adiposity demonstrate an increased risk for Cesarean delivery

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Abstract

OBJECTIVE: Increased fetal size is associated with labor dystocia and subsequent need for assisted delivery. We sought to investigate if increased fetal adiposity diagnosed sonographically was associated with increased risk of operative delivery.

METHOD: The Genesis Study recruited 2,392 nulliparous patients with a vertex presentation in a prospective multicenter study to examine prenatal and intra-partum predictors of cesarean delivery. Participants had ultrasound and clinical evaluation performed between 39 0/7 and 40 6/7 weeks' gestation. Data on fetal biometry was not revealed either to patients or their managing clinicians. A fetal adiposity composite of fetal thigh adiposity and fetal abdominal thickness was compiled for each infant in order to clarify if fetal adiposity >90th centile was associated with an increased risk of cesarean or instrumental delivery.

RESULTS: After exclusions data were available for 2,330 patients. Patients with a fetal adiposity composite >90th centile had a higher maternal BMI (24±4 vs. 25±5; p=0.005), birthweight (3872 ± 417g vs. 3585 ± 401g; p<0.0001) and rate of induction of labor (47% [108/232] vs. 40% [834/2098]; p=0.048) than those patients with an adiposity composite d90th centile. Fetuses with adiposity composite >90th centile were more likely to require cesarean delivery than fetuses with adiposity <90th centile (p<0.0001). After adjusting for birthweight, maternal BMI, and onset of labor, fetal adiposity >90th centile remained a risk factor for cesarean delivery (p<0.0001). A fetal adiposity composite >90th centile was found to be more predictive of the need for unplanned cesarean delivery than an estimated fetal weight >90th centile (OR= 2.20 [95% CI: 1.65 – 2.94; p<0.001] vs. OR=1.74 [1.29 – 2.35,

p<0.001]. Having a composite adiposity >90th centile was not found to be associated with an increased likelihood of operative vaginal delivery when compared with fetuses <90th centile (p=0.37).

CONCLUSION: Fetuses with increased adipose deposition were more likely to require cesarean delivery. Given that increased fetal adiposity is a risk factor for cesarean delivery, consideration should be given to adding fetal thigh and abdominal wall thickness to fetal sonographic assessment in late pregnancy.

Introduction

The clinical challenges associated with delivery of a macrosomic infant have been clearly documented[1,2] and it is known that macrosomia carries an increased risk to the fetus of birth trauma including shoulder dystocia and resultant brachial plexus injury.[3,4] Macrosomia also confers an increased maternal risk, with high rates of operative delivery, anal sphincter injury and post-partum hemorrhage.[5-7] While increased birthweight has been established as a potential predictor of difficult or traumatic delivery, the effect of fetal body composition on labor outcomes is less clear.

Much research effort has been focused on the effect of maternal metabolic profile, body composition and gestational weight gain on birthweight,[8-10] and it has been proposed that infants of obese mothers may develop an abnormal metabolic profile resulting in increased fetal adiposity in utero. This programming can result in both childhood and adult obesity as well as a cycling of obesity through generations.[11,12] Predictors of increased fetal birthweight and abnormal body composition are not yet clearly defined and it has, for instance, been shown in non-diabetic women that birthweight correlates with maternal fat

free mass and is not linked to maternal adiposity as has previously been reported in diabetic cohorts.[13,14]

Randomized trials of maternal diet and lifestyle to decrease birthweight in those most at risk of macrosomia have yet to result in significant clinical impact.[15,16]One large randomized trial has however shown a reduction in fetal adipose tissue deposition and measures of neonatal body composition after maternal dietary and lifestyle interventions.[17,18]

In view of the potential adverse maternal and neonatal oucomes associated with traumatic delivery, and the difficulty in predicting those mothers and infants most at risk of traumatic birth, we sought to investigate if sonographic markers of increased fetal adiposity were capable of identifying those at increased risk of complications of labor and delivery.

Methods

This is a secondary analysis of a prospective, multi-centre, blinded observational study to examine prenatal and intra-partum predictors of unplanned cesarean delivery. The GENESIS study[19] was carried out between October 2012 and June 2015, at each of the seven Perinatal Ireland Research Consortium sites (Rotunda Hospital, Dublin; National Maternity Hospital, Dublin; Coombe Women and Infants' University Hospital, Dublin; Galway University Hospital, Galway; University Maternity Hospital, Limerick; Cork University Maternity Hospital, Cork; Royal Jubilee Hospital, Belfast). Institutional Review Board ethical approval was obtained at each participating center prior to patient recruitment taking place. During the study period nulliparous women were invited to participate and had ultrasound and clinical evaluation performed.

Inclusion criteria for this study were nulliparous women with a singleton, cephalic presentation between 39 and 40+6 weeks' gestation in an uncomplicated pregnancy at enrolment. All participants had a confirmed estimated date of delivery by either first trimester ultrasound or a second trimester ultrasound which correlated with their menstrual dates. Those excluded from participation in the study were multiparous, multiple pregnancies, breech presentation, ruptured membranes (at time of study ultrasound) and pregnancy complications such as pre-eclampsia, hypertension (requiring anti-hypertensive medication) , fetal growth restriction, obstetric cholestasis and gestational diabetes. Pre-existing medical conditions such as cardiac disorders, pre-gestational diabetes, seizure disorder or bleeding disorders also lead to exclusion from the study. Finally, women who had an ultrasound performed after 34 weeks' gestation for fetal biometry were also excluded from the study, to

obviate the potential influence of late ultrasound-derived fetal size estimates on clinical decision-making regarding timing or mode of delivery.

Written informed consent was sought from all women participating in the study. At each site there was a Perinatal Ireland employed research sonographer who performed an ultrasound for fetal biometry between 39 and 40+6 weeks' gestation. Baseline maternal characteristics were gathered including such as age, weight, height, body mass index (BMI); (all obtained at the first antenatal visit), gestational weight gain assessed at the study visit, ethnicity, attendance at prenatal classes, model of antenatal care, presence of written birth plan, smoking status and highest level of education achieved.

Standard fetal biometry was measured including biparietal diameter (BPD), head circumference (HC), abdominal circumference (AC), and femur length (FL), yielding a calculated estimated fetal weight (EFW) using the Hadlock formula. All sonographers performing ultrasounds were given specialist training in obtaining fetal adiposity measurements prior to patient recruitment to ensure accuracy and reproducibility of images. Sonographic images were periodically reviewed for quality control throughout the project by a senior sonographer and obstetrician. A fetal adiposity composite consisting of the sum of fetal thigh adiposity and fetal abdominal thickness was compiled for each infant. The fetal abdominal adiposity measurement was obtained using a standard transverse image of fetal abdomen at the level of the fetal stomach and portal sinus as is used for the measurement of abdominal circumference. A measurement was taken of the subcutaneous tissue including the skin on the anterior abdominal wall in millimeters halfway between the edge of the rib

and the anterior abdominal wall using magnification. (fig 1). Three measurements were taken on each fetus and the average used for fetal abdominal adiposity.

The fetal thigh adiposity was measured by obtaining an image of the femur length used in standard biometry and magnifying it to visualize clearly the borders of the diaphysis of the femur and the skin surface. Femur length was measured and the calipers were then used to find the midpoint of the femur. From this midpoint the calipers were placed on the outer edge of the femur to the outer surface of the fetal skin on the mid thigh. A measurement was then taken again from the outer edge of the femur to the inner fat surface, the fetal thigh adiposity was calculated by subtracting this from the first measurement (Fig 2). This process was repeated three times and a mean measurment calculated to ensure accuracy.

Biometric data from this ultrasound examination were not revealed to study participants. Managing clinicians were also blinded from the results of fetal biometry, to control for potential bias of suspected fetal macrosomia influencing decisions relating to timing and mode of delivery. A biophysical score was performed and documented in the participants medical records. Findings of an abnormal biophysical profile (<6/8), a diagnosis of small for gestational age or an EFW >5,000 grams were revealed to the study participants and managing clinicians, with all such revealed cases being excluded from the study. Standard perinatal and obstetric data were collected contemporaneously and included gestational age at delivery, onset of labour, use of prostaglandin for pre-induction cervical

priming, amniotomy, use of oxytocin, maternal fever, type of analgesia used, duration of labour, mode of delivery, indication for operative delivery, perineal trauma and blood loss.

The primary outcome of the study was to investigate if fetal adiposity composite >90th centile was associated with an increased risk of unplanned intrapartum cesarean delivery. Secondary outcomes included the effects of a fetal adiposity composite >90th centile on risk of operative vaginal delivery, fetal outcomes such as Apgar scores <7 at 5 minutes, arterial cord pH <7.1, admission to the neonatal intensive care unit, shoulder sytocia and Erbs palsy and maternal outcomes such as rates of postpartum hemorrhage, red cell transfusion, episiotomy and 3rd or 4th degree tear.

Statistical Analysis

Statistical analysis was performed using the chi ‐ square test and Fisher's exact test. Comparison of means was accomplished with a Student's t-test. Two groups were compared: those with a fetal adiposity composite >90th centile and those with a composite d90th centile. Multiple logistic regression analysis was used to produce a multivariate model where prenatally identifiable characteristics which were significant on simple analysis were controlled for maternal body mass index, birthweight and onset of labor. The SPSS software package (version 20.0; SPSS, Chicago, IL, USA) was used and a two ‐ tailed probability value of $P < 0.05$ was considered significant.

Results

The GENESIS study recuited a total of 2,392 study participants. There were 61 participants excluded for the following reasons; lost to follow up (n=4), diagnosed with gestational diabetes (n=5), abnormal biophysical profile (n=33), EFW under 2.5kg or over 5kg (n= 5), EFW performed after enrolment (n=5) and pre-existing indication for caesarean delivery such as breech presentation or medical history (n=9). Therefore a total of 2,331 patients were included in the final analysis; these represented the cohort of nulliparous women who underwent a blinded ultrasound-evaluation of fetal weight after 39 weeks' gestational age and who were deemed suitable for trial of labour at the time of the study ultrasound. Data were available for 2,330 of the 2,331 study participants, as one patient had incomplete adiposity measurement data. In our study cohort, the mean fetal adiposity was 6.2 +/- 1.4 (+/- SD). It was normally distributed and the 90th centile was 8.1, used as a cutoff in the statistical summaries. Fetal adiposity was ascertained at the study visit (between 39+0 and 40+6 weeks) and within this narrow time-frame, fetal adiposity was not associated with the precise gestation at assessment (correlation=0.1).

Patients with a fetal adiposity composite >90th centile had a higher maternal BMI (25±5 vs. 24±4; p=0.005), birthweight (3872 ± 417g vs. 3585 ± 401g; p<0.0001) and rate of induction of labor (47% [108/232] vs. 40% [834/2098]; p=0.048) than those patients with an adiposity composite d90th centile. Patients with an adiposity index >90th centile were also more likely to have an infant >4000g and >4500g (p<0.0001). Those with an adiposity composite >90th centile were more likely to require oxytocin augmentation in labor (60% [140/232] vs. 49% [1038/2098]; p=0.002) and to have a second stage of labor longer than

three hours in duration (8% [19/232] vs. 4% [86/2098]; p=0.005). Patients with an adiposity index >90th centile were also more likely to have an intrapartum pyrexia (6% [15/232] vs. 3% [71/2098]; p=0.019). There was no difference in other metrics between both groups. Patient demographics and intrapartum characteristics can be seen in Tables 1 and 2.

Fetuses with an adiposity composite >90th centile were more likely to require cesarean delivery than fetuses with adiposity d90th centile (35% vs. 20% p<0.0001). After adjusting for birthweight, maternal BMI, and onset of labor, fetal adiposity >90th centile remained a risk factor for cesarean delivery (p<0.0001). Those with an adiposity composite >90th centile were hence less likely to have a spontaneous vaginal delivery (p<0.0001); this remained significant after adjusting for BMI, birthweight and onset of labor (p=0.009). Having a composite adiposity >90th centile was not found to be associated with an increased likelihood of operative vaginal delivery when compared with fetuses d90th centile (p=0.374); this remained the case after adjusting for significant characteristics (p=0.35). Differences in modes of delivery among both groups can be seen in Table 3.

A fetal adiposity composite >90th centile was found to be more predictive of the need for unplanned cesarean delivery than an estimated fetal weight >90th centile (OR= 2.20 [95% CI: 1.65 – 2.94; p<0.001] vs. OR=1.74 [1.29 – 2.35, p<0.001].

Maternal and fetal outcomes and markers of morbidity can be seen in Table 4. There was no difference in any maternal or fetal outcome seen between those with a fetal adiposity composite > or d 90th centile.

Discussion

In a large prospective cohort of nulliparous pregnancies, fetuses with increased adipose deposition were more likely to require cesarean delivery, and to show signs of obstructed labor such as intrapartum pyrexia, need for oxytocin augmentation, longer labors and a second stage of labor longer than three hours in duration. Those with a fetal adiposity composite >90th centile were however not more likely to require operative vaginal delivery and there was no increase in the rate of fetal or maternal morbidity compared with those with an adiposity composite d 90th centile. The effects of fetal adiposity on mode of delivery remained apparent on multiple logistic regression which controlled for prenatally identifiable characteristics which were different in cases with a fetal adiposity composite >90th centile; namely maternal BMI, birthweight and onset of labor. When compared with traditional fetal biometry and estimated fetal weight, increased fetal adipose deposition was also found to be a better prenatal predictor of the need for unplanned cesarean delivery.

Ultrasound-based measurement of fetal adiposity in the third trimester has been shown to be a predictor of both birthweight and newborn percentage body fat.[20-22] Varying methods of assessing adiposity have been investigated including fetal thigh and arm volume and fetal abdominal wall adiposity as well as using 2D and 3D ultrasound.[23,24] While an association between ultrasound measured fetal adiposity and neonatal body composition has been well investigated, the effect of increased fetal adiposity on mode of delivery and maternal and fetal outcomes in labor is less clear. Infants with increased adipose deposition may encounter intrapartum complications outside of those that are seen in those infants who simply have an above average birthweight. This argument is substantiated when it is

considered that those with an adiposity composite >90th centile in our study population were more likely to require cesarean delivery even once birthweight was controlled for on multiple logistic regression. These findings suggest that measurement of markers of fetal adiposity may be worthy of including as part of routine biometry for those having sonographic assessment in the third trimester.

This study has a number of strengths including its prospective, multi-center design and the blinding of both patients and clinicians' to findings of the study. Our study population was also largely homogenous and uncomplicated and those with gestational diabetes were excluded from our study cohort. Our statistical analysis whereby we controlled for maternal BMI, birthweight and onset of labor also adds weight to the argument that increased fetal adipose tissue deposition makes it more likely that these infants will require cesarean delivery. Our study is not without weaknesses and we would have liked to have access to neonatal adiposity measurements to correlate sonographic findings with those found clinically after delivery. Also our study was not powered to accurately reflect differences in more rare clinical outcomes such as shoulder dystocia and resultant Erb's palsy at vaginal delivery. These are morbidities, which infants with increased adipose deposition may be at risk of suffering, however given their infrequent occurrence appreciating a significant difference would require a much larger cohort. The measurement of adiposity is also not a routine sonographic procedure and as a result could be difficult to reproduce accurately, to overcome this training to all sonographers was provided by a senior clinician and images were reviewed regularly, also a stepwise approach to measuring adiposity were taken, and is described above. This was followed in every sonographic assessment carried out during the

study. We also did not explore the role of maternal factors and techniques such as sonographic pelvimetry in the need for cesarean delivery in our patient cohort. Some recent studies have suggested a role for pelvimetry, measured using CT or MRI, for the identification of those at high risk of cephalopelvic disproportion.[25,26] Combining maternal sonographic pelvimetry with fetal adiposity in an effort to assess risk of for unplanned intrapartum cesarean could form the basis of future work.

In conclusion our study found that fetuses with increased adipose deposition were more likely to require cesarean delivery; this remained the case after controlling for prenatally identifiable risk factors. Increased fetal adiposity was more predictive of the need for unplanned cesarean delivery than estimated fetal weight and this raises the potential for consideration to adding fetal thigh and abdominal wall thickness to standard sonographic fetal assessment in late pregnancy. This additional information may be useful in carrying out individualized risk assessments of unplanned cesarean delivery when patients and their care providers are making decisions regarding mode of delivery.

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Figure legends

Figure 1 shows the sonographic measurement of abdominal adiposity

Figure 2 shows the sonographic measurement of thigh adiposity

Table 1. Demographics & Maternal Characteristics

Characteristic		Fetal Adiposity d 90th centile (N=2098)	Fetal Adiposity > 90th centile (N=232)	P-value
Maternal Age (years)		29 ± 5	29 ± 5	0.170
Height (cm)		165 ± 6	165 ± 7	0.779
BMI (kg/m^2)		24 ± 4	25 ± 5	0.005
Gestational Weight Gain (kg)		13 ± 5	14 ± 6	0.061
Caucasian Ethnicity		1995 (95%)	225 (97%)	0.279
Prior Smoker		699 (33%)	70 (30%)	0.300
Current Smoker		185 (9%)	20 (9%)	0.743
Tertiary Education		1445 (69%)	151 (65%)	0.212
Type of care	Midwife-led	1006 (48%)	119 (51%)	0.352
	Physician-led	1096 (52%)	114 (49%)	
Prenatal Classes		1523 (73%)	176 (76%)	0.312
Birth plan		826 (39%)	106 (46%)	0.067

Table 2. Intrapartum Characteristics

Characteristic		Fetal Adiposity d 90th centile (N=2098)	Fetal Adiposity > 90th centile (N=232)	P-value
Gestation at Delivery (weeks)		40.8 ± 0.7	40.7 ± 0.7	0.83
Onset of labor	Spontaneous	1264 (60%)	124 (53%)	0.04
	Induction	834 (40%)	108 (47%)	
IOL Method	Oxytocin	395 (19%)	69 (30%)	<0.001
	ARM	377 (18%)	60 (26%)	0.004
	Prostin	592 (28%)	78 (34%)	0.09
IOL reason	Fetal total	47 (2%)	7 (3%)	0.75
	- APH	5 (<1%)	0	0.46
	- LGA	8 (<1%)	2 (<1%)	0.29
	- NRCTG	6 (<1%)	1 (<1%)	0.70
	- Reduced FM	17 (<1%)	4 (2%)	0.16
	- SGA	13 (<1%)	0	0.23
	Maternal total	128 (6%)	25 (1%)	0.01
	- Gest hypertension	44 (2%)	10 (4%)	0.03
	- maternal age	7 (<1%)	0	0.38
	- maternal disease	8 (<1%)	1 (<1%)	0.91
	- oligohydramnios	48 (2%)	8 (3%)	0.27
	- Pre - Eclampsia	23 (1%)	7 (3%)	0.01
	Post dates	466 (22%)	56 (24%)	0.51
	Rupture membranes	140 (7%)	17 (7%)	0.67
	Other	33 (2%)	2 (<1%)	0.57
Duration of Labour (hours)		6.6 ± 4.6	7.5 ± 5.5	0.01
Duration of 1st stage labour > 12 hrs		145 (7%)	15 (6%)	0.79

Duration of 2nd stage labour > 3 hrs	86 (4%)	19 (8%)	0.005
Total duration of Labour > 12 hrs	236 (12%)	43 (19%)	0.001
Oxytocin augmentation	1038 (49%)	140 (60%)	0.002
Epidural	1432 (68%)	162 (70%)	0.66
Meconium stained liquor	480 (23%)	59 (25%)	0.37
Intrapartum pyrexia	71 (3%)	15 (6%)	0.02
Birthweight (g)	3585 ± 401	3872 ± 417	<0.0001
Birthweight < 2500g	5 (<1%)	0	0.46
Birthweight > 4000g	296 (14%)	84 (36%)	<0.0001
Birthweight > 4500g	31 (1%)	15 (6%)	<0.0001

Overlap between IOL methods, not mutually exclusive.

ARM = Artificial Rupture of Membranes
APH = Antepartum Hemorrhage
LGA = Large for Gestational Age
NRCTG = Non-reassuring Cardiotocograph
FM = Fetal movements

Table 3. Mode of Delivery

Mode of Delivery		Fetal Adiposity d90th centile (N=2098)	Fetal Adiposity >90th centile (N=232)	Odds-ratio (P-value)	Adjusted[1] Odds-ratio (P-value)
UpCS		410 (20%)	81 (35%)	2.2 (<0.0001)	1.9 (<0.0001)
UpCS 2nd Stage		48 (2%)	14 (6%)	2.7 (<0.0001)	2.2 (0.03)
UpCS Indication[2]	APH	2 (<1%)	0	NA[3] (0.64)	NA[3] (0.97)
	Abnormal FBS	50 (2%)	6 (3%)	1.1 (0.85)	1.2 (0.82)
	Failure to advance	195 (9%)	49 (21%)	2.6 (<0.0001)	1.9 (<0.0001)
	Inability to treat	19 (<1%)	6 (3%)	2.9 (0.02)	2.8 (0.04)
	Malposition	21 (1%)	6 (3%)	2.6 (0.03)	2.9 (0.03)
	NRCTG	239 (11%)	44 (19%)	1.8 (<0.0001)	2.3 (0.001)
	Pyrexia	45 (2%)	11 (5%)	2.3 (0.01)	1.4 (0.29)
	Other	399 (19%)	77 (33%)	2.1 (<0.0001)	1.8 (<0.0001)
Instrumental delivery		784 (37%)	80 (34%)	0.9 (0.37)	0.9 (0.35)

SVD	908 (43%)	72 (31%)	0.6 (<0.0001)	0.7 (0.009)

Notes:

[1]Multiple linear/logistic regression analyses: Outcomes adjusted for Maternal BMI, birthweight and induction of labor.

[2]Overlap in indications for delivery, not mutually exclusive.

[3]NA (not available) due to insufficient number of events.

APH = Antepartum Hemorrhage

FBS = Fetal Blood Sample

UpCS = Unplanned Cesarean Section

NRCTG = Non-reassuring Cardiotocograph

SVD = Spontaneous Vaginal Delivery

Table 4. Maternal & Fetal Outcomes

Outcome	Fetal Adiposity d90th centile (N=2098)	Fetal Adiposity >90th centile (N=232)	P-value	Adjusted P-value#
Apgar < 7 @ 5min	12 (<1%)	1 (<1%)	0.78	0.97
Cord pH	7.24 ± 0.11	7.24 ± 0.35	0.96	0.69
Cord pH < 7.1	14 (1%)	1 (<1%)	0.53	0.48
Shoulder dystocia	22 (1%)	7 (3%)	0.01	0.24
Erbs palsy	5 (<1%)	1 (<1%)	0.58	0.74
NICU admission	159 (8%)	18 (8%)	0.58	0.58
3rd/4th degree tear	68 (3%)	8 (3%)	0.87	0.89
Episiotomy	866 (41%)	87 (38%)	0.26	0.15
PPH (EBL>500ml)	241 (11%)	38 (16%)	0.03	0.59
PPH (EBL>1000ml)	52 (2%)	4 (2%)	0.47	0.09
Blood transfusion	393 (19%)	64 (27%)	0.001	0.08

*overlap in indications for delivery, not mutually exclusive.

Multiple linear/logistic regression analyses: Outcomes adjusted for BMI, birthweight and induction of labor.

NICU = Neonatal Intensive Care Unit
PPH = Postpartum Hemorrhage
EBL = Estimated Blood Loss