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Small for gestational age infants and the association with placental and umbilical cord morphometry: a digital imaging study

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Small for gestational age infants and the association with placental and umbilical cord morphometry: a digital imaging study

Abstract:

Introduction:

Individual placental and umbilical cord morphometry have been previously identified to have an association with fetal growth. This study aims to identify which of the morphometric measurements in combination are associated with pregnancies with small for gestational age (SGA) infants using digital imaging of the delivered placenta.

Material and methods:

This study examined 1005 placentas from consecutively delivered singleton pregnancies in a tertiary center. Standardized images of each placenta were taken. Placental weight and thickness; umbilical cord length and diameter were measured on gross examination. Distance from placental cord insertion site to placental margin, length and breadth of the placenta and placental chorionic surface area were measured digitally using ImageJ software. Logistic regression models and area under the curve (AUC) were used to identify the best subset of morphometric measurements to classify infants as SGA (<10th centile).

Results:

Overall, 141 (14%) infants were SGA. The morphometric measurements at delivery most strongly associated with the classification of infants as SGA were placental weight (AUC=0.806) and placental surface area (AUC=0.749).Of the potential antenatal morphometric measurements, umbilical cord diameters, both placental (AUC=0.644) and fetal end (AUC=0.629) were most strongly associated with SGA. A logistic regression model with maternal age, smoking status, current history of pre-eclampsia, umbilical cord length, placental weight, birthweight to placental weight ratio and umbilical cord diameter (placental end) had a sensitivity of 53% and a false positive rate of 2% (AUC=0.945) for the classification of infants as SGA.

Conclusion:

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Placental and umbilical cord morphometry measured at delivery are different between SGA and non-SGA infants. Further studies are warranted to investigate the feasibility and accuracy of ultrasound to measure placental and umbilical cord morphometry during pregnancy.

Keywords: small for gestational age; placental measurements; umbilical cord measurements; morphometry; digital imaging; birthweight

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Introduction

Small for gestational age (SGA) is a term used to describe infants with birthweight of less than the 10th percentile for their gestational age at delivery. 10% of all pregnancies are affected by inadequate fetal growth [1]. SGA infants are at an increased risk of perinatal morbidity and mortality compared to infants with birthweight that is appropriate for gestational age [2]. SGA infants are also known to have an increased risk of developing coronary heart disease, stroke, hypertension and type II diabetes mellitus in later life [3, 4].

Research focuses on timely antenatal detection of SGA, to reduce associated risks of perinatal morbidity and mortality. Compared to SGA fetuses identified antenatally, SGA fetuses that have not been identified antenatally have four times the odds of adverse fetal outcome (odds ratio, 4.1; 95% CI, 2.5-6.8) [5]. Whenever SGA is diagnosed during the antenatal period, increased surveillance and timely delivery aims to improve perinatal outcome, balancing the risk of antepartum stillbirth by remaining in utero and iatrogenic prematurity potentially causing significant morbidity or neonatal death by too early intervention [6]. The detection rate of SGA using fetal biometry varies between reported studies [7, 8, 9], with improvement in the detection rate when customized charts were used adjusting to maternal variables [10].

Multiple factors contribute to infants being SGA, including placental and umbilical cord abnormalities. The placenta performs the diversity of functions of all major organs while these develop and mature in the fetus [11]. It is accepted that placental weight correlates with birthweight [12, 13]. Placental weight has been found to be a justifiable proxy of fetal metabolic rate, and placental efficiency can be calculated from placental weight and birthweight [14]. Non-central placental cord insertions have also been associated with reduced transport efficiency [15] and adverse pregnancy outcomes including SGA [16, 17]. Proctor et al developed a nomogram of umbilical cord diameter for pathological examination of the placenta using a high-risk population, and found an association between a thin umbilical cord (<10th centile) and SGA [18].

The role of these morphometric measurements in combination has never been examined. A combination of different placental and umbilical cord morphometry may be a more sensitive tool to identify SGA. The objective of this study was therefore to examine and identify different morphometry of the placenta and umbilical cord at delivery using digital imaging and use these measurements to classify infants as SGA. We aimed to identify which of the placental and umbilical cord variables are individually most strongly associated with SGA. We then aimed to develop a multivariable model to classify infants as SGA using a combination of the individual morphometric measurements. This will inform future prospective studies where the feasibility and accuracy of ultrasound to measure these during pregnancy can be examined.

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Materials and Methods

This study was conducted between 28th January 2016 and 27th April 2016 in a tertiary university teaching hospital, with 4800 deliveries per annum. Consecutive singleton pregnancies delivered at or after 24 weeks gestation during the study period were eligible for recruitment. Women were identified from the delivery registers and those who labored spontaneously were approached within 24 hours of delivery. Women who were admitted for elective caesarean delivery or induction of labor were approached on admission. Multiple pregnancies were excluded.

Placentas from consecutively delivered singleton pregnancies between 24 and 42 weeks gestation were routinely examined by the midwife at delivery and placed in separate labeled plastic containers after delivery. The containers were kept in the placental refrigerator with the temperature maintained between 4 and 6^{o}C. All study placentas were identified and examined within 48 hours following delivery by two researchers who were blinded to the pregnancy outcomes, under supervision from a perinatal pathologist. Complete pathological examination of the placenta was only performed for clinical indications, with no routine pathological examination performed for all placentas. The placentas selected for complete laboratory analysis were examined prior to formalin fixation.

A unique study identification number was given to each placenta. The membranes were then trimmed and the umbilical cord excised from the placenta, about 1 cm from the insertion site. Morphometric measurements documented on gross examination include trimmed placental weight (in grams), placental thickness at the placental cord insertion site (in mm), umbilical cord length (in cm), umbilical cord diameters at the placental and fetal ends (in mm), umbilical cord handedness (left or right handedness) and number of coils. Coiling index was calculated by dividing the number of coils by umbilical cord length. The placenta was then placed on the base of the photo reproduction table with lamp ring (Figure 1). A standardised digital image of the placental fetal surface without the umbilical cord and a separate image of the umbilical cord were then taken using Nikon D3100 Digital Single-lens Reflex (DSLR) camera, attached at a fixed distance from the base of the photo reproduction table. Rulers were placed for calibration purposes.

Distance from PCI to placental margin (in mm), and length and breadth of the placenta (in cm) were measured using ImageJ software version 1.50 (Figure 2), available freely from http://rsb.info.nih.gov/ij. ImageJ is an open platform for scientific image analysis that allows automatic analysis of images using macro programming. Placental chorionic surface area (cm^2) was calculated by first creating a black image of the placenta in a white background, and then using the measure and ruler option in Image J to calculate the surface area of the black image (Figure 3).

Maternal characteristics obtained from the medical charts included maternal age, height, booking weight, body mass index (BMI), parity, smoking status at booking and medical history. Obesity was defined as BMI of equal or greater than 30 kg/m^2. Birth weight, gestation age and gender of the newborns were recorded. The placental weight/ birthweight (PW/BW) ratio was calculated. Birthweight of less than the 10^{th} percentile for gestational age was defined as small for gestational age (SGA). The birthweight percentile was calculated using the customized chart for the population of Ireland [19].

Statistical analysis

Numeric variables were tested for normality and presented as mean (SD) for normally distributed variables. Maternal demographics and placental and umbilical cord morphometry were compared across groups (SGA, non-SGA) using independent samples t test for comparing means and chi-squared tests for categorical variables. A 5% level of significance was used for all tests and no adjustment was made for multiple testing. Pearson's correlation coefficient (r) was used to measure the strength of the association between placental and umbilical cord morphometry with absolute values of r from 0.40-0.59 considered moderately strong, 0.60-0.79 considered strong and ≥ 0.8 considered very strong [20]. Receiver Operating Characteristic (ROC) curves were generated and the Area under the Curve (AUC) used to compare the ability of each placental and umbilical cord morphometry to distinguish between SGA and non-SGA infants. Multiple logistic regression analysis was then used to classify infants as SGA using all placental and umbilical cord morphometry, adjusting for known confounders (maternal age, parity, BMI, smoking status and medical history). Variable selection was used to identify the best subset of morphometric measurements to maximize AUC. All statistical analyses were carried out using the software package IBM SPSS for Windows version 22.

Ethical approval

Approval for the study was obtained from the institutional review board, the Health Service Executive Research Ethics Committee (REC Ref 32/13). An information leaflet was given to all participants. Written informed consent was obtained during recruitment from each participant for placental examination, placental digital imaging and medical chart review.

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Results

A total of 1140 infants between 24+0 and 42+0 weeks gestation were delivered between 28th January 2016 and 27th April 2016. After excluding multiple pregnancies (n=19 sets), 1102 singleton pregnancies were deemed suitable for the study. 35 (3.3%) women declined to participate, 25 placentas (2.3%) were not labeled and 29 (2.6%) of placentas were not available for analysis. Eight women (0.8%) did not have complete data and were excluded from the analysis, leaving 1005 (91.2%) of women and placentas in the dataset for analysis. 31 (3%) placentas had complete pathological examination.

Maternal demographics are summarized in Table 1. The mean maternal age was 32 years (SD 5.5), with 36.0% of the women aged 35 and over. The majority of the women were of white ethnicity (92.9%) and 36.9% women were nulliparous. The demographic profile of the study cohort is consistent with the overall obstetric population in Ireland[21]. 14% of babies were characterized as SGA (141/1005) while 86% (863/1005) were non-SGA. Six (4%) placentas from the 141 SGA infants had complete pathological examination.

Table 2 describes the demographics of women in the SGA and non-SGA groups. There were significantly more nulliparous women in the SGA group compared to the non-SGA group (45.4% vs. 35.5%, P=0.035). There were also significantly more smokers (29.1% vs. 13.4%, P<0.0001), more women with essential hypertension (5.7% vs. 1.3%, P<0.0001), and women with pre-eclampsia (4.3% vs. 1.5%, P=0.027).

Table 3 compares placental and umbilical cord morphometry for the SGA and non-SGA infants. There were statistically significant (P<0.05) differences in placental morphometric measurements including placental weight, thickness at placental cord insertion, distance of placental cord insertion to placental margin, placental surface area and BW/PW ratio for SGA placentas compared to non-SGA placentas (Table 3). Similarly, there were statistically significant differences (P<0.05) in umbilical cord morphometric measurements including umbilical cord length, umbilical cord diameters (placental and fetal ends) and coiling index in SGA umbilical cords compared to non-SGA umbilical cords (Table 3). The morphometric measurements most strongly associated with SGA were placental weight (AUC=0.806) and placental surface area (AUC=0.749) (Figure 4). Placental weight and surface area were moderately strongly correlated (r=0.59, P<0001). Of the potential antenatal morphometric measurements, umbilical cord diameters, both placental (AUC=0.644) and fetal end (AUC=0.629) were most strongly associated with SGA. Both cord diameters were strongly correlated (r=0.66, P<0.001).

The best fitting logistic regression model included maternal age, smoking status, current history of pre-eclampsia, umbilical cord length, placental weight, birthweight to placental weight ratio and umbilical cord diameter (placental end) (Table 4) with a sensitivity of 53% and a false positive rate of 2% (AUC=0.945) for the classification of infants as SGA (Figure 5).

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Discussion

Our findings demonstrate differences between placental and umbilical cord morphometry of non-SGA and SGA infants at delivery. Of these measurements, placental weight and surface area were most strongly associated with SGA. Distance from placental cord insertion to placental margin, placental thickness, diameter of umbilical cord (both placental and fetal ends) and coiling index can potentially be measured using obstetric ultrasound. Of these, diameters of umbilical cords were identified in this study as most strongly associated with SGA though not as strong as placental weight and surface area. Combining maternal characteristics, placental and umbilical cord morphometry was shown to improve the sensitivity of the model for the classification of infants as SGA.

The dimensions of the delivered placenta measured after delivery reveals its cumulative development from conception to delivery [13]. The growth of the placenta is directly related to its functional efficiency as the sole fetal source of both nutrients and oxygen [13]. Advancement in obstetric ultrasonography allows accurate identification and measurements of placental biometry and has increased the obstetricians' interest in ultrasonographic placental examination. Jauniaux et al in 1994 reported an association between abnormal placental development detected on ultrasound and subsequent abnormal fetal growth [22]. Since then, the use of 2-dimensional sonographic placental morphometric measurements, including placental diameter and thickness was found to have predictive ability for fetal growth [23]. 3-dimensional ultrasonography has also been shown to allow accurate placental morphometric measurements and these may be used as early predictors of fetal growth [24].

Currently, no direct measures of placental and umbilical cord biometry are used in clinical practice for screening of SGA. Our study provides an important initial step to identify both placental and umbilical cord morphometry that are potentially associated with SGA and to assess their use individually and in combination to correctly classify infants as SGA. The results can be used to inform future prospective antenatal studies where the feasibility and accuracy of measuring the placental and umbilical cord morphometry on ultrasound can be examined.

Research on antenatal detection of SGA is usually focused on ultrasonographic fetal measurements and Doppler studies. A prospective cohort study by Sovio et al investigating the diagnostic effectiveness of ultrasonic fetal biometry in the third trimester as a screening test for SGA reported a sensitivity of 57% for universal ultrasonography using fetal biometry and estimated fetal weight in the third trimester with a false positive rate of 10% [9]. Miranda et al reported a sensitivity of 52% for detecting SGA using estimated fetal weight (EFW) between 32 to 36 weeks gestation with a false positive rate of 10% [25]. By using a screening model combining maternal characteristics, EFW, uterine artery Doppler, Placental Growth Factor (PlGF) and conjugated estriol, their sensitivity increased to 61% though the inclusion of the biochemical markers increases the cost of screening [25]. The results of the above studies may possibly be improved by adding ultrasound measurements of both the placenta and umbilical cord as part of the screening tool. Our findings suggest that the placental and umbilical cord morphometry may contribute as a component to a multivariable prediction model to screen for SGA.

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The present study has several limitations. We were unable to differentiate between infants with fetal growth restriction or constitutionally small infants in the SGA cohort. Routine pathological examination was not performed for all placentas in this study, thus limiting our assessment of other pathology associated with SGA such as vilitis and thrombotic disease. There may be other factors contributing to SGA not accounted for in our analysis. Further, generalization of our results to other populations may be limited due to the relative homogenous white European population in our cohort.

A major strength of this study is the recruitment of participants from consecutive singleton deliveries thus minimizing selection/ascertainment bias. To minimize the observer and reporting bias, the researchers were blinded to the outcomes including gestational age and birthweight. The large number of placentas for examination allows precise comparison between the SGA and non-SGA groups.

Our results identified differences in placental and umbilical cord morphometry at delivery between non-SGA and SGA infants. Combining fetal biometry with placental and umbilical cord morphometry on ultrasound may potentially improve the SGA detection rate. Morphometry identifiable antenatally on ultrasound may be useful as predictors for SGA but prospective cohort studies are warranted to investigate its feasibility and accuracy.

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Declaration of Interest Statement

The authors report no conflict of interest.

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Table 1: Maternal demographics of the study population (n=1005)[a]

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Characteristics		n (%)	Mean (SD)
Age (years)			32 (5.5)
under35	Yes	643 (64.0%)	
	No	362 (36.0%)	
Ethnicity	White Irish	813 (81.3%)	
	Eastern European	82 (8.2%)	
	Other White	34 (3.4%)	
	African	14 (1.4%)	
	Asian	44 (4.4%)	
	Other	13 (1.3%)	
BMI at first visit (kg/m^2)			25.7 (5.3)
BMI Group	Underweight (<18.5)	21 (2.2%)	
	normal weight (18.5-24.9)	517 (53.0%)	
	Overweight (25.0-29.9)	266 (27.3%)	
	Obese (30.0-34.9)	107 (11.0%)	
	Extremely obese (>35)	65 (6.7%)	
Smoker	Yes	149 (15.6%)	
	No	804 (84.4%)	
Parity	Nulliparous	370 (36.9%)	

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	Multiparous	632 (63.1%)	
Conception	Spontaneous	976 (97.1%)	
	ART	29 (2.9%)	
Previous CD	No	844 (84.2%)	
	Yes	158 (15.8%)	
Previous Miscarriage	No	708 (70.7%)	
	Yes	294 (29.3%)	

[a]Missing data for some variables, % of valid responses given
BMI: body mass index; CD: cesarean delivery; ART: assisted reproductive technology

Table 2: Maternal demographics across groups (non-SGA and SGA)

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	Non-SGA (n=863)	SGA (n=141)	P-value
Maternal age ≥35 years	318 (36.8%)	44 (31.2%)	0.19
Parity 0 1+	306 (35.5%) 587 (64.5%)	64 (45.4%) 77 (54.6%)	**0.035**
Smoker	110 (13.4%)	39 (29.1%)	**<0.0001**
Essential hypertension	11 (1.3%)	8 (5.7%)	**<0.0001**
Current pre-eclampsia	13 (1.5%)	6 (4.3%)	**0.027**
Conception Spontaneous ART	839 (97.2%) 24 (2.8%)	136 (96.5%) 5 (3.5%)	0.62
BMI Group Underweight (<18.5) Normal weight (18.5-24.9) Overweight (25.0-29.9) Obese (30.0-34.9) Extremely obese (>35)	18 (2.1%) 441 (52.6%) 226 (26.9%) 94 (11.2%) 60 (7.2%)	3 (2.2%) 76 (55.5%) 40 (29.2%) 13 (9.5%) 5 (3.6%)	0.58

ART: assisted reproductive technology; BMI: body mass index; SGA: small for gestational age

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Table 3: Comparison of different morphometry between non-SGA and SGA

Morphometry		Non-SGA[1] (n=863)	SGA[1] (n=141)	P-value[2]	AUC
Placenta	Placental weight (grams)	492.78 (97.93)	389.22 (77.15)	<0.0001	0.806
	Surface area (cm^2)	303.78 (54.52)	255.98 (49.74)	<0.0001	0.749
	Distance of PCI to placental margin[3]	5.21 (2.16)	4.69 (2.31)	0.009	0.563
	Birthweight/Placental weight (BW/PW) ratio	7.43 (1.21)	7.16 (1.41)	0.021	0.564
	Placental thickness (mm)[3]	19.94 (5.77)	18.60 (7.70)	0.015	0.590
Umbilical cord	Length (mm)	483.66 (108.63)	441.56 (113.3)	<0.0001	0.617
	Diameter – placental end (mm)[3]	10.72 (2.11)	9.83 (2.47)	<0.0001	0.644
	Diameter – fetal end (mm)[3]	13.36 (2.71)	12.27 (2.79)	<0.0001	0.629
	Coiling index (coils/ cm)[3]	0.031 (0.0086)	0.033 (0.0096)	0.041	0.551

[1] Data reported as mean (SD)

[2] P-value from independent samples t test

[3] Possible antenatal measurements

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SGA: small for gestational age; PCI: placental cord insertion; AUC: Area under the curve

Table 4: Multivariable logistic regression of predictor variables for SGA infants (n=1005)

Predictor variables	OR (95% CI)	P-value
Maternal age (in years)	0.95 (0.91-0.99)	**0.02**
Smoker No Yes	1.00 1.93 (1.04-3.58)	**0.04**
Current pre-eclampsia No Yes	1.00 12.25 (1.57-95.55)	**0.02**
Umbilical cord length	1.002 (1.000-1.005)	0.05
Birthweight/Placental weight (BWPW) ratio	0.17 (0.12-0.25)	**<0.001**
Placental weight	0.96 (0.96-0.97)	**<0.001**
Cord diameter (placental end)	0.83 (0.73-0.93)	**0.002**

JUST ACCEPTED

SGA: small for gestational age; OR: odds ratios; CI: confidence intervals

JUST ACCEPTED

Figure Legends

Figure 1: Photo reproduction table with lamp ring

Figure 2: Digital measurements of fetal surface of placenta

The digital images of the placentas were analyzed digitally using ImageJ software version 1.50, freely downloaded from http://rsb.info.nih.gov/ij

Figure 3: Black and white image of placenta for surface area calculation

The digital images of the placentas were analyzed digitally using ImageJ software version 1.50, freely downloaded from http://rsb.info.nih.gov/ij

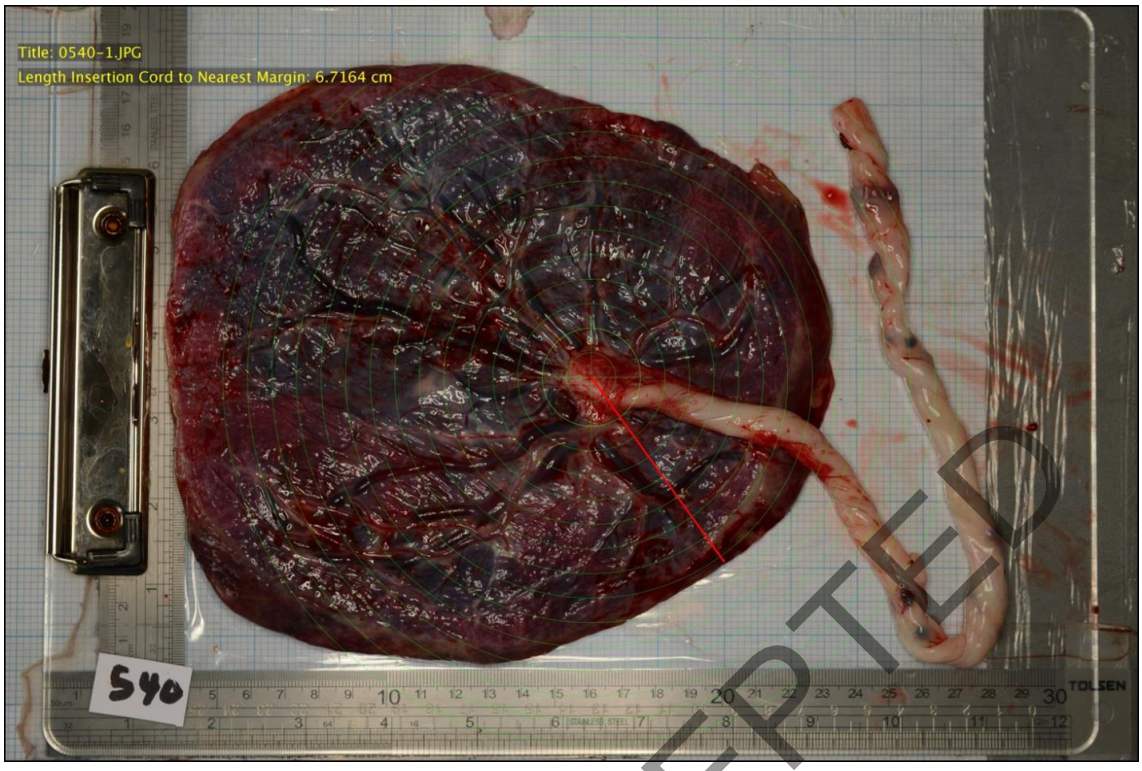
Figure 4: Receiver–operating characteristics curves for prediction of small-for-gestational-age infants by placental weight and placental chorionic surface area

Figure 5: Receiver-operating characteristics curve combining maternal smoking status, present pre-eclampsia, umbilical cord length, birthweight/placental weight ratio, placental weight and umbilical cord diameter (placental end)

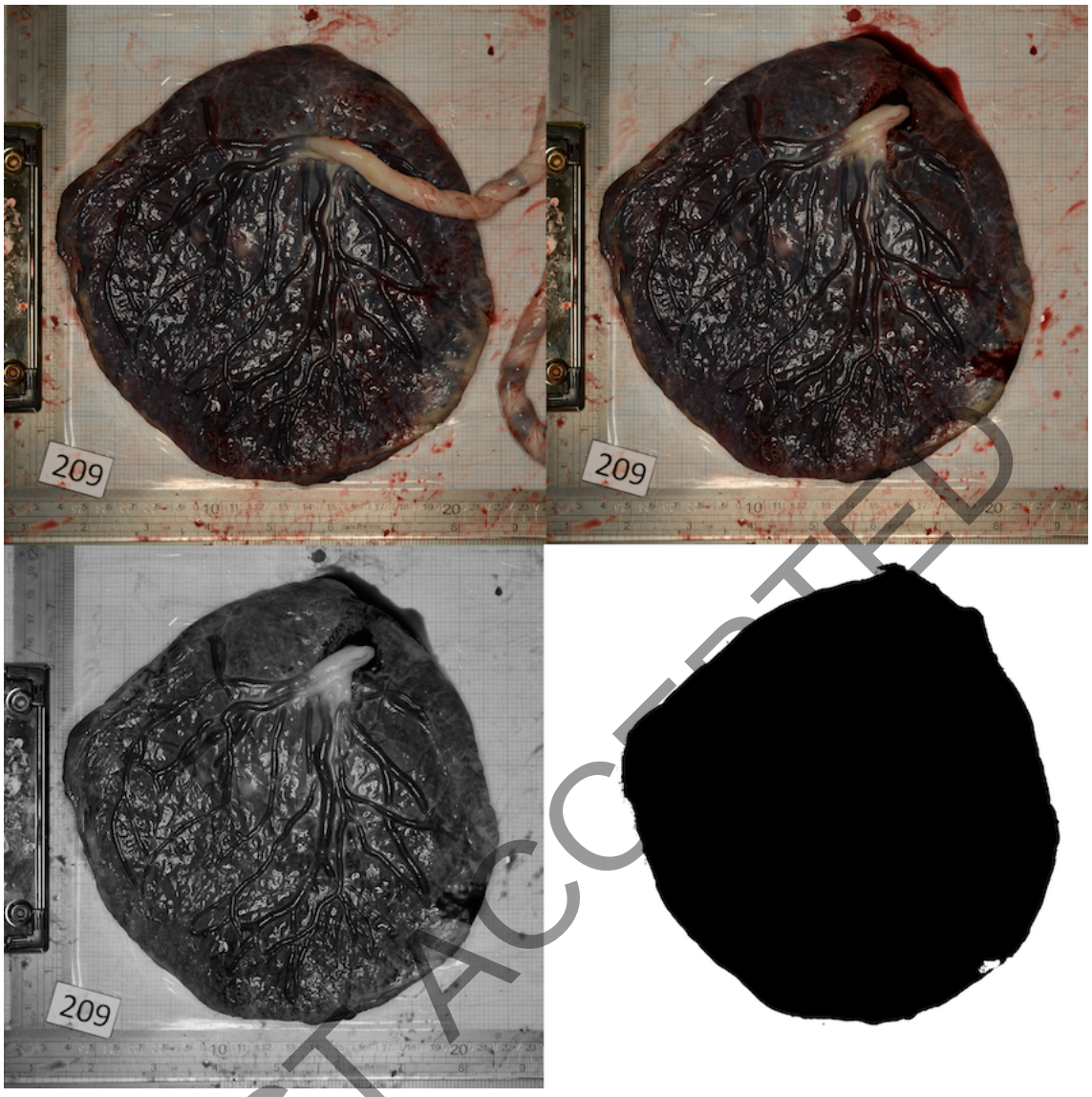
JUST ACCEPTED



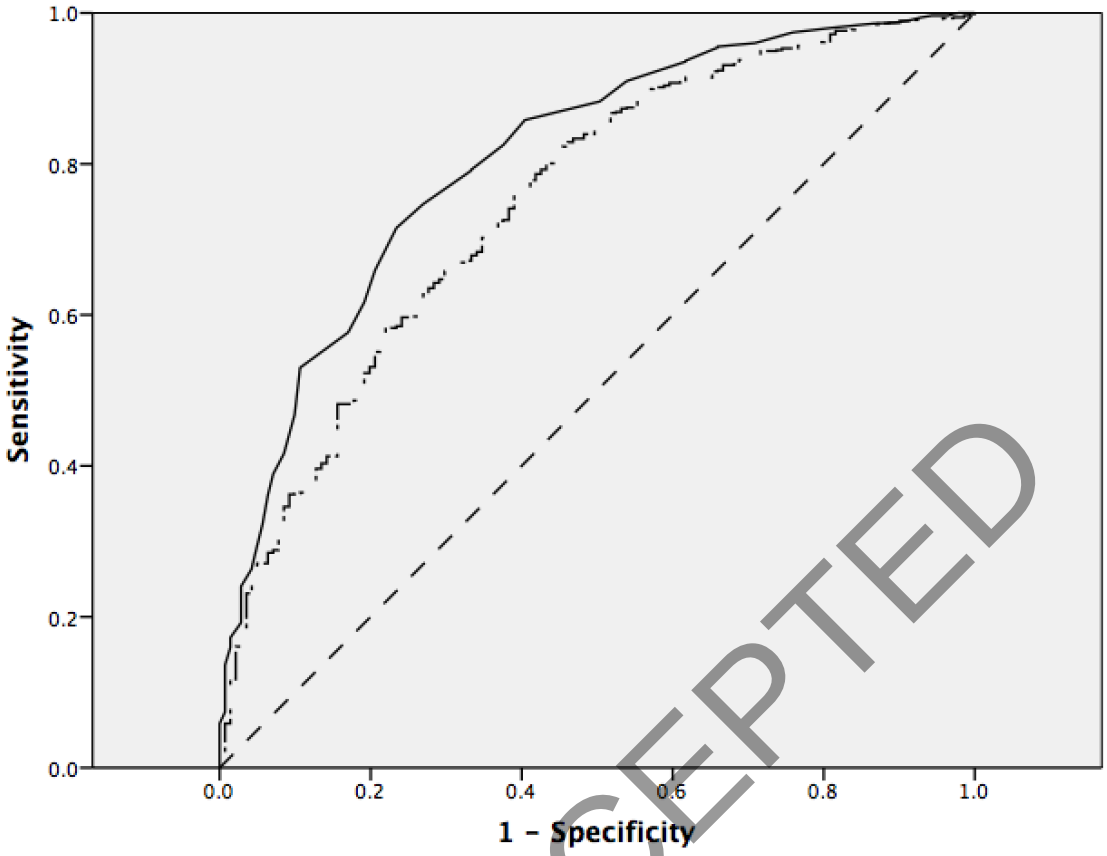
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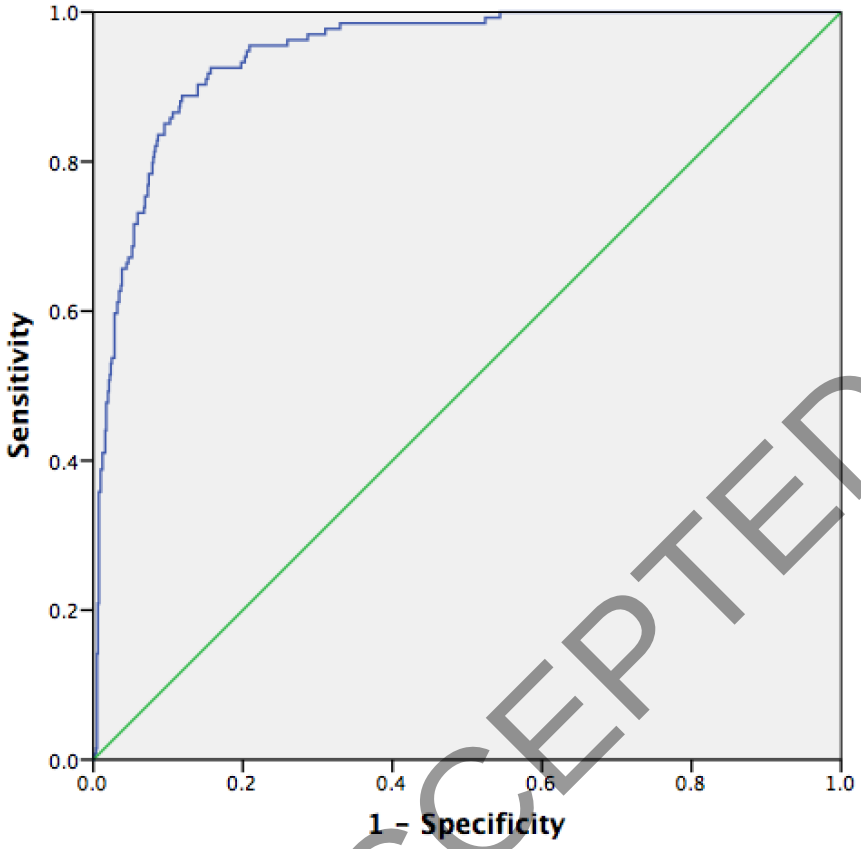
JUST ACCEPTED



JUST ACCEPTED



JUST ACCEPTED



JUST ACCEPTED