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Screening for small-for-gestational-age fetuses

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ABSTRACT

Introduction: It is well established that correct antenatal identification of small-for-gestational-age (SGA) fetuses reduces their risk of adverse perinatal outcome with long-term consequences. Ultrasound estimates of fetal weight (EFW_{us}) is the ultimate tool for this identification. It can be conducted as a "universal screening", ie all pregnant women at a specific gestational age. However, in Denmark it is conducted as "selective screening", ie only on clinical indication. The aim of this study was to assess the performance of the Danish national SGA screening program and the consequences of false positive and false negative SGA cases. **Material and methods:** In this retrospective cohort study, we included 2928 women with singleton pregnancies with due date in 2015. We defined "risk of SGA" by an $EFW_{us} \leq -15\%$ of expected for the gestational age and "SGA" as birthweight $\leq -22\%$ of expected for gestational age. **Results:** At birth, the prevalence of SGA was 3.3%. The overall sensitivity of the Danish screening program was 62% at a false-positive rate of 5.6%. Within the entire cohort, 63% had an EFW_{us} as compared to 79% of the SGA-cases. The sensitivity was 79% for those born before 37 weeks' gestation but only 40% for those born after 40 weeks' gestation. The sensitivity was also associated to birthweight deviation; 73% among extreme SGA cases (birthweight deviation $\leq -33\%$) and 55% among mild SGA (birthweight deviation between -22% and 27%). False diagnosis of SGA was associated with an increased rate of induction of labor ($OR_{adj} = 2.51$, 95% CI; 1.70 to 3.71) and cesarean section ($OR_{adj} = 1.44$, 95% CI; 0.96 to 2.18). **Conclusions:** The performance of the Danish national screening program for SGA based on selective EFW_{us} on clinical indication have improved considerably over the last 20 years. Limitations of the program are the large proportion of women referred to ultrasound scan and the low performance post-term.

Keywords

Small-for-gestational-age, estimated fetal weight, ultrasound, screening, performance, outcome.

Abbreviations

SGA, small-for-gestational-age

AGA, appropriate-for-gestational-age

EFW, estimated fetal weight

EFW_{us}, ultrasound-based estimation of fetal weight

BW, birthweight

GA, gestational age

FPR, false-positive rate

OR, odds ratio

OR_{adj}, adjusted odds ratio

Key message

We assessed the performance of the Danish screening program for small-for-gestational-age fetuses for the first time in 20 years. Performance have improved considerably. In spite of a large proportion of women referred additional ultrasound, the detection of small-for-gestational-age babies post-term remains low.

INTRODUCTION

It is well established that small-for-gestational-age (SGA) fetuses are at increased risk of adverse perinatal outcome[1] and long term consequences such as metabolic syndrome[2] and cardiovascular disease.[3] Antenatal detection of SGA improves the perinatal outcome by enabling timely delivery.[4] Unfortunately, false suspicion of SGA may increase the risk of unnecessary obstetric interventions and thereby increases the risk of adverse neonatal outcome.[5]

When using ultrasound in the screening for SGA, there are two approaches; "universal ultrasound screening" with routine ultrasound estimation of fetal weight (EFW_{us}) conducted in all pregnant women at a specific gestational age (GA) and "selective ultrasound screening" with EFW_{us} conducted only on clinical indication.

Universal EFW_{us} screening has a sensitivity of 68%-77% (birthweight (BW) $\leq 3^{rd}$ centile) at a false positive rate (FPR) of 5-13% [6,7] as compared to selective EFW_{us} screening with a sensitivity of 29-32% at a FPR of 3%.[7,8] The performance of selective ultrasound screening is highly depended on the clinical indications used for referral of patients to EFW_{us}, which dictates the proportion of women referred for ultrasound.

In Denmark, SGA is defined by a BW below -22% of the expected for GA[9] and the prevalence is approximately 3% among singleton pregnancies.[8] The routine antenatal fetal growth assessment includes clinical examination and symphysis-fundal height measurements performed by midwifes and general practitioners every 3 to 4 weeks in pregnancy from 14 weeks' gestation until delivery. Only high-risk pregnancies based on the 1^{st} trimester risk stratification (previous obstetric or medical history) and complications in current pregnancy are referred to obstetric control including EFW_{us}. If EFW_{us} is $\leq$ -15% of the expected weight for the GA, the fetus will be considered at risk of SGA.[10]

The most recent publication on selective EFW_{us} screening in Denmark was based on data from 1997-98, where only 3.7% had an EFW giving a sensitivity of 29% at a FPR of 0.26%.[8] However, based on clinical experience, the proportion of women referred for EFW_{us} have increased considerably over the last decades. Therefore, the actual performance of the screening for SGA in Denmark is currently unknown.

The aim of this study was to investigate the performance of the Danish national screening program for SGA including selective EFW_{us}. In addition, the obstetric consequences of false positive and false negative SGA cases are investigated.

MATERIAL AND METHODS

We included all 3113 women with singleton pregnancies from Aalborg University Hospital, who according to their nuchal translucency scan had a due date between January 1st 2015 to December 31st 2015. The staff members were all certified by the Fetal Medicine Foundation.[11] A total of 185 women were excluded due to either abortion/miscarriage < 22 weeks of gestation or delivery outside North Denmark Region. Consequently, a total of 2928 women remained in this study. EFW_{us} (gram) was calculated by the formula by Hadlock et.al. (based on head circumference, abdominal circumference and femur length)[12] and EFW_{us} deviation (%) was calculated using the reference curve by Maršál et.al.[9]

Information regarding maternal characteristics, pregnancy and delivery were obtained from electronic patient records (Clinical Suite™ version 18.0.4.0; DXC Technology, Tysons, VA, USA) and the local Fetal Medicine database (Astraia software gmbh version 1.24.10; Munich, Germany).

Statistical analyses

The performance of the national screening program for SGA was described by calculation of the sensitivity and the FPR using the binary cut-off value for expected SGA during pregnancy as $EFW_{us} \leq$-15% and binary outcome for SGA at birth as BW ≤-22%. Logistic regression was performed to compare the odds ratio (OR) of obstetric and neonatal outcomes between expected and unexpected groups of SGA and AGA neonates. ORs were adjusted for GA at birth, BW deviation, maternal body mass index and parity (OR_{adj}).

The statistical software package Stata MP version 15.0 (StataCorp LP, College Station, TX, USA) was used for data analysis. *P*-values <0.05 were considered statistically significant.

Ethical approval

The study was approved August 18th 2016 and additional protocol was approved August 3rd 2018 by the Danish Patient Safety Authority, journal number 3-3013-1673/1. Data storage was approved by a regional notification to the Danish Data Protection Agency, journal number 2008-58-0028 with local reference-ID 2016-61 (March 31st 2016) and 2018-104 (June 12th 2018).

RESULTS

Within this cohort of 2928 unselected singleton pregnancies, 3.3% had SGA when defined as BW≤-22% (Figure 1) and 63% had a selective EFW_{us}. Concerning the entire cohort, the sensitivity was 62% given a FPR of 5.6% for SGA defined as BW≤-22%. Performance for SGA defined as BW≤-15% is added for comparison (Table 1). For those with mild SGA (BW -22% to -27%), the sensitivity of the screening program was 55%; for those with extreme SGA (BW ≤ 33%) it was 73% (Supporting Information Table S1); whereas it was only 40% (14/35) for newborns delivered after 40^{+0} weeks (Table 2).

For the calculation of these sensitivities, we defined "screen positive" by the last $EFW_{us} \leq -15\%$.[10] Using an $EFW_{us} \leq -12\%$ would give a sensitivity of 86% at a FPR of 17%; using $EFW_{us} \leq -22\%$, would give a sensitivity 57% at a FPR of 1.6% (Supporting Information Table S2).

The maternal and neonatal characteristics for the SGA and AGA pregnancies are presented in Supporting Information Table S3 (SGA) and Table S4 (AGA).

Among the SGA fetuses, we could not demonstrate different perinatal outcome among those identified by EFW_{us} and those not identified by EFW_{us} (Table 3) even though the identified SGA were more likely to have induction of labor (OR_{adj} = 0.13, 95% CI; 0.04 to 0.41) and elective cesarean section (27% vs. 0%, $P< 0.01$). Among the AGA fetuses, 5.6% were falsely expected SGA and these were more likely to have induction of labor (OR_{adj} = 2.51, 95% CI; 1.70 to 3.71) and cesarean delivery (OR_{adj} = 1.44, 95% CI; 0.96 to 2.18) (Table 4).

DISCUSSION

In this study, we investigated the performance of the screening program for SGA defined as BW≤-22% in the North Denmark Region based on selective EFW_{us}. No less than 63% had an EFW_{us} giving a sensitivity of 62%, however much higher for fetuses with extreme SGA. We could not demonstrate improved perinatal outcome among SGA fetuses identified by EFW_{us} when compared to those not identified by EFW_{us}. The FPR was 5.6% and false positive SGA cases were at an increased risk of obstetric interventions.

It is a strength of this study that the cohort can be classified as unselected, as we included more than 95% of the pregnant population in a well-defined geographic area[13] with a lost to follow-up rate of only 5.9%. Furthermore, the validity of the data was very high as it is based on the unique Danish personal identification number. It is a limitation that the study is not powered to assess rare neonatal outcomes. In addition, referral for EFW_{us} followed the national guidelines. Unfortunately, the specific indication for referral is not consistently available in the patient record, and therefore the association between SGA and specific indications cannot be evaluated in this study.

In this study, the sensitivity on SGA screening using selective EFW_{us} on clinical indication was 62%, which is markedly higher than previous studies on selective ultrasound screening reporting a sensitivity of 29% to 46%.[7,8,14] This could be explained by a larger proportion of women referred to EFW_{us} in our study (63%) as compared to prior studies (3.7-42%).[7,8,14] The large proportion of women referred to EFW_{us} may partly be explained by the inclusion of multiparous women in our study (54% of the total cohort). Among multiparous women, indications for EFW_{us} include previous obstetric complications such as SGA or preeclampsia, which leads to a higher number of referrals.[10,15] Moreover, the referral pattern in Aalborg and Denmark might be different than other countries.[10] Even with such large proportion of all women referred for ultrasound, 21% of SGA pregnancies was not referred for EFW_{us}. Moreover, a large proportion of AGA pregnancies (63%) underwent EFW_{us}.

We defined a screen positive case in accordance with the national guidelines on SGA screening as last $EFW_{us} \leq -15\%$, ie by a relatively slight estimated weight deviation. Therefore, it is disappointing that the sensitivity was only 73% (8/11) for extreme SGA (BW ≤ -33%); two cases

did not have an EFW_{us} due to a false negative "clinical screening" based on risk factors and symphysis-fundal height measurement; one case had an EFW_{us} >-15% which was performed 29 days prior to birth (Supporting Information Table S1). Previous publications have not addressed this extreme SGA-sensitivity even though these cases are most in need of prenatal detection and must be the primary target when we consider potential improvements to our screening program as discussed below. It is more acceptable that the sensitivity for mild SGA (BW between -22% and -27%) was only 55% (29/53) even though they might also benefit from prenatal detection, especially when born post term.[16] In fact, the EFW_{us} standard deviation of 8% when using The Hadlock Formula[12] implies that a significant fraction of mild SGA fetuses will remain undetected (EFW_{us} >-15%) even when identified by the clinical screening (eg symphysis-fundal height) with correct referral for EFW_{us}.

The sensitivity decreased markedly with increasing GA; from 72% (GA 37^{+0} – 39^{+6}) to 38% (GA $\geq 41^{+0}$) leaving 22% (21/98) undiagnosed at birth after term (Table 2). Among these, 67% (14/21) did not have an EFW_{us} whereas 33% (7/21) had an EFW_{us} > -15%. This is highly problematical, as it is generally accepted that SGA babies need to be delivered at least at term.[16]

We confirmed the results from a Swedish[4] study showing increased risk of interventions among SGA cased identified correctly before birth (Table 3). However, our study did not have statistically power to address their finding of improved neonatal outcome. The FPR is also of interest, ie AGA cases falsely expected to be SGA (Table 4), showed an increased rate of labor induction (OR_{adj} 2.51, 95% CI; 1.70 to 3.71) and an increased cesarean section rate (OR_{adj} 1.44, 95% CI; 0.96 to 2.18) confirming results from one prior study.[5]

In order to improve the screening for SGA in Denmark, several issues could be considered; Selection of pregnancies for EFW_{us}, accuracy of EFW_{us}, and 3rd trimester routine EFW_{us} ("universal ultrasound screening"). Improved selection of pregnancies for EFW_{us} might be achieved by the use of 1st trimester maternal serum markers[17,18] and uterine artery Doppler flow[19,20], and by improved symphysis-fundal height measurements using a single person throughout the pregnancy.[21,22] An obvious possibility would be to change the "risk of SGA" definition to $EFW_{us} \leq$ -12% on the expense of a doubled FPR. Furthermore 3D ultrasound[23] and Magnetic Resonance Imaging[24,25] for better estimates of EFW could be considered. Introducing routine EFW_{us} ("universal ultrasound screening") have shown to increase the sensitivity from 29-33% to 42-80%, but on the expense of increased FPR from 0.26-3% to 5-13% in previous

studies.[7,14,26,27] Routine EFW_{us} performs best when applied close to delivery[26,27]; ie a sensitivity of 89% if delivery was within 2 weeks from routine EFW_{us} in GA 35-37 weeks, at a FPR of 5%.[27] As suggested by our data, the main limitation of the Danish SGA screening program was in the antenatal detection of post term SGA babies. Therefore, introducing a late routine EFW_{us} either at term or post term (GA 41^{+0}) would likely increase the sensitivity but also the FPR.

This manuscript focuses on screening for SGA, as small fetal size is regarded a proxy of placental dysfunction. However, fetal size is not a perfect marker of placental function, and even a perfect screening for SGA may not identify all fetuses at risk because of placental dysfunction.[28] New markers of placental dysfunction based on maternal serum[18] or placental MRI[29] may be able to identify placental dysfunction directly, and the clinical potential of these methods are currently being investigated.

CONCLUSION

The performance of the Danish national screening program for SGA based on selective EFW_{us} on clinical indication have improved considerably over the last 20 years with an increased sensitivity from 29% (1998) to 62% (2015) and FPR from 0.26% (1998) to 5.6% (2015).[8] However, the selection of pregnancies for ultrasound is a limitation of the program as a large proportion of AGA pregnancies are referred to ultrasound and a large proportion of SGA pregnancies are not. In addition, the detection of SGA babies post-term remains rather low when compared to earlier gestation. This paper gives a detailed insight in the current screening program, and provides ideas for further improvement of SGA screening.

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Supporting Information legends

Table S1: Performance of the screening program for small-for-gestational-age in Denmark in relation to birthweight deviation.

Table S2: Screening performance at different ultrasound estimated fetal weight cut-off values.

Table S3: Maternal and neonatal characteristics of small-for-gestational-age-pregnancies.

Table S4: Maternal and neonatal characteristics of appropriate-for-gestational-age-pregnancies.

Figure and table legends

Figure 1: Flowchart of the study population. SGA, small-for-gestational-age; BW, birthweight; EFW_{us}, estimated fetal weight by ultrasound scan; AGA, appropriate-for-gestational-age. SGA is defined by BW≤-22% (in accordance with Danish national guidelines) and for comparison by BW≤-15%.

Table 1: Performance of the screening program for small for gestational age in Denmark.

Table 2: Performance of the screening program for small for gestational age in Denmark in relation to gestational age at birth.

Table 3: Outcome for small for gestational age -pregnancies.

Table 4: Outcome for AGA-pregnancies.

Table 1: Performance of the screening program for small for gestational age in Denmark.

Total population, n	2928	
Women never referred to ultrasound	37% (1079/2928)	
Women referred to ultrasound	63% (1849/2928)	
Time between last ultrasound and birth, days (median(interquartile range))	11 (2, 28)	
SGA cut-off	**BW ≤-22%**	**BW≤-15%**
SGA at birth	3.3% (98/2928)	10.3% (303/2928)
Last EFW_{us}≤-15%	7.5% (219/2928)	7.5% (219/2928)
Sensitivity (last EFW_{us}≤-15% AND SGA at birth)	62% (61/98)	41.6% (126/303)
False positive rate	5.6% (158/2830)	3.5% (93/2625)

SGA is defined by BW≤-22% (in accordance with Danish national guidelines) and for comparison by BW≤-15%.

SGA, small for gestational age; BW, birthweight; EFWus, estimated fetal weight by ultrasound scan.

TABLE 2: Performance of the screening program for small for gestational age in Denmark in relation to gestational age at birth.

	Overall	Gestational age at birth				
		<34 weeks	**34^0-36^6 weeks**	**37^0-39^6 weeks**	**40^0-40^6 weeks**	**≥ 41 weeks**
Total population, n	2928	46	130	1,146	845	761
SGA at birth (BW≤-22%)	3.3% (98/2928)	24% (11/46)	10% (13/130)	3.4% (39/1146)	2.2% (19/845)	2.1% (16/761)
Sensitivity of screening program	62% (61/98)	73% (8/11)	85% (11/13)	72% (28/39)	42% (8/19)	38% (6/16)
SGA referred to ultrasound	79% (77/98)	82% (9/11)	92% (12/13)	90% (35/39)	68% (13/19)	50% (8/16)
Last EFW_{us} ≤ -15%	7.5% (219/2928)	26% (12/46)	15% (20/130)	8.6% (99/1146)	4.7% (40/845)	6.3% (48/761)
False positive rate	5.6% (158/2830)	11% (4/35)	7.7% (9/117)	6.4% (71/1107)	3.9% (32/826)	5.6% (42/745)

Sensitivity for SGA defined by BW≤-22% using the following cut off; EFWus ≤-15% at last ultrasound scan.

SGA, small-for-gestational-age; BW, birghtweight; EFWus, estimated fetal weight by ultrasound scan.

Table 3: Outcome for small for gestational age -pregnancies.

Outcome	SGA				
	Total **n=98**	**Expected SGA** (Last EFW_{us}≤-15%) **n=61**	**Expected AGA** (Last EFW_{us}>-15% or no EFW_{us}) **n=37**	**OR (95% CI), *P*-value**	**Adjusted[1] OR (95% CI), *P*-value**
Cesarean delivery	36% (35/98)	47% (26/61)	24% (9/37)	0.43 (0.17-1.07), *P*=0.07	0.71 (0.24-2.13), *P*=0.54
Elective cesarean sectio among all cesarean sectio	20% (7/35)	27% (7/26)	0	**	**
Intended vaginal delivery	77% (75/98)	72% (44/61)	84% (31/37)	2.31 (0.93-5.72), *P*=0.07	1.41 (0.47-4.22), *P*=0.54
Induction among intended vaginal delivery	57% (44/75)	83% (34/44)	35% (10/31)	0.14 (0.05-0.39), *P*=0.00*	0.13 (0.04-0.41), *P*=0.00*
Vacuum among vaginal delivery	13% (8/63)	17% (6/35)	7.1% (2/28)	0.37 (0.07-2.01), *P*=0.25	0.41 (0.07-2.30), *P*=0.31
Umbilical artery pH <7.1	7.0% (6/86)	7.1% (4/56)	6.7% (2/30)	0.93 (0.16-5.39), *P*=0.93	0.54 (0.08-3.58), *P*=0.52
Apgar score < 7 after 5 minutes	4.2% (4/95)	5.0% (3/60)	2.9% (1/35)	0.56 (0.06-5.59), *P*=0.62	0.50 (0.04-5.78), *P*=0.58
Stillborn	2.0% (2/98)	1.6% (1/61)	2.7% (1/37)	1.67 (0.10-27.47), *P*=0.72	0.66 (0.02-27.39), *P*=0.83
Neonatal death	1.0% (1/98)	1.6% (1/61)	0	**	**
Adverse outcome[2]	11% (11/98)	13% (8/61)	8.1% (3/37)	0.58 (0.14-2.36), *P*=0.45	0.53 (0.12-2.37), *P*=0.41

SGA = BW≤-22%. Expected SGA = EFWus ≤ - 15% at last ultrasound scan. Expected AGA = normal symphysis-fundal-height measurements and/or EFWus > -15% at last ultrasound scan. Logistic Regression are used to compare the groups of SGA (expected SGA and expected AGA) using SGA-expected SGA as a reference. 1. Adjusted for gestational age at birth (weeks in total), birthweight deviation (%), maternal body mass index and parity. 2. Umbilical artery pH<7.1, Apgar score <7 after 5 minutes, stillborn and neonatal death in one variable. * P-value < 0.05. ** Logistic regression not possible, because no cases within expected AGA-group.

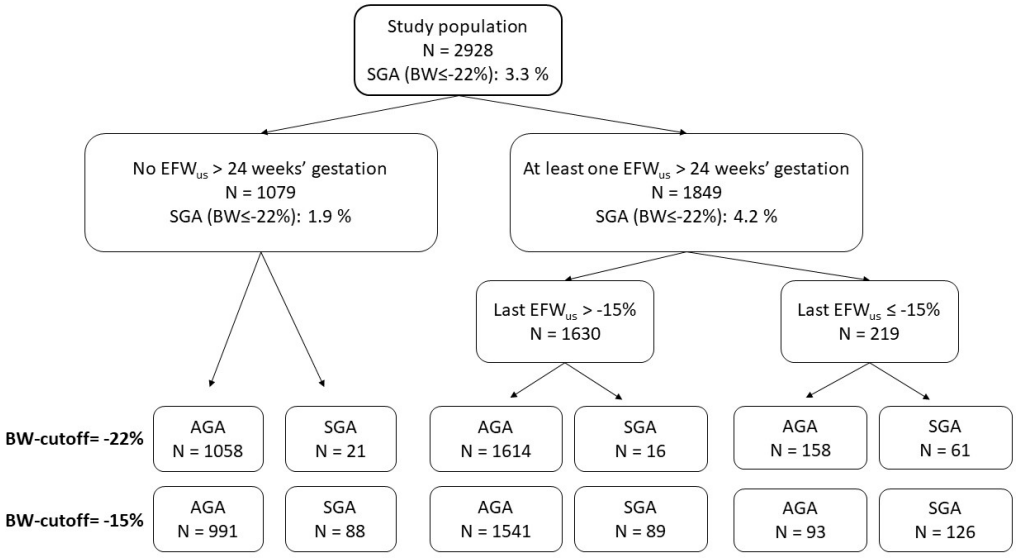
SGA, small-for-gestational-age; AGA, appropriate-for-gestational-age; EFWus, estimated fetal weight by ultrasound scan; OR, odds ratio; CI, confidence interval.

Table 4: Outcome for appropriate-for-gestational-age-pregnancies.

Outcome	AGA				
	Total **n=2830**	**Expected AGA** (Last EFW_{us}>-15% or no EFW_{us}) **n=2672**	**Expected SGA** (Last EFW_{us}≤-15%) **n=158**	**OR (95% CI), *P*-value**	**Adjusted[1] OR (95% CI), *P*-value**
Cesarean delivery	20% (572/2830)	20% (535/2672)	23% (37/158)	1.22 (0.84-1.79), *P*=0.30	1.44 (0.96-2.18), *P*=0.08
Elective cesarean sectio among all cesarean sectio	38% (215/572)	38% (203/535)	32% (12/37)	0.79 (0.39-1.60), *P*=0.50	1.49 (0.68-3.26), *P*=0.32
Intended vaginal delivery	83% (2349/2830)	83% (2221/2672)	81% (128/158)	0.82 (0.56-1.20), *P*=0.30	0.69 (0.46-1.05), *P*=0.08
Induction among intended vaginal delivery	29% (688/2349)	28% (631/2221)	45% (57/128)	2.02 (1.41-2.90), *P*=0.00*	2.51 (1.70-3.71), *P*=0.00*
Vacuum among vaginal delivery	8.3% (187/2258)	8.4% (179/2137)	6.6% (8/121)	0.77 (0.37-1.61), *P*=0.49	0.66 (0.31-1.44), *P*=0.30
Umbilical artery pH <7.1	4.6% (118/2590)	4.6% (113/2443)	3.4% (5/147)	0.73 (0.29-1.81), *P*=0.49	0.73 (0.28-1.87), *P*=0.51
Apgar score < 7 after 5 minutes	0.8% (22/2812)	0.8% (21/2654)	0.6% (1/158)	0.80 (0.11-5.98), *P*=0.83	0.65 (0.08-5.22), *P*=0.68
Stillborn	0.3% (9/2830)	0.3% (9/2672)	0	**	**
Neonatal death	0.1% (2/2830)	0.8% (2/2672)	0	**	**
Adverse outcome[2]	5.1% (144/2830)	5.2% (138/2672)	3.8% (6/158)	0.72 (0.31-1.67), *P*=0.45	0.63 (0.27-1.50), *P*=0.30

AGA = BW>-22%. Expected SGA = EFWus ≤ - 15% at last ultrasound scan. Expected AGA = normal symphysis-fundal-height measurements and/or EFWus > -15% at last ultrasound scan. Logistic Regression are used to compare the groups of AGA (expected AGA and expected SGA) using AGA-expected AGA as a reference 1. Adjusted for gestational age at birth (weeks in total), birthweight deviation (%), maternal body mass index and parity. 2. Umbilical artery pH<7.1, Apgar score <7 after 5 minutes, stillborn and neonatal death in one variable. * P-value < 0.05. ** Logistic Regression not possible, because no cases within expected SGA-group.

SGA, small-for-gestational-age; AGA, appropriate-for-gestational-age; EFWus, estimated fetal weight by ultrasound scan;OR, odds ratio; CI, confidence interval.



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