# Clinical phenotypes for risk stratification in small for gestational age fetuses

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**Short title**: Clinical phenotypes of small for gestational age fetuses

## ABSTRACT

**Objective:** This study evaluates whether clinical phenotypes of small for gestational (SGA) fetuses can be identified and used for adverse perinatal outcome risk stratification to facilitate decision-making.

**Methods:** This multicentre observational cohort study was conducted in two tertiary care university hospitals. It included 17,631 consecutive singleton pregnancies, among which 1274 (7.2%) were defined as SGA at birth according to INTERGROWTH-21st standards. The main outcome was the development of clinical clusters of SGA phenotypes.

**Results:** Nine SGA clinical phenotypes were identified using a predefined conceptual framework. Every delivery and perinatal outcome analysed showed statistically significant differences between phenotypes. The total SGA cohort had a 3 times increased risk of perinatal mortality than non-SGA fetuses (1.4% vs 0.4%; p<0.001). The SGA clinical phenotypes exhibited three patterns of perinatal mortality risk: the highest risk included the congenital anomalies and second- or third-trimester haemorrhage clusters (8.3%; odds ratio [OR] 17.17, 95% confidence interval [CI] 2.17-136.12 for congenital anomalies and OR 9.94, 95% CI 1.23-72.57 for second- or third-trimester haemorrhage); the medium risk included the gestational diabetes (3.8%; OR 9.59, 95% CI 1.27-72.57), preterm birth (3.2%; OR 4.65, 95% CI 0.62-35.01), and intrauterine growth restriction (3.1%; OR 5.93, 95% CI 3.21-10.95) clusters; and the lowest risk included the remaining clusters. Perinatal mortality rate did not differ between SGA fetuses without other clinical conditions (which encompassed 54.1% of SGA fetuses) and appropriate for gestational age fetuses (0.1% vs 0.4%; p=0.27; OR 0.41, 95% CI 0.06-2.94). SGA combined with other obstetric pathologies significantly increased perinatal mortality risk, highlighting in maternal diabetes (OR 24.40, 95% CI 1.31-453.91).

**Conclusions:** We identified nine SGA clinical phenotypes associated with different patterns of risk for adverse perinatal outcomes. Our results suggest that adding clinical characteristics to ultrasound results would improve risk stratification and decision-making for SGA fetuses. Future clinical trials on the control of fetuses with SGA should take into account, in addition to Doppler and estimated fetal weight, this clinical information.

**Key Words**: Small for gestational age, phenotypes, perinatal mortality, stillbirth, fetal growth restriction

**Acknowledgements:** C. Paules, S. Ruiz-Martinez and D. Oros were supported by a research grant from the Instituto de Salud Carlos III (CM18/00202, JR19/00006, BA18/ 0026).

## INTRODUCTION

Small for gestational age (SGA) is usually defined by a statistical deviation of ultrasound estimated fetal weight or abdominal circumference from a population-based reference, with the typical threshold set at the 10$^{th}$ percentile.[1] SGA is associated with increased perinatal mortality and morbidity,[2] suboptimal cardiovascular and neurologic development,[3] and long-term health problems.[4,5,6] Although identification of SGA fetuses is associated with a reduction in adverse perinatal outcomes,[7] a key aspect of clinical management is the ability to differentiate SGA fetuses at higher risk of adverse outcomes.

Growth restriction is a complex condition with multiple etiologic factors that will determine its risk and consequences. After excluding abnormal SGA fetuses resulting from chromosomal, structural, or infective abnormalities,[8] Doppler assessment of placental function and fetal well-being forms the basis for identifying intrauterine growth restriction (IUGR) in current clinical protocols.[1,9] Fetuses with neither abnormal SGA nor IUGR are presumed to be constitutionally SGA. Although SGA fetuses with Doppler alterations have worse perinatal outcomes, [10] such constitutionally SGA fetuses also have higher risks of poor perinatal and long-term outcomes when compared to appropriate weight for gestational age (AGA) fetuses.[11] Thus, it is necessary to search for new strategies to better identify high-risk SGA patients.

Fetal growth can be affected by various pathologic conditions during gestation with obvious clinical manifestations. To promote more targeted interventions, we propose phenotypic sub-classification of SGA fetuses based on not only Doppler parameters, but also on easily obtained clinical information. The aim of this study is to evaluate whether clinical phenotypes of SGA fetuses can be identified and used to aid in risk stratification.

## METHODS

A multicentre observational cohort study was conducted in two Spanish tertiary care university hospitals: Hospital Clínico Universitario Lozano Blesa in Zaragoza and Hospital Universitario Virgen de la Arrixaca in Murcia. A total of 17,631 consecutive singleton pregnancies were prospectively enrolled. SGA was defined as a birthweight below the 10$^{th}$ percentile according to INTERGROWTH-21[12] standards. In all cases, gestational age was defined by fetal crown-rump length on the first ultrasound at 11–13 weeks gestation.[13,] Data regarding maternal clinical and demographic characteristics, as well as perinatal outcomes, were obtained from medical records. The ethics committee approved the protocol for this study. Both centres used similar clinical protocols, which included a routine ultrasound scan between 32 and 37 weeks of gestation. Ultrasound recordings were performed by one experienced operator. Fetuses with estimated fetal weight below the <10th percentile according to local standards[14], were considered and consequently managed as suspected SGA during pregnancy. Patients were always managed by senior obstetricians, according to standard protocols for every clinical condition

Following a previously published conceptual framework for developing a clinical phenotypic classification for preterm birth,[15] SGA was classified according to maternal, fetal, and placental conditions causally associated with SGA (Table 1). After a comprehensive descriptive analysis following a hierarchical, agglomerative approach combining individual cases into clusters as different from one another as possible, a nine-cluster model provided a categorization of SGA clinical phenotypes highly consistent with our *a priori* conceptual classification. Therefore, every SGA fetus in our study was grouped into four clusters related to maternal conditions (hypertension/preeclampsia, gestational diabetes, other chronic maternal diseases, and assisted-reproduction techniques), three clusters related to fetal conditions (congenital anomalies, intrauterine growth restriction, and preterm birth), and one cluster related to

placental condition (second- or third-trimester haemorrhage). The remaining SGA fetuses with no associated clinical manifestation were grouped into another cluster (none).

Statistical analyses were performed using SPSS, version 19. Because many fetuses exhibited more than one maternal, fetal, or placental condition, we used a two-step cluster algorithm.[16,17] In step 1, we analysed perinatal mortality rates for each of the nine clusters, with cases initially classified in more than one cluster if appropriate. In step 2, the cases initially included in more than one group were reclassified and assigned to only one cluster, which was their cluster with the highest mortality risk. Thus, in the final analysis, every patient was placed in only a single cluster. Preterm cases that were also included in another group were not assigned to the prematurity group because the preterm birth was medically indicated in most cases. To evaluate the independence of each cluster as a clinical entity, we calculated perinatal mortality and neonatal intensive care unit (NICU) admission rates.

## RESULTS

Of the 17,631 consecutive singleton pregnancies included in this study, 1274 (7.2%) were defined as SGA. We found differences in baseline sociodemographic characteristics, as well as evolution of the pregnancy, between SGA and non-SGA fetus groups. As expected, the overall SGA cohort had worse perinatal outcomes, with an approximately 3 times higher rate of perinatal mortality (14.13 **%** vs 4.16**%**; p<0.001) (Table 2).

Fetuses initially included in more than one group were reclassified and assigned to only their cluster with the highest mortality risk (based on the analysis of step 1 clusters) (Supplementary Table 1). Table 3 summarizes the distribution of SGA neonates into the final nine clusters. Of note, two clusters encompassed more than 85% of all cases: the “none” cluster (54.1%) and IUGR (according to The International Society of Ultrasound in Obstetrics and Gynecology

(ISUOG) definition[16]) cluster (33.2%). The remaining SGA cases were distributed evenly across the other seven clusters.

After reclassifying each case into a single clinical cluster, all delivery and perinatal outcomes exhibited statistically significant differences between clusters (Supplementary Table 2, Figures 1–3). We also calculated the odds ratios (ORs) of each SGA clinical phenotype compared with non-SGA fetuses, adjusted for gestational age, for delivery and perinatal outcomes (Table 4). The rate of caesarean section was highest in the second- or third-trimester haemorrhage cluster (91.7%; OR 19.59, 95% confidence interval [CI] 2.47-155.5) and hypertension/preeclampsia cluster (71.4%; OR 5.20, 95% CI 2.24-12.07). Conversely, caesarean section rates were similar between SGA and non-SGA fetuses in the assisted reproduction techniques and none clusters. Of note, the rate of caesarean section for fetal acidosis was 50% in the second- or third-trimester haemorrhage cluster (OR 17.98, 95% CI 5.71-56.60); this was much higher than the rates for other clusters, which ranged from 9.8% to 16%. The gestational diabetes cluster (88.5%; OR 14.40, 95% CI 4.32-48.97) and hypertension/preeclampsia cluster (74.1%; OR 6.11, 95 CI 2.45-15.26) had the highest rates of elective delivery.

Regarding perinatal outcomes, the clusters of second- or third-trimester haemorrhage and congenital had the worst outcomes, with NICU admission rates of 66.7% (OR 5.19, 95% CI 1.14-23.72) and 58.3% (OR 10.65, 95% CI 3.07-36.97), respectively, and 5-min Apgar score < 7 rates of 18% in both clusters (OR 5.38, 95% CI 1.03-28.04 for second- or third-trimester haemorrhage and OR 14.05, 95% CI 2.91-67.85 for congenital anomalies). The hypertension/preeclampsia, preterm birth, and IUGR phenotypes were also associated with an increased risk of poor perinatal outcomes, with NICU admission rates of 60.7% (OR 7.31, 95% CI 3.12-17.17), 51.6% (OR 4.08, 95% CI 1.91-8.72), and 36.2% (OR 5.32, 95% CI 4.18-6.78), respectively.

We also calculated the added risk of being SGA or non-SGA for each clinical condition, adjusted for gestational age (Supplementary Table 3). For example, in gestational diabetic pregnancies,

SGA fetuses had a significantly higher risk of perinatal mortality (OR 24.40, 95% CI 1.31-453.91) than gestational diabetic pregnancies with AGA fetuses.

Finally, we classified our SGA fetuses into three patterns of stillbirth or perinatal mortality risk (Figure 3 and Table 4). The highest risk pattern included congenital anomalies (8.3%; OR for mortality 17.17, 95% CI 2.17-136.12) and second- or third-trimester haemorrhage (8.3%; OR for mortality 9.94, 95% CI 1.23-80.02); the medium risk pattern included gestational diabetes (3.8%; OR for mortality 9.59, 95% CI 1.27–72.57), preterm birth (3.2%; OR for mortality 4.65, 95% CI 0.62-35.01), and IUGR (3.1%; OR for mortality 5.93, 95% CI 3.21-10.95); and the lowest risk pattern included the remaining clusters (none, hypertension/preeclampsia, assisted reproduction techniques, and maternal chronic pathologies). It is noteworthy that we found no difference in perinatal mortality rates between the none cluster (which encompassed 54.1% of our SGA group) and the non-SGA cohort (0.1% vs 0.4%; p=0.27; OR 0.41, 95% CI 0.06-2.94).

## DISCUSSION

In this study, we identified nine SGA clinical phenotypes associated with statistically significant different patterns of risk for adverse perinatal outcomes. Accordingly, we proposed a practical sub-classification system of SGA fetuses based on Doppler parameters, as well as easily obtained clinical information, to open new research pathways for developing more targeted interventions.

Doppler is undeniably important for managing SGA fetuses, as it is the main tool, together with estimated fetal weight, for diagnosing and monitoring foetuses with IUGR.[18] The etiologic complexities of growth restriction remain inadequately understood, but are required for the development of better preventive and treatment measures. Pending establishment of the role of angiogenic markers in managing SGA,[19,20,21] fetal monitoring for SGA continues to focus on

ultrasound and Doppler results[22] and this is the main tool for risk stratification.[10,23] However, according to current classification systems,[1,8] the group of SGA fetuses, after excluding those with Doppler alterations or congenital anomalies, continues to have worse perinatal and long-term results than their AGA peers[11]. Our results support this concept: based on previously established criteria,[8] 33.3% of SGA fetuses in our study were classified as IUGR,[21] and 13 of the 18 (72%) perinatal deaths in our cohort occurred in this group.

Interventions for SGA have had limited benefit because they tend to improve outcomes in only specific subsets of cases. As healthcare evolves from reactive care to more cost-effective predictive, preventive, and personalized care (treating the causes rather than symptoms of disease),[24] intensive research activity has focused on placental biomarkers for phenotypic characterization and risk stratification of fetal smallness.[25,26] Despite important advances in the biological basis of growth restriction,[27,28,29] the information currently available is complex and has not yet been translated into clinical practice. Some authors have suggested that we can better characterize and phenotype pathologies, such as preterm birth[15] or IUGR,[30] based on maternal, fetal, and placental clinical conditions. Accordingly, 12 preterm birth phenotypes associated with differing neonatal outcomes[16] and neurodevelopmental outcomes up to age 2 years[31] were recently identified. Following this pragmatic conceptual framework and considering easily obtainable clinical information, in addition to commonly accepted SGA clinical phenotypes (IUGR, constitutional SGA, congenital anomalies), we identified six more clinical phenotypes (Preterm birth, Hypertension/preeclampsia, Assisted reproduction techniques, Chronic maternal diseases, Gestational diabetes and Third trimester bleeding that encompassing 11.8% of all SGA fetuses) with a significantly increased risk of adverse perinatal outcomes. This set of fetuses, which would have been considered low-risk SGA according to current classification systems, accounted for 3 of the 4 perinatal deaths in fetuses outside the IUGR or congenital anomalies clusters (i.e., fetuses without specific pathology detected by Doppler or ultrasound). When excluding these fetuses, the remaining 54.1% of SGA fetuses with

206 no other clinical conditions (i.e., the none cluster) had similar risks of 5-min Apgar score < 7,
207 NICU admission, stillbirth, and perinatal mortality, when compared with non-SGA fetuses.

208 Focusing on clinical management of SGA, three practical conclusions can be derived from our
209 results. First, according to international consensus, SGA fetuses without congenital anomalies
210 and normal Doppler findings should be monitored closely, with delivery near term.[32,33] However,
211 when considering other clinical conditions in addition to Doppler results, we identified a small
212 group of fetuses (11.8%) with significantly worse perinatal outcomes. Second, exclusion of this
213 small number of SGA fetuses with other clinical conditions considerably reduces the perinatal
214 risk of the remaining SGA fetuses. Third, it is important to highlight the increased risk when SGA
215 is accompanied by other obstetric pathologies, including the significantly increased perinatal
216 mortality in the presence of gestational diabetes (OR 24.40). Our data do not allow specific
217 clinical management recommendations but emphasise the need to include the identified clinical
218 variables both in routine clinical practice and in future studies to better select SGA fetuses
219 requiring intervention.

220 The study had some limitations. Each patient in our cohort is represented in only one cluster
221 although the same fetus may exhibit several concomitant clinical conditions. Nevertheless, we
222 opted for a two-step cluster analysis to simplify the analysis and potential clinical management.
223 Including each fetus in its highest risk cluster is consistent with the usual and practical reasoning
224 employed in clinical management. Our analysis generated distinct, clinically reasonable clusters
225 with different mortality and morbidity rates, supporting its usefulness in classifying our study
226 population. Another limitation was that the sample size was insufficient for adequate statistical
227 power when analysing infrequent perinatal outcomes. However, despite wide CIs, we found
228 significant differences in variables with major clinical relevance. Unfortunately, we do not have
229 data regarding medium- and long-term infant development. Despite these drawbacks, this study

meets the main goal of generating hypotheses. Larger clinical studies are necessary to develop specific guidelines for action; and to establish aetiological phenotypes.

In conclusion, we identified nine SGA clinical phenotypes associated with different patterns of perinatal outcomes. Our results suggest that adding clinical characteristics to ultrasound examination would improve risk stratification and decision-making for SGA fetuses. In addition to Doppler and fetal weigh, future clinical trials on the control of fetuses with SGA should take into account clinical information.

# REFERENCES


[1] Gordijn SJ, Beune IM, Thilaganathan B, Papageorghiou A, Baschat AA, Baker PN, Silver RM, Wynia K, Ganzevoort W. Consensus definition of fetal growth restriction: a Delphi procedure. Ultrasound Obstet Gynecol. 2016 Sep;48(3):333-9. doi: 10.1002/uog.15884.

[2] Moraitis AA, Wood AM, Fleming M, Smith GC. Birth weight percentile and the risk of term perinatal death. Obstet Gynecol 2014; 124: 274–283.

[3] Crispi F, Miranda J, Gratacós E. Long-term cardiovascular consequences of fetal growth restriction: biology, clinical implications, and opportunities for prevention of adult disease. Am J Obstet Gynecol. 2018 Feb;218(2S):S869-S879

[4] Francis JH, Permezel M, Davey MA. Perinatal mortality by birthweight centile. Aust N Z J Obstet Gynecol 2014; 54: 354–359.

[5] Risnes KR, Vatten LJ, Baker JL, Jameson K, Sovio U, et al. (2011) Birthweight and mortality in adulthood: a systematic review and meta-analysis. Int J Epidemiol 40: 647–661.

[6] Barker, David J.P., Osmond, Clive, Forsen, Tom J., Kajantie, Eero and Eriksson, Johan G. (2005) Trajectories of growth among children who have coronary events as adults. New England Journal of Medicine, 353 (17), 1802-1809. (doi:10.1056/NEJMoa044160).

[7] Nohuz E, Rivière O, Coste K, Vendittelli F. Prenatal identification of small-for-gestational-age and risk of neonatal morbidity and stillbirth. Ultrasound Obstet Gynecol 2020; 55: 621–628.

[8] Soothill PW, Bobrow CS, Holmes R. Small for gestational age is not a diagnosis. Ultrasound Obstet Gynecol. 1999 Apr;13(4):225-8.

[9] McCowan LM, Figueras F, Anderson NH. Evidence-based national guidelines for the management of suspected fetal growth restriction: comparison, consensus, and controversy. Am J Obstet Gynecol. 2018 Feb;218(2S):S855-S868.

[10] Sovio U, White IR, Dacey A, Pasupathy D, Smith GCS. Screening for fetal growth restriction with universal third trimester ultrasonography in nulliparous women in the Pregnancy Outcome Prediction (POP) study: a prospective cohort study. Lancet 2015; 386: 2089–2097.

[11] Illa M, Coloma JL, Eixarch E, Meler E, Iraola A, Gardosi J, Gratacós E, Figueras F. Growth deficit in term small-for-gestational fetuses with normal umbilical artery Doppler is associated with adverse outcome.
J Perinat Med. 2009;37(1):48-52.

[12] Villar J, Altman D, Purwar M, Noble J, Knight H, Ruyan P, Cheikh Ismail L, Barros F, Lambert. A, Papageorghiou A, Carvalho M, Jaffer Y, Bertino E, Gravett M, Bhutta Z, Kennedy S, for the International Fetal and Newborn Growth Consortium for the 21st Century (INTERGROWTH-21st). The objectives, design and implementation of the INTERGROWTH-21st Project. BJOG 2013; 120. (Suppl. 2): 9–26.

[13] Napolitano R, Dhami J, Ohuma EO, Ioannou C, Conde-Agudelo A, Kennedy SH, Villar J, Papageorghiou AT. Pregnancy dating by fetal crown-rump length: systematic review. of charts. BJOG. 2014 Apr;121(5):556-65. doi: 10.1111/1471-0528.12478. Epub 2014 Jan 6.

[14] Figueras F, Meler E, Iraola A, Eixarch E, Coll O, Figueras J, Francis A, Gratacos E, Gardosi J. Customized birthweight standards for a Spanish population. Eur J Obstet Gynecol Reprod Biol 2008; 136: 20–24.

[15] Villar J, Papageorghiou AT, Knight HE, Gravett MG, Iams J, Waller SA, Kramer M, Culhane JF, Barros FC, Conde-Agudelo A, Bhutta ZA, Goldenberg RL. The preterm birth syndrome: a prototype phenotypic classification. Am J Obstet Gynecol. 2012 Feb;206(2):119-23. doi: 10.1016/j.ajog.2011.10.866. Epub 2011 Oct 25.

[16] Barros FC, Papageorghiou AT, Victora CG, Noble JA, Pang R, Iams J, Cheikh Ismail L, Goldenberg RL, Lambert A, Kramer MS, Carvalho M, Conde-Agudelo A, Jaffer YA, Bertino E, Gravett MG, Altman DG, Ohuma EO, Purwar M, Frederick IO, Bhutta ZA, Kennedy SH, Villar J; International Fetal and Newborn Growth Consortium for the 21st Century. The distribution of clinical phenotypes of preterm birth syndrome: implications for prevention. JAMA Pediatr. 2015 Mar;169(3):220-9.

[17] Kent P, Jensen RK, Kongsted A. A comparison of three clustering methods for finding subgroups in MRI, SMS or clinical data: SPSS TwoStep Cluster analysis, Latent Gold and SNOB. BMC Med Res Methodol. 2014;14:113.

[18] Alfirevic Z, Stampalija T, Dowswell T.Fetal and umbilical Doppler ultrasound in high-risk pregnancies. Cochrane Database Syst Rev. 2017 Jun 13;6(6):CD007529

[19] Peguero A, Fernandez-Blanco L, Mazarico E, Benitez L, Gonzalez A, Youssef L, Crispi F, Hernandez S, Figueras F. Added prognostic value of longitudinal changes of angiogenic factors in early-onset severe pre-eclampsia: a prospective cohort study. BJOG. 2020 Jun 27. doi: 10.1111/1471-0528.16383. Online ahead of print

[20] Mendoza M, Hurtado I, Bonacina E, Garcia-Manau P, Serrano B, Tur H, Rodo C, Maiz N, Carreras E. Individual risk assessment for prenatal counseling in early-onset growth-restricted and small-for-gestational-age fetuses. Acta Obstet Gynecol Scand. 2020 Oct 23. doi: 10.1111/aogs.14032. Online ahead of print

[21] Herraiz I, Quezada MS, Rodriguez-Calvo J, Gómez-Montes E, Villalaín C, Galindo A. Longitudinal change of sFlt-1/PlGF ratio in a singleton pregnancy with early-onset fetal growth restriction. Ultrasound Obstet 471 Gynecol 2018 Nov;52(5):631-638. doi: 10.1002/uog.18894.

[22] Lees CC, Stampalija T, Baschat A, da Silva Costa F, Ferrazzi E, Figueras F, Hecher K, Kingdom J, Poon LC, Salomon LJ, Unterscheider J. ISUOG Practice Guidelines: diagnosis and management of small-for-gestational-age fetus and fetal growth restriction. Ultrasound Obstet Gynecol. 2020 Aug;56(2):298-312. doi: 10.1002/uog.22134.

[23] Meler E, Mazarico E, Eixarch E, Gonzalez A, Peguero A, Martinez J, Boada D, Vellvé K, Gomez-Roi MD, Gratacós E, Figueras F. Ten-year experience of protocol-based management of small-for-gestational-age fetuses: perinatal outcome in late-pregnancy cases diagnosed after 32 weeks. Ultrasound Obstet Gynecol. 2021 Jan;57(1):62-69. doi: 10.1002/uog.23537.

[24] Flores M, Glusman G, Brogaard K, Price ND, Hood L. P4 medicine: how systems medicine will transform the healthcare sector and societyPer Med. 2013;10(6):565-576. doi: 10.2217/pme.13.57.

[25] Gómez-Roig MD, Mazarico E, Cárdenas D, Fernandez MT, Díaz M, Ruiz de Gauna B, Vela A, Gratacós E, Figueras F. Placental 11B-Hydroxysteroid Dehydrogenase Type 2 mRNA Levels in Intrauterine Growth Restriction versus Small-for-Gestational-Age Fetuses. Fetal Diagn Ther. 2016;39(2):147-51.

[26] Paules C, Youssef L, Miranda J, Crovetto F, Estanyol JM, Fernandez G, Crispi F, Gratacós E. Maternal proteomic profiling reveals alterations in lipid metabolism in late-onset fetal growth restriction. Sci Rep. 2020 Dec 3;10(1):21033.

[27] Mazaki-Tovi S, Romero R, Kim SK, Vaisbuch E, Kusanovic JP, Erez O, Chaiworapongsa T, Gotsch F, Mittal P, Nhan-Chang CL, Than NG, Gomez R, Nien JK, Edwin SS, Pacora P, Yeo L, Hassan SS.J Could alterations in maternal plasma visfatin concentration participate in the phenotype definition of preeclampsia and SGA? Matern Fetal Neonatal Med. 2010 Aug;23(8):857-68.

[28] Whitehead CL, McNamara H, Walker SP, Alexiadis M, Fuller PJ, Vickers DK, Hannan NJ, Hastie R, Tuohey L, Kaitu'u-Lino TJ, Tong S. Identifying late-onset fetal growth restriction by measuring circulating placental RNA in the maternal blood at 28 weeks' gestation. Am J Obstet Gynecol. 2016 Apr;214(4):521.e1-521.e8. doi: 10.1016/j.ajog.2016.01.191.

[29] Miranda J, Romero R, Korzeniewski SJ, Schwartz AG, Chaemsaithong P, Stampalija T, Yeo L, Dong Z, Hassan SS, Chrousos GP, Gold P, Chaiworapongsa T. The anti-aging factor α-klotho during human pregnancy and its expression in pregnancies complicated by small-for-gestational-age neonates and/or preeclampsia. J Matern Fetal Neonatal Med. 2014 Mar;27(5):449-57. doi: 10.3109/14767058.2013.818652. Epub 2013 Aug 19.

[30] Kennedy SH, Victora CG, Craik R, Ash S, Barros FC, Barsosio HC, Berkley JA, Carvalho M, Fernandes M, Cheikh Ismail L, Lambert A, Lindgren CM, McGready R, Munim S, Nellåker C, Noble JA, Norris SA, Nosten F, Ohuma EO, Papageorghiou AT, Stein A, Stones W, Tshivuila-Matala COO, Staines Urias E, Vatish M, Wulff K, Zainab G, Zondervan KT, Uauy R, Bhutta ZA, Villar J. Deep clinical and biological phenotyping of the preterm birth and small for gestational age syndromes: The INTERBIO-21 (st) Newborn Case-Control Study protocol. Gates Open Res. 2019 Feb 5;2:49. doi: 10.12688/gatesopenres.12869.2. eCollection 2018.

[31] Villar J, Restrepo-Méndez MC, McGready R, Barros FC, Victora CG, Munim S, Papageorghiou AT, Ochieng R, Craik R, Barsosio HC, Berkley JA, Carvalho M, Fernandes M, Cheikh Ismail L, Lambert A, Norris SA, Ohuma EO, Stein A, Tshivuila-Matala COO, Zondervan KT, Winsey A, Nosten F, Uauy R, Bhutta ZA, Kennedy SH. Association Between Preterm-Birth Phenotypes and Differential Morbidity, Growth, and Neurodevelopment at Age 2 Years: Results From the INTERBIO-21st Newborn Study. JAMA Pediatr. 2021 Mar 1:e206087. doi: 10.1001/jamapediatrics.2020.6087. Online ahead of print

[32] McCowan LM, Figueras F, Anderson NH. Evidence-based national guidelines for the management of suspected fetal growth restriction: comparison, consensus, and controversy. Am J Obstet Gynecol. 2018 Feb;218(2S):S855-S868. doi: 10.1016/j.ajog.2017.12.004.

[33] Boers KE, Vijgen SM, Bijlenga D, van der Post JA, Bekedam DJ, Kwee A, van der Salm PC, van Pampus MG, Spaanderman ME, de Boer K, Duvekot JJ, Bremer HA, Hasaart TH, Delemarre FM, Bloemenkamp KW, van Meir CA, Willekes C, Wijnen EJ, Rijken M, le Cessie S, Roumen FJ,

Thornton JG, van Lith JM, Mol BW, Scherjon SA; DIGITAT study group. Induction versus expectant monitoring for intrauterine growth restriction at term: randomised equivalence trial (DIGITAT). BMJ. 2010 Dec 21;341:c7087. doi: 10.1136/bmj.c7087.

[34] ACOG Practice Bulletin No. 202: Gestational Hypertension and Preeclampsia.Obstet Gynecol. 2019 Jan;133(1):e1-e25. doi: 10.1097/AOG.0000000000003018.

[35] ACOG Practice Bulletin No. 190: Gestational Diabetes Mellitus. Obstet Gynecol. 2018 Feb;131(2):e49-e64. doi: 10.1097/AOG.0000000000002501.

[36] Valenzuela-Alcaraz B, Crispi F, Manau D, Cruz-Lemini M, Borras A, Balasch J, Gratacós E. Differential effect of mode of conception and infertility treatment on fetal growth and prematurity. Matern Fetal Neonatal Med. 2016 Dec;29(23):3879-84. doi: 10.3109/14767058.2016.1151868. Epub 2016 Mar 3.

[37] Bhide A, Acharya G, Bilardo CM, Brezinka C, Cafici D, Hernandez-Andrade E, et al. ISUOG practice guidelines: use of Doppler ultrasonography in obstetrics. Ultrasound Obstet Gynecol [Internet]. 2013 Feb [cited 2019 Aug 3];41(2):233–9. Available from: http://www.ncbi.nlm.nih.gov/pubmed/23371348

*Table 1: Definitions of Maternal, Fetal, and Placental Conditions*

| Condition | Description |
|---|---|
| ***Maternal*** | |
| Hypertension disorders[34] | Blood pressure > 140/90 mmHg<br>Including<br>➢ Pregnancy-induced hypertension<br>➢ Chronic hypertension prior to pregnancy<br>➢ Preeclampsia<br>➢ Eclampsia<br>➢ HELLP syndrome |
| Chronic maternal diseases | Autoimmune diseases, maternal chronic diseases, diabetes mellitus or chronic infections (e.g., human immunodeficiency virus, hepatitis B virus). |
| Gestational diabetes[35] | Oral glucose tolerance test with two elevated values, with or without insulin (normal values: 105, 190, 165, and 145 mg/dL at baseline) |
| Assisted reproductive techniques[36] | Artificial insemination, in vitro fertilization, with or without egg donation |
| ***Fetal*** | |
| Congenital anomalies | Chromosomal anomalies, morphologic alterations, or intrauterine infections. |
| Intrauterine growth restriction[16] | Birthweight < 3$^{rd}$ percentile<br>Birthweight < 10$^{th}$ percentile and Doppler alterations (PI UA > 95$^{th}$ percentile, PI MCA < 5$^{th}$ percentile, CPR < 5$^{th}$ percentile, or mean PI UtA > 95$^{th}$ percentile) [37]. |
| Preterm birth | Spontaneous delivery before 37 weeks gestation |
| ***Placental*** | |
| Second- or third-trimester bleeding | Previous placenta, placental accreta, or abruptio placenta |

*CPR, cerebroplacental ratio; MCA, middle cerebral artery; PI, pulsatility index; UA, umbilical artery; UtA, uterine artery.*

411 *Table 2. Sociodemographic characteristics and perinatal outcomes among small for gestational*

412 *age and appropriate for gestational age cohorts*

| Characteristics and Outcomes | Appropriate for gestational age fetuses (n=16,357) | Small for gestational age fetuses (n=1274) | *P value* |
|---|---|---|---|
| **Maternal age, y (SD)** | 31.7 (5.7) | 31.5 (5.9) | *0.244* |
| **Maternal BMI, kg/m$^2$ (SD)** | 25.0 (4.8) | 24.0 (4.6) | *<0.001* |
| **Caucasian ethnicity (%)** | 15,634 (95.6) | 1222 (95.9) | *0.570* |
| **Smoker (%)** | 2162 (13.6) | 335 (27.1) | *<0.001* |
| **Nulliparity (%)** | 8252 (50.4) | 827 (64.9) | *<0.001* |
| **Previous caesarean section (%)** | 286 (1.7) | 17 (1.3) | *0.273* |
| **Assisted reproduction technique (%)** | 575 (3.5) | 56 (4.4) | *0.103* |
| **Gestational age at delivery, d (SD)** | 276.8 (16.3) | 270.4 (21.1) | *<0.001* |
| **Preterm birth (%)** | 1027 (6.3) | 182 (14.3) | *<0.001* |
| **Hypertension/preeclampsia (%)** | 283 (1.7) | 66 (5.2) | *<0.001* |
| **Gestational diabetes (%)** | 422 (2.6) | 21 (1.6) | *0.041* |
| **Female fetus (%)** | 8493 (52) | 639 (50.2) | *0.226* |
| **Fetal anomalies (%)** | 149 (0.9) | 13 (1.0) | *0.693* |
| **Elective delivery (%)*** | 5655 (34.6) | 623 (49.3) | *<0.001* |
| **Instrumental delivery (%)** | 2894(17.7) | 192(15.1) | *<0.001* |
| **Caesarean section** | 3649 (22.3) | 387 (30.4) | *<0.001* |
| **Caesarean section for fetal acidosis$^+$ (%)** | 679 (4.2) | 154 (12.1) | *<0.001* |
| **5-min Apgar score < 7 (%)** | 168 (1.0) | 46 (3.7) | *<0.001* |
| **NICU admission (%)** | 1011 (6.2) | 246 (19.3) | *<0.001* |
| **Stillbirth (%)** | 63 (0.4) | 15 (1.2) | *<0.001* |
| **Perinatal mortality (%)** | 68 (0.4) | 18 (1.4) | *<0.001* |
| **Perinatal mortality rate (%)** | 4.16 | 14.13 | |

413 **Labour induction or elective caesarean section*

414 *+ Umbilical artery pH < 7.10*

415 *BMI, body mass index; NICU, neonatal intensive care unit; SD, standard deviation.*

416

*Table 3. Distribution of nine clinical phenotypes of small for gestational age neonates according to main individual maternal, fetal, or placental conditions*

| Cluster | Main condition | Number (%) |
|---|---|---|
| 1 | None | 689 (54.1) |
| 2 | Intrauterine growth restriction | 423 (33.2) |
| 3 | Preterm birth | 31 (2.4) |
| 4 | Hypertension/preeclampsia | 27 (2.1) |
| 5 | Assisted reproduction techniques | 28 (2.2) |
| 6 | Chronic maternal diseases | 26 (2) |
| 7 | Gestational diabetes | 26 (2) |
| 8 | Congenital anomalies | 12 (0.9) |
| 9 | Third trimester bleeding | 12 (0.9) |

*Table 4. Perinatal outcomes for each small for gestational age clinical phenotype compared with appropriate for gestational age foetuses, adjusted for gestational age.*

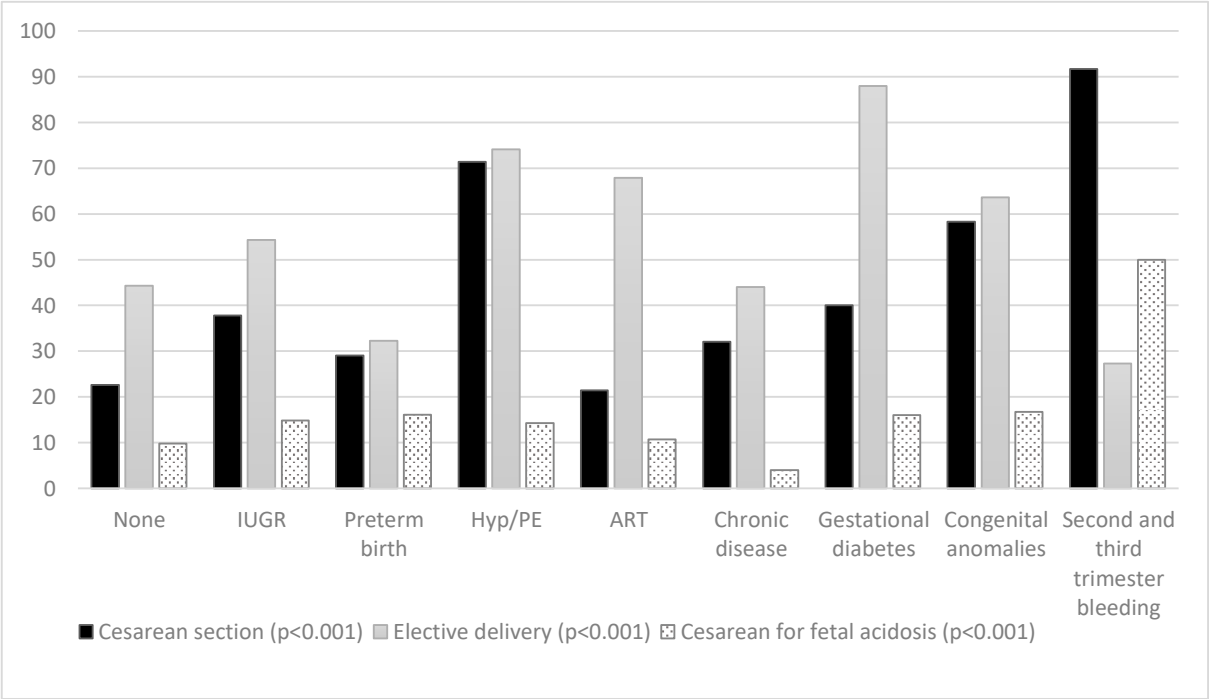
| Outcomes | None, OR (95% CI) | Intrauterine growth restriction, OR (95% CI) | Preterm birth, OR (95% CI) | Hypertension/ preeclampsia, OR (95% CI) | Assisted reproduction techniques, OR (95% CI) | Maternal chronic pathologies, OR (95% CI) | Gestational diabetes, OR (95% CI) | Congenital anomalies, OR (95% CI) | Second- or third-trimester haemorrhage, OR (95% CI) |
|---|---|---|---|---|---|---|---|---|---|
| **Caesarean section** | 1.05 (0.87-1.26) | 1.65 (1.34-2.03) | 0.78 (0.35-1.73) | 5.20 (2.24-12.07) | 1.00 (0.403-2.467) | 1.62 (0.71-3.68) | 2.39 (1.086-5.249) | 3.56 (1.11-11.37) | 19.59 (2.47-155.50) |
| **Caesarean section for fetal acidosis** | 2.52 (1.93-3.28) | 3.71 (2.79-4.92) | 3.68 (1.40-9.69) | 3.42 (1.17-9.98) | 2.80 (0.84-9.31) | 0.88 (0.119-6.52) | 4.08 (1.40-11.90) | 4.15 (0.91-19.01) | 17.98 (5.71-56.60) |
| **Elective delivery** | 1.50 (1.28-1.75) | 2.21 (1.82-2.70) | 0.87 (0.41-1.85) | 6.11 (2.45-15.26) | 4.00 (1.807-8.838) | 1.37 (0.63-2.99) | 14.40 (4.32-48.97) | 3.24 (0.95-11.08) | 0.68 (0.18-2.55) |
| **5-min Apgar score < 7** | 1.35 (0.66-2.76) | 3.53 (2.21-5.64) | 5.25 (1.67-16.51) | 5.13 (1.43-18.35) | NA | NA | NA | 14.05 (2.91-67.85) | 5.38 (1.03-28.04) |
| **NICU admission** | 1.00 (0.71-1.43) | 5.32 (4.18-6.78) | 4.08 (1.91-8.72) | 7.31 (3.12-17.17) | 1.48 (0.34-6.33) | 2.47 (0.80-7.65) | 2.33 (0.71-7.63) | 10.65 (3.07-36.97) | 5.19 (1.14-23.72) |
| **Stillbirth** | 0.43 (0.06-3.14) | 6.02 (3.19-11.35) | NA | NA | NA | NA | NA | 18.71 (2.36-148.29) | 11.16 (1.39-89.70) |
| **Perinatal mortality** | 0.41 (0.06-2.94) | 5.93 (3.21-10.95) | 4.65 (0.62-35.01) | NA | NA | NA | 9.59 (1.27-72.57) | 17.17 (2.17-136.12) | 9.94 (1.23-80.02) |

*CI, confidence interval; NA, not applicable; NICU, neonatal intensive care unit; OR, odds ratio.*

433 *Figure 1. Delivery characteristics according to small for gestational age clinical phenotypes*

434 *(n=1274).*

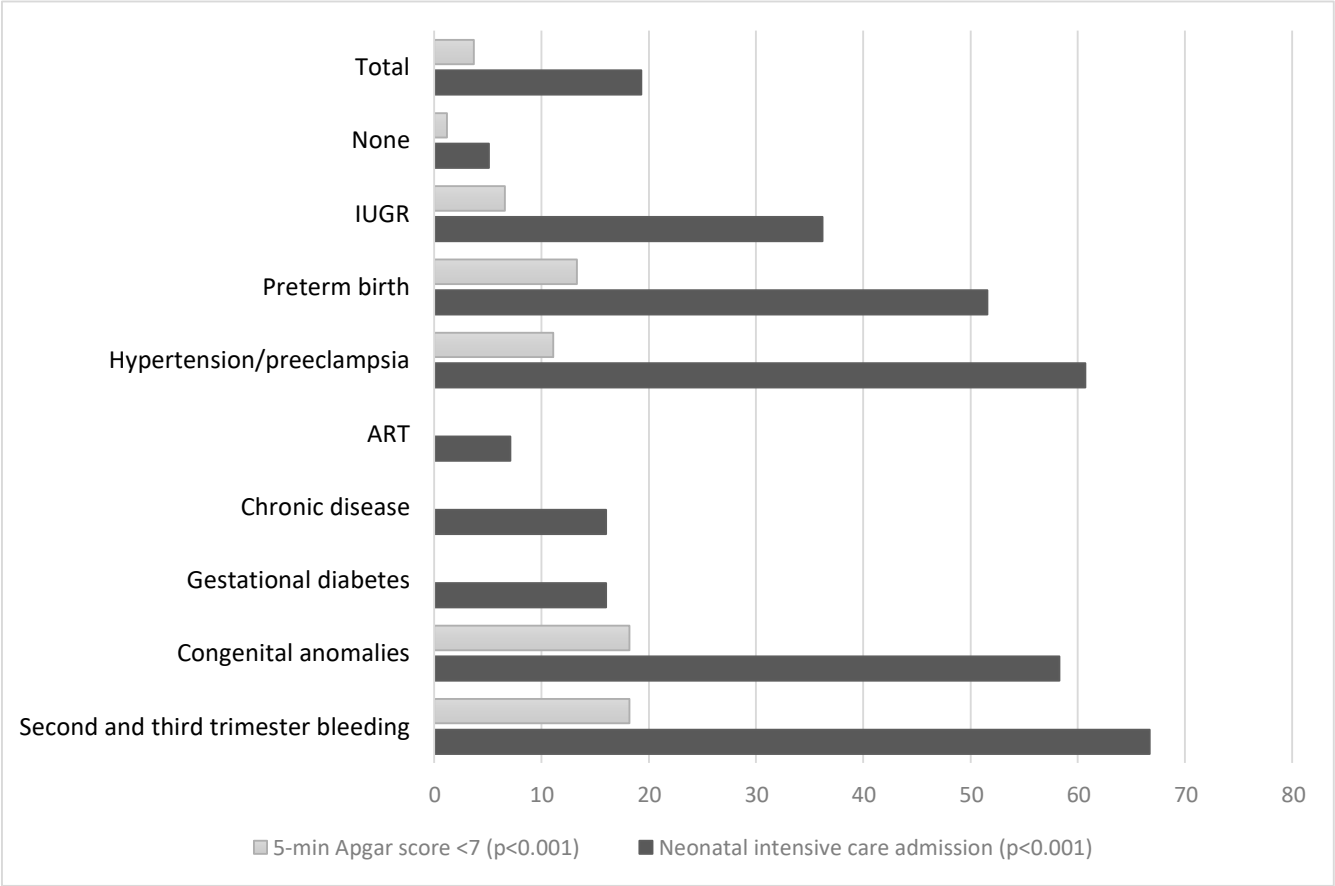
435




436 *ART, assisted reproduction techniques; Hyp/PE: Hypertension/preeclampsia; IUGR, intrauterine*
437 *growth restriction.*

438

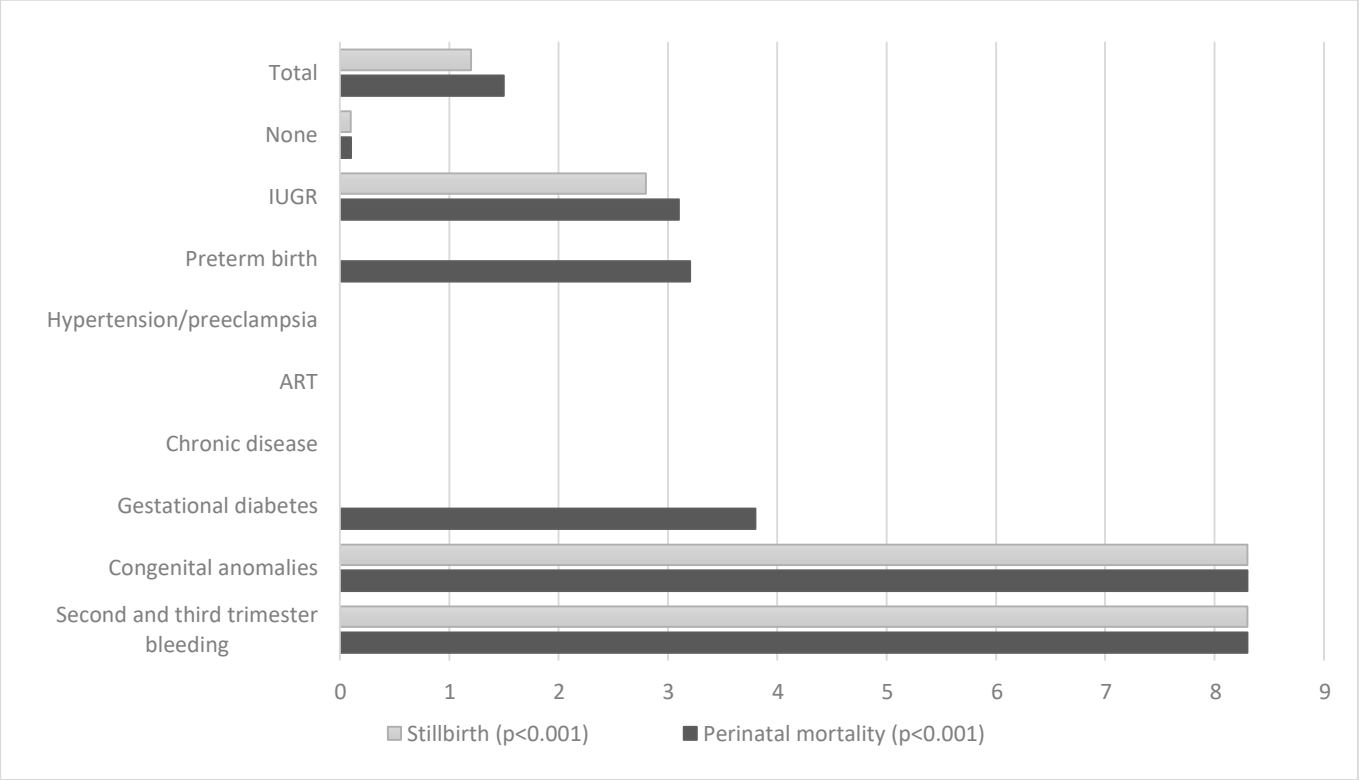
*Figure 2. Neonatal intensive care unit admission and 5-min Apgar score < 7 according to small for gestational age clinical phenotypes (n=1274).*




*ART, assisted reproduction techniques; IUGR, intrauterine growth restriction.*

443 *Figure 3. Stillbirth and perinatal mortality rates according to small for gestational age clinical*

444 *phenotypes (n=1274).*




445 *ART, assisted reproduction techniques; IUGR, intrauterine growth restriction.*

446

*Supplementary Table 1. Perinatal mortality of each step 1 cluster.*

*Some cases are included in more than one cluster.*

| Clinical cluster | Perinatal mortality, number (%) |
|---|---|
| Preterm | 18 (9.9) |
| Second- or third-trimester bleeding | 1 (8.3) |
| Congenital anomalies | 1 (7.7) |
| Gestational diabetes | 1 (4) |
| IUGR | 16 (3.6) |
| Chronic maternal diseases | 1 (2.4) |
| Hypertension/preeclampsia | 1 (1.5) |
| None | 1 (0.1) |
| Assisted reproductive techniques | 0 |

*IUGR, intrauterine growth restriction.*

*Supplementary Table 2: Perinatal outcomes of small for gestational age fetuses according to clinical phenotype*

| Outcome | Total, n (%) | None, n (%) | Intrauterine growth restriction, n (%) | Preterm birth, n (%) | Hypertension/ preeclampsia, n (%) | Assisted reproduction techniques, n (%) | Maternal chronic pathologies, n (%) | Gestational diabetes, n (%) | Congenital anomalies, n (%) | Second- or third-trimester haemorrhage, n (%) | P value |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Caesarean section** | 387 (30.4) | 156 (22.6) | 160 (37.8) | 9 (29) | 20 (71.4) | 6 (21.4) | 9 (34.6) | 11 (42.3) | 7 (58.3) | 11 (91.7) | <0.001 |
| **Caesarean section for fetal acidosis** | 154 (12.1) | 67 (9.8) | 62 (14.8) | 5 (16.1) | 4 (14.3) | 3 (10.7) | 1 (3.8) | 4 (15.4) | 2 (16.7) | 6 (50) | <0.001 |
| **Elective delivery** | 623 (48.9) | 305 (44.3) | 226 (54.3) | 10 (32.2) | 20 (74.1) | 19 (67.9) | 11 (42.3) | 23 (88.5) | 7 (63.7) | 3 (27.3) | <0.001 |
| **5-min Apgar score < 7** | 46 (3.6) | 8 (1.2) | 27 (6.6) | 4 (13.3) | 3 (11.1) | 0 | 0 | 0 | 2 (18.2) | 2 (18.2) | <0.001 |
| **NICU admission** | 246 (19.3) | 35 (5.1) | 153 (36.2) | 16 (51.6) | 17 (60.7) | 2 (7.1) | 5 (19.2) | 4 (15.4) | 7 (58.3) | 8 (66.7) | <0.001 |
| **Stillbirth** | 15 (1.2) | 1 (0.1) | 12 (2.8) | 0 | 0 | 0 | 0 | 0 | 1 (8.3) | 1 (8.3) | <0.001 |
| **Perinatal mortality** | 18 (1.4) | 1 (0.1) | 13 (3.1) | 1 (3.2) | 0 | 0 | 0 | 1 (3.8) | 1 (8.3) | 1 (8.3) | <0.001 |

*NICU, neonatal intensive care unit*

*Supplementary Table 3. Perinatal outcomes of each small for gestational age clinical phenotype compared with appropriate for gestational age fetuses with the same clinical condition, adjusted for gestational age.*

| Outcome | None, OR (95% CI) | Preterm birth, OR (95% CI) | Hypertension/ preeclampsia, OR (95% CI) | Assisted reproduction techniques, OR (95% CI) | Maternal chronic pathologies, OR (95% CI) | Gestational diabetes, OR (95% CI) | Congenital anomalies, OR (95% CI) | Second- or third-trimester haemorrhage, OR (95% CI) |
|---|---|---|---|---|---|---|---|---|
| **Caesarean section** | 1.18 (0.98-1.42) | 1.02 (0.46-2.26) | 1.27 (0.49-3.33) | 0.55 (0.22-1.38) | 1.11 (0.47-2.59) | 1.29 (0.58-3.00) | 1.90 (0.55-6.50) | 1.54 (0.18-13.09) |
| **Caesarean section for fetal acidosis** | 2.98 (2.28-3.90) | 4.12 (1.49-11.42) | 1.02 (0.31-3.40) | 2.30 (0.64-8.30) | 0.53 (0.07-4.03) | 2.71 (0.87-8.48) | 3.96 (0.69-22.65) | 1.93 (0.52-7.09) |
| **Elective delivery** | 1.81 (1.55-2.11) | 0.99 (0.46-2.15) | 0.67 (0.24-1.90) | 2.26 (1.00-5.11) | 0.71 (0.33-1.52) | 2.27 (0.66-7.74) | 1.86 (0.52-6.68) | 0.57 (0.12-2.60) |
| **5-min Apgar score < 7** | 2.16 (1.32-4.50) | 2.40 (0.80-7.20) | 0.58 (0.11-3.15) | NA | NA | NA | 7.43 (0.78-71.08) | 0.40 (0.06-2.81) |
| **NICU admission** | 1.49 (1.04-2.12) | 1.94 (0.94-3.99) | 1.71 (0.54-5.39) | 2.51 (0.51-12.26) | 1.45 (0.38-5.48) | 2.41 (0.78-7.47) | 1.24 (0.35-4.39) | 2.43 (0.57-10.50) |
| **Stillbirth** | 0.84 (0.11-6.30) | NA | NA | NA | NA | NA | 3.70 (0.33-41.30) | 0.67 (0.07-6.47) |
| **Perinatal mortality** | 0.84 (0.11-6.30) | 0.89 (0.12-6.77) | NA | NA | NA | 24.40 (1.31-453.91) | 3.70 (0.33-41.30) | 0.67 (0.07-6.47) |

*CI, confidence interval; NA, not applicable; NICU, neonatal intensive care unit; OR, odds ratio*