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Small for gestational age in mild and moderate preterm delivery at Split University Hospital Centre: effect of delivery mode on neonatal outcome a three year retrospective study

Hipotrofična novorođenčad iz umjerenih i blago nedonošenih trudnoća u Kliničkom bolničkom centru Split: učinak načina porođaja na neonatalni ishod – retrospektivna trogodišnja studija

Luka Vulić, Marko Vulić*

Summary

In the present study, we aim to assess whether there is a difference in cesarean delivery incidence in moderate and mild preterm birth.

This retrospective study included singleton pregnancies with moderate and mild preterm birth in the period from January 1, 2015 to December 31, 2017. The following variables were investigated: maternal age (years), parity, week of pregnancy (≤32-33$^{+6/7}$ and 34-36$^{+6/7}$), and mode of delivery (vaginal and cesarean section), birth weight (grams) and 5 min Apgar score (≤7, 8-10). Five hundred and eighty six women had preterm delivery in that period and 521 met inclusion criteria. Sixty-nine were born from 32-33$^{+6/7}$ and 452 from 34-36$^{+6/7}$ weeks of pregnancy. There was not a statistically significant difference in the age and parity between groups (p=0.6406). There was a statistically significant difference in delivery mode (χ^2=21.5634; p<0.001), the rate of small for gestational age (SGA) neonates (χ^2=22.6002; p<0.001) and Apgar score (χ^2=77.8317; p<0.01) between the study groups.

Statistical analysis revealed the difference in APGAR score according to delivery mode between moderate and mild SGA newborns (χ^2=16.2398; p<0.0001).

We found a difference in incidence of cesarean delivery according to the relation of newborn weight with gestational age between the investigated groups. (χ^2=43.8247; p<0.0001).

We found a correlation of APGAR score and mode of delivery in mild (χ^2=24.3262; p<0.0004) but not in moderate (χ^2=5.8245; p<0.4413) newborns.

There was a statistical difference in APGAR score according to mode of delivery in mild and moderate SGA newborns (χ^2=16.2398; p<0.001).

In conclusion, we found that the delivery mode has no impact on perinatal outcome according to APGAR score in the 5th minute. There is increased incidence of SGA and cesarean delivery in moderate preterm group. There is a difference in APGAR score in 5th minute between mild and moderate preterm infants. In subgroup of SGA newborns, delivery mode has an impact on APGAR score in the 5th minute. Increased incidence of SGA babies in moderate preterm birth group could be an indicator of hostile intrauterine environment and preterm birth could be seen as a protective mechanism.

Key words: perinatal outcome, preterm birth, SGA

Sažetak

Cilj rada je bio ustanoviti ima li razlike u učestalosti carskoga reza u jednoplodnih trudnoća iz umjerene i blage nedonošenosti.

Retrospektivna studija obuhvatila je razdoblje od 1. siječnja 2015. do 31. prosinca 2017. Istraživane su sljedeće varijable: majčinska dob (godine), paritet, trajanje trudnoće (navršeni tjedni trudnoće; umjerena nedonošenost (32-33$^{+6/7}$), te blaga nedonošenost (34-36$^{+6/7}$)), način porođaja (vaginalno i carski rez),

* **Health Centre Split, Croatia** (Luka Vulić, MD), **Split University Hospital Centre, Department of gynecologic and obstetrics** (prof. Marko Vulić, MD, PhD), **University of Split, School of medicine** (prof. Marko Vulić, MD, PhD)

Correspondence address / *Adresa za dopisivanje:* Prof. Marko Vulić, MD, PhD, Department of gynecology and obstetrics, Split University Hospital Centre, School of medicine, University of Split, Spinčićeva 1, HR- 21000 Split, Croatia
E-mail: marko.vulic1@st.t-com.hr

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porođajna masa (grami), trofičnost (hipo, eu i hipertrofično), te APGAR zbroj u petoj minuti nakon porođaja (≤7, 8-10).

586 žena rodilo je umjereno i blago nednonošenu djecu, a 521 je ispunilo kriterije uključenja u studiju. 69 djece rodilo se između 32-33$^{+6/7}$ (umjerena nedonošenost), a 452 između 34-36$^{+6/7}$ (blaga nedonošenost) navršenih tjedana trudnoće. Nije bilo statistički značajne razlike u dobi i paritetu majki između istraživanih skupina. Pronašli smo statistički značajnu razliku u učestalosti hipotrofične djece (χ^2=22.6002; p<0.001), Apgar zbroju (χ^2=77.8317; p<0.001) i načinu porođaja (χ^2=21.5634; p<0.001) i između promatranih skupina. Našli smo razliku i u učestalosti načina dovršetka porođaja između umjerene i blage nednonošenosti s obzirom na trofičnost novorođenčadi (χ^2=43,8247; p<0.0001). Pronašli smo razliku u Apgar zbroju blago nedonošene novorođenčadi u odnosu na način porođaja, te trofičnost djece (χ^2=24,3262; p<0,0004), ali ne i u skupini umjerene nedonošene novorođenčadi (χ^2=5,8245; p<0,4413). U podskupini hipotrofične djece pronašli smo razliku u Apgar zbroju između umjereno i blago nedonošene novorođenčadi s obzirom na način porođaja (χ^2=16,2398; p<0.001).

U zaključku smo pokazali da način dovršetka trudnoće nema utjecaja na perinatalni ishod blage i umjereno nedonošene djece mjeren zbrojem po Apgarovoj u petoj minuti. U našem istraživanju smo dokazali da postoji razlika u stopi carskog reza, zbroja po Apgarovoj, kao i učestalosti rađanja hipotrofične djece između umjerenih i blago nedonošenih trudnoća. Postoji razlika između učestalosti dovršetka trudnoće carskim rezom između promatranih skupina s obzirom na trofičnost djece. U skupini blago nedonošene djece, način dovršetka trudnoće ima utjecaja na zbroj po Apgarovoj novorođenčadi. U podskupini hipotrofične djece način porođaja povezan je sa zbrojem po Apgarovoj. Veća učestalost hipotrofične djece u umjerenoj, u usporedbi s blagom nednonošenosti, mogla bi biti pokazatelj nepovoljnog unutarmaterničnog okružja, te posljedično prijevremenom porođaju koji bi se mogao promatrati kao zaštitni mehanizam.

Ključne riječi: prijevremeni porođaj, perinatalni ishod, hipotrofično dijete

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Introduction

Fetal growth restriction (FGR) refers to fetuses not attaining a biologically determined growth potential.[1] To date, the most widely used correlate of FGR has been an estimated fetal weight <10th percentile for gestational age (GA), otherwise known as small for GA (SGA).[2-3]

Preterm birth (PTB) is a significant and growing public health problem leading to increased neonatal morbidity and mortality and entailing substantial social and economic costs. In 2004, the rate of PTB was 12.5% of live births in the USA and 8.2% in Canada.[4]

Some discrepancies in preterm birth terminology remain, but there is now a greater consistency within the published literature. Mild preterm birth has been accepted as birth between 34^{+0} and 36^{+6} weeks gestation. Although there has been no such consensus for a classification of birth between 32^{+0} and 33^{+6} weeks, 'moderately preterm' is now commonly used. Birth at 28–31 weeks gestation is defined as very preterm and accounts for less than 1% of all deliveries and about 10% of preterm births. Immediate survival is expected with a significant proportion of short to long-term morbidity. Below 28 weeks is regarded as extremely preterm (less than 5% of all preterm births) where early neonatal mortality is high with up to 50% of severe handicaps occurring among survivors born below 26 weeks.[5]

Late (or mild) and moderately preterm (LMPT) births account for approximately 6–7% of UK births and 75% of all preterm births and 84% are due to mild and moderate (32–33 weeks) preterm combined.[6] Outcomes of those infants born late (34–36^{+6} weeks of gestation) or moderately (32–33^{+6} weeks of gestation) preterm remain less frequently characterized than outcomes for births at earlier gestations, despite the fact of an encountered majority of preterm births. Increased attention has recently been given to a better understanding of the reasons for the high rate of mild and moderate preterm birth, its causes, short and long-term sequelae, and opportunities for prevention. Published data suggest that LMPT infants are at increased risk of adverse growth, neuropsychological, educational, and behavioral outcomes.[7] A pregnancy resulting in a preterm birth (PTB) and concomitant small for gestational age birth weight (SGA) – 'PTB–SGA' - is thought to be most pathological, in terms of both being due to placental dysfunction and their adverse sequelae for the newborn infant.[8-10] Preterm and SGA births are both well documented to increase the risk of morbidity and mortality, and newborns who are both preterm and SGA have the highest risk.[11]

Relative to infants born either PTB alone or SGA alone, those affected by PTB–SGA are 15 times more likely to die in the first month of life.[10]

In this study we sought to find out if there is a difference in SGA incidence in moderate and mild preterm birth and whether the mode of delivery has an impact on perinatal outcome.

Materials and methods

We conducted a retrospective study that included singleton pregnancies with mild and moderate preterm birth in the period from January 1, 2015 to December 31, 2016. The following variables were investigated: maternal age (years), parity, body mass index (BMI, kg/m^2), week ($\leq 36^{+6/7}$ and $\geq$ 37) and mode (vaginal and cesarean section) of delivery, birth weight (grams) and Apgar score in 5th minute ($\leq$7, 8-10). Multiple pregnancies, stillbirths, aneuploidy and pregnancies with congenital anomaly were excluded from the study. Small for gestational age (SGA) babies were calculated from the tables of birth weights for singletons which were adjusted for local specificity.[12] The gestational age at birth was calculated by the first day of the last menstrual period, adding 14 days to the day of ovum pick-up as the week of amenorrhea for the in vitro fertilization (IVF) group and by adding 14 days to the presumed day of ovulation for the ovulation induction group. Statistical analysis was performed with Statistica SPSS version 14.0 (SPSS, Chicago, IL, USA) using Student's t-test and χ^2-test. The values of $p<0.05$ were considered statistically significant.

Results

During the three-year period, 586 women had preterm delivery and 521 met inclusion criteria. Sixty-nine singletons were born from 32-$33^{+6/7}$ and 452 from 34-$36^{+6/7}$ weeks of pregnancy. The mean age of women with moderate preterm birth was 31.8 ± 4.1 years, whereas in the mild preterm birth group it was 30.9 ± 4.6 years. The difference in the mean age was not statistically significant. In the moderate preterm group, there were 36 primiparas and 33 multiparas whereas in the mild preterm group there were 259 primiparas and 193 multiparas. There was not a statistically significant difference in the parity between groups (χ^2=0.6406; p=0.4235).

Table 1 Demographic data and perinatal outcome of women and newborns who gave moderate and mild preterm birth.
Tablica 1. Demografski podaci i perinatalni ishod žena i novorođenčadi za umjereno i blago prijevremeno rođenje.

	Moderate preterm birth, N=69 (%) *Umjereno prijevremeni porod*	Mild preterm birth, N=452 (%) *Blago prijevremeni porod*	p value *p vrijednost*
Age (yrs)/*starost*	31.8±4.1	30.9±4.6	NS*
Primiparae *Prvorotka*	36 (52.17)	259 (57.3)	**p=0.6406
Multiparae *Višerotka*	33 (47.83)	193 (42.7)	χ^2=0.4235
Mean birth weight (grams) *Prosječna težina pri porodu*	1824±399	2692±451	*p<0.001
Mean birth length (cm) *Prosječna dužina pri porodu*	41,6±3,3	47,6±3,6	*p<0.001
Cesarean section *Carski rez*	42 (60.86)	145 (32.07)	**p<0.001
Vaginal delivery *Vaginalni porod*	27 (39.14)	307 (67.93)	χ^2=21.5634
SGA	21 (30.43)	46 (10.17)	**p<0.001
AGA	44 (63,77)	385 (85.19)	χ^2=22.6002
LGA	4 (5.8)	21 (4.64)	
Apgar score/*rezultat* ≤7	32 (46.37)	36 (7.96)	** p<0.001
Apgar score/*rezultat* 8-10	37 (53.63)	416 (92.04)	χ^2=77.3817

*Student's t-test; **χ^2-test; SGA = small for gestational age; AGA = appropriate for gestational age; LGA = large for gestational age / **Studentov t-test; **χ^2-test; SGA = malo za gestacijsku dob; AGA = prikladno za gestacijsku dob; LGA = veliko za gestacijsku dob*

Table 2 Mode of delivery in moderate and mild preterm birth according to relation of newborn size and gestational age
Tablica 2. Način porođaja u umjerenom i blagom prijevremenom rođenju u skladu s veličinom novorođenčadi i gestacijskom dobi

	Moderate preterm birth, N=69 (%) *Umjereno prijevremeni porod*		Mild preterm birth, N=452 (%) *Blago prijevremeni porod*		*p value *p vrijednost*
	SC	VAG	SC	VAG	
SGA	16	5	27	19	p<0.0001
AGA	24	20	109	276	χ^2=43,8247
LGA	2	2	9	12	

*χ^2-test, SGA = small for gestational age; AGA = appropriate for gestational age; LGA = large for gestational age, SC = Cesarean Section, VAG = vaginal

**χ^2-test; SGA = malo za gestacijsku dob; AGA = prikladno za gestacijsku dob; LGA = veliko za gestacijsku dob, SC = carski rez, VAG = vaginalno*

Table 3 Correlation of Apgar score and mode of delivery in moderate preterm newborns according to relation of newborn size and gestational age
Tablica 3. Povezanost Apgarovog rezultata i umjereno prijevremenog porođaja u nedonoščadi u odnosu na veličinu novorođenčadi i gestacijsku dob

Moderate preterm birth, N = 69 (%) / *Umjereno prijevremeni porod*					
	SC		VAG		*p value / *p vrijednost*
Apgar score	≤7	8-10	≤7	8-10	
SGA	7	9	4	1	p<0.44132
AGA	8	16	11	7	χ^2=5,8245
LGA	1	1	1	2	

*χ^2-test, SGA = small for gestational age; AGA = appropriate for gestational age; LGA = large for gestational age, SC = Cesarean Section, VAG = vaginal / **χ^2-test; SGA = malo za gestacijsku dob; AGA = prikladno za gestacijsku dob; LGA = veliko za gestacijsku dob, SC = carski rez, VAG = vaginalno*

The mean birth weight and length in the moderate group were 1824±399 grams and 41.6±3,3 cm and in the mild preterm group were 2692±451grams and 47.6±3.6 cm. This difference was statistically significant (p<0.001). Cesarean section was performed in 42 women from the moderate preterm group women and in 145 women from the mild preterm group. Statistical analysis showed a difference in the mode of delivery rates (χ^2=21.5634; p<0.001). In the moderate preterm group, 21 out of 69 babies were SGA, while in the mild group 46 out of 521 infants were SGA. This difference was statistically significant (χ^2=22.6002; p<0.001). Apgar scores also yielded between-group differences (χ^2=77.8317; p<0.001). We found a difference in the delivery mode between moderate and mild preterm newborns according to the relation of newborn size and gestational age between the investigated groups (χ^2=43.8247; p<0.0001).

We did not find a statistical significant difference in Apgar score according to the mode of delivery and relation of fetal size to gestational age in moderate preterm newborns (χ^2=5.8245; p<0.4413), but we find it in mild preterm newborns (χ^2=24,3262; p<0,0004). Finally, when we compared the Apgar score of moderate and mild SGA newborns according to mode of delivery we found a difference (χ^2=16.2398; p=0.001).

Table 4 Correlation of Apgar score and mode of delivery in mild preterm newborns according to relation of newborn size and gestational age
Tablica 4. Povezanost Apgarovog rezultata i blago prijevremenog porođaja u nedonoščadi u odnosu na veličinu novorođenčadi i gestacijsku dob

	Mild preterm birth, N = 452 (%) / *Blago prijevremeni porod*				
	SC		VAG		*p value / *p vrijednost*
Apgar score / *Apgar rezultat*	≤7	8-10	≤7	8-10	
SGA	3	24	2	17	p<0.0004
AGA	25	84	8	268	χ^2=24,3262
LGA	2	7	1	11	

*χ^2-test, SGA = small for gestational age; AGA = appropriate for gestational age; LGA = large for gestational age, SC = Cesarean Section, VAG = vaginal / *χ^2-test; SGA = malo za gestacijsku dob; AGA = prikladno za gestacijsku dob; LGA = veliko za gestacijsku dob, SC = carski rez, VAG = vaginalno*

Table 5 Correlation of Apgar score and mode of delivery in mild and moderate preterm SGA newborns
Tablica 6. *Povezanost Apgarovog rezultata i načina porođaja kod umjereno i blago prijevremenog poroda SGA novorođenčadi*

	Moderate and mild preterm SGA newborns *Umjereni i blago prijevremeni porod SGA novorođenčadi*				
	SC		VAG		*p value / *p vrijednost*
Apgar score	≤7	8-10	≤7	8-10	
Moderate preterm *Umjereno prijevremeni porod*	7	9	4	1	p<0.001
Mild preterm *Blago prijevremeni porod*	3	24	2	17	χ^2=16.2398

SGA = small for gestational age, SC = Cesarean Section, VAG=vaginal / *SGA = malo za gestacijsku dob; SC = carski rez, VAG = vaginalno*

Discussion

Our study demonstrated that there is a difference in the incidence of SGA babies in moderate and mild preterm deliveries. It also shows that the delivery mode has no impact on perinatal outcome, and the difference in lower Apgar score in the 5th minute is primarily the consequence of pregnancy duration and increased incidence of SGA in the moderate preterm group. Unfortunately, the lack of reliable information from our medical documentation is a key factor that we cannot make any conclusion on the possible differences in the subgroups of preterm delivery (spontaneous, preterm premature rupture of membranes and iatrogenic).

Intrauterine growth restriction (IUGR) is one of the causes for mild preterm delivery, and it occurs more often in mild preterm infants than term ones. It constitutes a risk factor for morbidity and mortality.

Of all preterm neonates, approximately 13 to 20% are small-for-gestational age (SGA), with birth weight less than the 10th percentile.[13] Our study confirmed that, and the other fact that the incidence of SGA babies in moderate preterm birth is almost 2.5 times higher than in the mild preterm birth. While some SGA neonates result from non-pathologic constitutional growth, others result from intrauterine growth restriction due to placental insufficiency, maternal co-morbidities, or intrinsic fetal etiologies including aneuploidy and structural anomalies.[13]

Similar incidence of SGA in our studies confirms that our population has similar growth charts as those previously mentioned. But some **s**tudies have shown that, for instance, UK-born South Asians, for example, are 200–300 g lighter at birth compared with white British infants, and this fact may have implications on the assessment of health in these subgroups when using a population-derived birth weight chart, such as the

UK-WHO.[14-15] Therefore, our strong recommendation is that each department creates, calculates and uses birth weight charts specific for singletons and twins from local subpopulation.

There is still an ongoing debate among perinatologists on the optimal mode of delivery for preterm birth. Even the latest Cochrane review could not provide a clear answer to this issue. Alfirevic et al. in their study reported that there is no difference in the rates of neonatal asphyxia, respiratory distress syndrome, and the Apgar score at 5 min with respect to the delivery mode.[16] Concerning preterm birth between 23 and $36^{+6/7}$ gestational weeks, a study from the USA showed that after the cesarean section, there are no improved outcomes when infants were stratified by the mode of delivery, both in the presence or absence of antenatal corticosteroid administration between.[17] At gestational age from 31–33 weeks, the current data regarding the outcome of vaginally delivered and cesarean delivered SGA infants suggest no statistically significant differences. By contrast, at gestational ages of 34 weeks or more, mortality rates were reported to be significantly lower for SGA infants delivered vaginally.[18]

The Apgar score is a simple and effective method for assessing neonatal health in the immediate period after birth. It has been used worldwide to evaluate infants' condition immediately after birth, to determine their need for resuscitation, and to evaluate the effectiveness of resuscitation. The Apgar score was never intended for the prediction of outcome beyond the immediate postnatal period; however, since low scores correlate with prenatal and perinatal adversities, multiple studies have examined the relation between the value of Apgar score and duration of low Apgar score (≤7) and subsequent death or neurologic disability. A severely low Apgar score at 5 minutes is strongly associated with an increased risk of neonatal encephalopathy, subsequent cerebral palsy (CP) and learning difficulties, although a low score may be due to conditions other than brain injury or intrapartum events.

In conclusion, our data indicate that the cesarean section has no impact in mild moderate preterm SGA infants' perinatal outcome in terms of 5 min Apgar score.

With advances in the management of preterm neonates, the chances of survival have increased even among preterm and SGA born.

Infants who are SGA are considered at higher risk of physical and neurodevelopmental abnormalities, although the reported impacts of SGA status at birth on neurodevelopmental outcomes in long-term outcomes studies have varied.[19]

Preterm SGA infants are at increased risk of impairment in neuro-motoric, cognitive, behavioral and scholastic attainments compared with preterm non-SGA infants.[20]

The association between SGA/AGA and neurologic status on cognitive outcomes at each age was also examined. The comparison of SGA and AGA infants of similar gestational ages have shown that SGA had significantly poorer cognitive scores at each age. Normal neurologic status was more likely at all assessments for the AGA than for SGA infants of comparable gestational age. There were no differences between SGA and AGA children in cognitive or neurologic outcomes at any age when grouped by birth weight. Cognitive impairment was closely associated with neurologic abnormality in both SGA and AGA groups. There was, nevertheless, a significant effect of SGA on cognitive outcome independent of the neurologic status at all ages except 3 years. Irrespective of the degree of prematurity, SGA infants are at greater risk for neurodevelopmental impairment than are equally premature AGA infants. The cognitive impairment can be largely, but not entirely, attributed to a higher incidence of neurologic abnormalities in SGA infants at each gestational age.[20]

In two previous studies, infants who were SGA at term were found to be at increased risk for neurocognitive impairment at 8 months (OR = 1.92, 95% CI: 1.64 to 2.25), and 48 months (OR = 1.47, 95% CI: 1.18 to 1.83) when compared with appropriately grown for gestational age (AGA) term infants.[19]

However, in another cohort of premature infants born before 32 weeks gestation, SGA was not found to be significantly associated with neurocognitive impairment or use of speech and language therapy at 5 years of life.[7]

Finally, recent studies among surviving infants born at preterm gestational ages did not find an association between SGA and neurocognitive impairment at 2 years of corrected age. In this study, preterm SGA was associated with an increased risk of fetal or infant death, even when adjusting for possible confounders. These findings need to be confirmed in larger prospective studies using current neonatal growth curves and neurocognitive assessments. These investigations may be useful to clinicians counseling patients with SGA at preterm gestational ages.[13] Despite all these data, the effect of SGA on neurocognitive outcomes in those born at preterm gestational age remains unclear.

There still is the unanswered question "Should we focus on delivery mode in SGA-PTB infants or "prolonging pregnancy" with effective fetal monitoring. The paper by Ting and co gives an excellent

explanation to this dilemma: "Despite substantial advances in effective noninvasive fetal monitoring methods to safely prolong pregnancy, especially the application of fetal Doppler studies, the ultimate obstetric intervention of delivery mode has surprisingly received minimal attention. Further research is encouraged to aid clinicians in the decision between inductions of labor and planned cesarean birth for the pregnancies with suspected SGA fetus regardless the duration of pregnancy. Standardization of definitions, monitoring methods, and the design of adequately powered studies are urgently needed to further improve outcomes in these high-risk pregnancies".[21]

To conclude our knowledge, this is the first study of difference in perinatal outcome between moderate and mild preterm birth performed at our department, so we find it very important for our daily clinical practice. Future studies should focus on the impact of SGA in a moderate and mild preterm birth on neurocognitive impairment in our population.

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