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## EARLY NEONATAL OUTCOME OF WOMEN WITH GESTATIONAL DIABETES

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**SUMMARY.** Gestational diabetes (GD) is one of the most common metabolic complications in pregnancy. Pregnant diabetic women have more often complications during pregnancy and childbirth. Hypoglycemia, hypocalcemia, macrosomia, lower Apgar score and infection, jaundice, birth injuries and cyanosis are often seen in their newborns. *Aim.* We compared two groups – newborns of diabetic mothers and controls during two years period and try to determine whether there are any differences among them – Apgar score, birth weight, clinical characteristics, need for oxygenation and duration of hospitalization. *Methods.* There were 262 newborns of mothers with GD during 2015 and 2018 at Clinical hospital center Osijek. Retrospective case control study was done. The controls (n=262) were first neonates born after the examinees in 2015 and 2018 whose mother were healthy. *Results.* Pregnant women with GD were older and also tend to have more complications during the delivery. Their infants were more often macrosomic, hypoglycemic, and hypocalcemic when compared to control group. They require more oxygen treatment, longer hospitalization and they are more often born by elective and urgent C-section. *Conclusion.* Gestational diabetic mothers was still connected with worse early neonatal outcome.

### Introduction

Gestational diabetes (GD) is a common metabolic disorder and had a common obstetric problem. Poor control of pregnant women with diabetes is associated with elevated perinatal mortality and morbidity. According to the guidelines of the World Health Organization gestational diabetes is diagnosed in the presence of the following criteria: fasting plasma glucose 5.1–6.9 mmol/L; glucose after 1 hour  $\geq$  10.0 mmol/L or glucose after 2 hours 8.5–11.0 mmol/L after loading 75 g of glucose orally. If the blood glucose is higher than 11,1 mmol/L diabetes mellitus is manifested. In such pregnant women, the birth of a macrosomic newborn is more frequent, as well as birth injuries (e.g. shoulder dystocia), premature birth, hypoglycemia and cesarean delivery.<sup>1–3</sup> About 27.9% of infants of diabetic mothers have a birth weight above the 90th centile for gestational age.<sup>4</sup> The prevalence of GD in Croatia is 4.6% and still rises.<sup>5</sup> The rate of preterm birth in pregnant women with GD is about 15.2%. The most important risk factors in GD pregnancy are: obesity, multiparity, the presence of diabetes mellitus in the family, polycystic ovary syndrome, GD in previous pregnancy, and poor perinatal outcome in previous pregnancy, preeclampsia and multiple pregnancies.<sup>6</sup>

GD has been associated with an increased risk of infection in both mother and child.<sup>7</sup> Preeclampsia is a systemic disease with widespread endothelial damage and the potential to affect future cardiovascular diseases. It is characterized by the development of hypertension and can cause proteinuria, but does not always end with the delivery. Eclampsia characterized by seizures.<sup>9</sup> In diabetic pregnant women, polyhydramnion is also common.<sup>10</sup> Women with GD are also more likely to

have chronic illnesses – hypothyroidism or hyperthyroidism. Those with hypertension as a chronic disease often experience exacerbation due to GD.<sup>11</sup> In pregnant women with GD, cesarean section is more frequent – according to the literature, up to 13.5% of births<sup>6</sup> (due to the higher incidence of complications – preeclampsia and fetal macrosomia).<sup>11</sup> In poorly controlled GD, the deposition of fibrin deposits in the placenta and its thickening occur. Abruption of the placenta<sup>12</sup> is more common which occurs in 1.6% of pregnant women with GD.<sup>6</sup> A study conducted on neonates of pregnant women with and without GD showed a lower Apgar score in the first group.<sup>3</sup> Newborns of such mothers are at increased risk of jaundice, more frequently develop RDS, hypoglycemia and are hospitalized longer.<sup>13</sup> According to some studies, 16.3% of newborns of mothers with GD had pathological jaundice.<sup>6</sup> The incidence of respiratory complications in children whose mothers have GD is 34% higher than that of mothers who do not have it.<sup>14</sup> There is a positive correlation between CRP concentration and insulin resistance. Elevated CRP levels have been found in children of mothers with GD<sup>16</sup>, and the incidence of sepsis among their infants is 0.6%.<sup>4</sup> Newborn's asphyxia may be associated with GD in pregnant women. Studies of hypertrophic infants of diabetic mothers with a cord pH below 7 found that they had a higher incidence of asphyxia.<sup>16</sup> Most newborns of mothers with GD have transient asymptomatic hypoglycemia one to four hours postnatal, after which glucose levels spontaneously return to normal. Hypoglycemia consequently leads to cyanosis. If the mother was well controlled during pregnancy, hypoglycemia in the newborn would be less pronounced<sup>17</sup>. The incidence of hypoglycemia among children whose mothers have GD ranges from 2.1% to 4.6%.<sup>11</sup> Hypertrophic infants tend

Table 1. Newborns characteristic in 2015 and 2018 year

		Pregnant women								
		2015			2018			Total		
		N (%)		P	N (%)		P	N (%)		P
GD	C	GD	C		GD	C				
Gender	female	58 (42.6)	60 (44.1)	0.81	56 (44.4)	64 (50.8)	0.31	114 (43.5)	124 (47.3)	0.38
	male	78 (57.4)	76 (55.9)		70 (55.6)	62 (49.2)		148 (56.5)	138 (52.7)	
Mode of delivery	1	72 (52.9)	90 (66.2)	0.07	76 (60.3)	101 (80.2)	<b>0.003</b>	148 (56.5)	191 (72.9)	<b>0.001</b>
	2	28 (20.6)	17 (12.5)		18 (14.3)	10 (7.9)		46 (17.6)	27 (10.3)	
	3	36 (26.5)	29 (21.3)		32 (25.4)	15 (11.9)		68 (26)	44 (16.8)	
Apgar score	<7	13 (9.6)	6 (4.4)	0.10	13 (10.3)	4 (3.2)	<b>0.02</b>	26 (9.9)	10 (3.8)	<b>0.006</b>
	≥7	123 (90.4)	130 (95.6)		113 (89.7)	122 (96.8)		236 (90.1)	252 (96.2)	
Birth weight	Eutrophic	91 (66.9)	99 (72.8)	0.33	75 (59.5)	98 (77.8)	<b>0.001</b>	166 (63.4)	197 (75.2)	<b>0.002</b>
	Hypotrophic	24 (17.6)	24 (17.6)		25 (19.8)	20 (15.9)		49 (18.7)	44 (16.8)	
	Hypertrophic	21 (15.4)	13 (9.6)		26 (20.6)	8 (6.3)		47 (17.9)	21 (8)	
Duration of pregnancy	<37	17 (12.5)	9 (6.6)	0.10	23 (18.3)	13 (10.3)	0.07	40 (15.3)	22 (8.4)	<b>0.01</b>
	37≥	119 (87.5)	127 (93.4)		103 (81.7)	113 (89.7)		222 (84.7)	240 (91.6)	
CRP	≤5	112 (82.4)	117 (86)	0.41	109 (86.5)	97 (77)	0.050	221 (84.4)	214 (81.7)	0.42
	> 5	24 (17.6)	19 (14)		17 (13.5)	29 (23)		41 (15.6)	48 (18.3)	
Maternal age	<20	2 (1.5)	4 (2.9)	0.19	1 (0.8)	6 (4.8)	<b>0.001</b>	3 (1.1)	10 (3.8)	<b>0.001</b>
	20–40	121 (89)	126 (92.6)		108 (85.7)	117 (92.9)		229 (87.4)	243 (92.7)	
	>40	13 (9.6)	6 (4.4)		17 (13.5)	3 (2.4)		30 (11.5)	9 (3.4)	
Total		136	136		126	126		262	262	

GD – gestational diabetes, Control group, N – number, 1 – vaginal, 2 – elective cesarian section, 3 – emergency cesarian section

to have shoulder dystocia more frequently and more easily during vaginal delivery.<sup>11</sup> Shoulder dystocia is a rare but extremely serious trauma. Difficulties in giving birth first shoulders after the head can lead to long-term infant injuries such as nerve trauma and skeletal fractures.<sup>18</sup> Birth trauma in such children may also be intracranial hemorrhage, as well as central and peripheral nervous system injuries, skull bone injuries as well as skeletal bones.<sup>19</sup> Congenital heart problems in neonates of mothers with GD arise from exposure to teratogenic effects in the early stages of cardiac development. The most common birth defects in such newborns are ventricular septal defect with incidence of 2,5 to 12% and hypertrophic cardiomyopathy (transitory) with an incidence of 6–15%.<sup>20</sup> Withdrawal symptoms occur between weeks 2 and 4 of the infant's life while septal hypertrophy recedes within 2 to 12 months.<sup>2</sup> Hypocalcemia and hypomagnesemia occur within the first 72 hours of birth. Asphyxiated infants with RDS are at increased risk of hypocalcemia. Maternal parathyroid hormones and vitamin D do not exceed the placenta in significant amounts. The parathyroid system becomes more active after 72 hours. The symptoms of hypocalcemia itself are similar to those of hypoglycemia (irritability, sweating and tachypnea). Newborns of mothers who have poorly controlled GD are at higher risk of developing hypocalcemia<sup>21</sup> with the incidence of 1.8%.<sup>22</sup>

The aim of the investigation was to found out the incidence of acute, chronic and reproductive diseases in

pregnant women with GD, as well as complications in childbirth and to describe early neonatal outcome based on the length of hospitalization, need for oxygen therapy, and mechanical ventilation. We compared some characteristics of newborns in two observed groups: mode of deliveries, birth weight, duration of pregnancy, vitality at birth and possible co-morbidity in the child.

## Materials and methods

This retrospective case control study include neonates born to mothers who had GD in 2015 and in 2018 year. Control group consists of neonates (first born afterwards) whose mother did not have GD. During the study, neonatal lists from the Department of neonatology and gynecological protocols from the Department of gynecology were used. Maternal age, acute illnesses (preeclampsia, eclampsia, polyhydramnios, infections, thrombocytopenia) and chronic (hypertension, pulmonary and heart disease, hypo or hyperthyroidism) were analyzed. Spontaneous abortions, in vitro fertilization have also been reported. Method of delivery and complications of delivery were observed: with umbilical cord prolapsed, placental abruption, premature rupture of membranes and possibly irregular position of the newborn during delivery. Infant data included were: gender, date of birth, Apgar score at first and fifth minute, gestational age, birth weight, CRP, hypoglycemia and hypocalcemia, length of hospitalization, and need for oxygenation or mechanical ventilation, as well as congenital heart diseases. The results are presented in

Table 2. Maternal complications

Clinical characteristics	Pregnant women									
	2015			2018			Total in 2015 and 2018			
	N (%)		P	N (%)		P	N (%)		P	
	GD	C		GD	C		GD	C		
Mothers illnesses*	0	61 (44.9)	78 (57.4)	<b>0.04</b>	39 (31)	70 (55.6)	<b>&lt;0.001</b>	100 (38.2)	148 (56.5)	<b>&lt;0.001</b>
	1	40 (29.4)	26 (19.1)	<b>0.05</b>	62 (49.2)	33 (26.2)	<b>&lt;0.001</b>	102 (38.9)	59 (22.5)	<b>&lt;0.001</b>
	2	26 (19.1)	17 (12.5)	0.13	25 (19.8)	15 (11.9)	0.08	51 (19.5)	32 (12.2)	0.02
	3	34 (25)	27 (19.9)	0.31	23 (18.3)	16 (12.7)	0.22	57 (21.8)	43 (16.4)	0.12
Complications in delivery**	0	63 (46.3)	69 (50.7)	0.47	62 (49.2)	63 (50)	0.90	125 (47.7)	132 (50.4)	0.54
	1	37 (27.2)	39 (28.7)	0.79	27 (21.4)	35 (27.8)	0.24	64 (24.4)	74 (28.2)	0.32
	2	5 (3.7)	5 (3.7)	1.00	9 (7.1)	10 (7.9)	0.81	14 (5.3)	15 (5.7)	0.85
	3	26 (19.1)	27 (19.9)	0.88	24 (19)	27 (21.4)	0.64	50 (19.1)	54 (20.6)	0.66
	4	13 (9.6)	5 (3.7)	0.05	11 (8.7)	5 (4)	0.12	24 (9.2)	10 (3.8)	<b>0.01</b>
Total N of newborns		136	136		126	126		262	262	

GD – mothers with gestational diabetes, C – control group, N – number

\*0 – without illness, 1 – acute, 2 – chronic, 3 – reproductive

\*\*0 – without complications, 1 – with umbilical cord, 2 – with placenta, 3 – premature rupture of membranes, 4 – irregular baby position

Table 3. Hypoglycemia, hypocalcemia, length of hospitalization and need for oxygenation in newborns in 2015 and 2018 year

Clinical features	Pregnant women									
	2015			2018			Total			
	N (%)		P	N (%)		P	N (%)		P	
	GD	C		GD	C		GD	C		
Hypoglycemia	Yes	13(9.6)	3 (2.2)	<b>0.01</b>	7 (5.6)	2(1.6)	0.08	20 (7.6)	5 (1.9)	<b>0.002</b>
	No	123 (90.4)	133 (97.8)		119 (94.4)	124 (98.4)		242 (92.4)	257 (98.1)	
Hypocalcemia	Yes	9 (6.6)	3 (2.2)	<b>0.07</b>	4 (3.2)	1 (0.8)	0.17	13 (5)	4 (1.5)	<b>0.03</b>
	No	127 (93.4)	133 (97.8)		122 (96.8)	125 (99.2)		249 (95)	258 (98.5)	
Length of hospitalization	Cesarian section – up to 6 days	35 (25.7)	37 (27.2)		33 (26.2)	18 (14.3)		68 (26)	55 (21)	
	Caesarian section > 6 days	29 (21.3)	9 (6.6)	<b>0.01</b>	17 (13.5)	7 (5.6)	<b>0.01</b>	46 (17.6)	16 (6.1)	<b>0.001</b>
	Vaginal delivery up to 3 days	37 (27.2)	38 (27.9)		57 (45.2)	67 (53.2)		94 (35.9)	105 (40.1)	
	Vaginal delivery > 3 days	35 (25.7)	52 (38.2)		19 (15.1)	34 (27)		54 (20.6)	86 (32.8)	
Mechanical ventilation	yes	5 (3.7)	3 (2.2)	0.473	7 (5.6)	6 (4.8)	0.78	12 (4.6)	9 (3.4)	0.504
	no	131 (96.3)	133 (97.8)		119 (94.4)	120 (95.2)		250 (95.4)	253 (96.6)	
Oxygenation	no	95 (69.9)	112 (82.4)	<b>0.02</b>	97 (77)	110 (87.3)	<b>0.03</b>	192 (73.3)	222 (84.7)	<b>0.001</b>
	yes	41 (30.1)	24 (17.6)		29 (23)	16 (12.7)		70 (26.7)	40 (15.3)	
Total N of newborns		136	136		126	126		262	262	

GD – mothers with gestational diabetes, Control group, N – number

absolute and relative frequencies, and the significance of differences among independent samples with  $X^2$  test with 95% confidence interval,  $P < 0.05$ . For the smaller  $X^2$  sample, the test was performed with Yates correction. The data were analyzed by statistical procedures for testing differences and correlations using statistical Microsoft Excel version 2016.

## Results

There was a significant difference in maternal age between two groups ( $P < 0.001$ ). Table 1. There was a significant difference in the mode of delivery. Newborns of

mothers with GD were more often born by cesarean section ( $P < 0.001$ ). The difference in the prevalence of newborns born by emergency cesarean section was also significant between two study groups. Children of mothers with GD had Apgar score less than 7 ( $P = 0.006$ ). In the group of infants whose mothers had GD, there were two times more preterm infants than in the control group ( $P = 0.01$ ).

Table 2 shows difference in the prevalence of pregnancy complications in mothers with and without GD over a 2-year period ( $P < 0.001$ ). Mothers with GD more frequently had complications. Acute diseases were

more common in mothers with GD ( $P<0.001$ ) and chronic diseases as well as ( $P=0.02$ ). Irregular child's position during delivery is 2.5 times more common in newborns of mothers with GD ( $P=0.01$ ). There was a difference in the incidence of heart defects between the infants of mothers with GD and the control group, but only in 2015 the difference has been significant ( $P=0.03$ ). In the *Table 3* we see that there was an important difference in the incidence of neonatal hypoglycemia ( $P<0.05$ ) over a two-year period, as well as in neonatal hypocalcemia ( $P<0.05$ ) between two groups. We also see that there is an important difference in the length of hospitalization ( $P<0.001$ ). Infants of mothers with GD born by cesarean section were hospitalized almost three times more frequently for more than 6 days than infants of mothers without GD ( $P<0.01$ ). Children of diabetic mothers are more likely mechanically ventilated, but this difference is not significant in 2015 or in 2018. Oxygenation was almost twice as frequent in infants of diabetic mothers in both 2015 ( $P=0.02$ ) and 2018 ( $P=0.03$ ). The difference in oxygenation of newborns over a 2-year period was also significant, infants of mothers with GD almost 2 times more frequently needed oxygen ( $P=0.001$ ).

## Discussion

In 2015, 2165 children were born, of whom 6.3% were newborns from mothers who had diabetes. In 2018, there were 1954 births and 6.4% were born to mothers who had diabetes. The literature reported an incidence of 4.7%.<sup>6</sup> The infants of the study group were almost four times more likely to have a mother over 40 and three times less frequently to have a mother under 20. The literature states that maternal age is a risk factor for the development of gestational diabetes. According to the literature, 6.8% of mothers over 40 receive gestational diabetes.<sup>23</sup>

Women with GD were more likely to have elective and even an emergency cesarean section. These data are like those in the literature.<sup>6</sup> According to research, in 13.5% of women with GD mode of delivery was cesarean section.<sup>4</sup> In our study, this number is doubled, 43.6% of newborns of mothers with GD were born by cesarean section. In the control group, the percentage of infants born by the operative route is also high 27.1%. GD is a risk factor for a child's lower vitality.<sup>3</sup> The difference in the study is evident in the overall comparison for the two years where almost three times as many infants had Apgar score less than 7 in the study group versus controls. Maternal diabetes has been shown to lead to newborn hypertrophy.<sup>11</sup> Hypertrophic newborns were almost twice often in those mothers in our study. Literature shows that mothers with diabetes have hypertrophic infants in 27.9%.<sup>4</sup> In the group of mothers with GD, 15.3% had preterm infants, twice as many as in the group of mothers without GD. This is in line with the literature because diabetes is a risk factor for preterm delivery in 15.2% of cases.<sup>22</sup> GD is a potential risk for

elevated level of CRP because assisted births are more likely to be performed in such pregnant women, and this may increase CRP levels.<sup>14</sup> In our study there was no significant difference in CRP concentration. Acute diseases and conditions in pregnancy such as infections, and preeclampsia and eclampsia were significantly more frequent in the infants of mothers with GD, and they were twice as likely to occur. The data agree with the literature.<sup>9</sup> According to research, preeclampsia is experienced by 10–20% of diabetic pregnant women.<sup>11</sup> In our study, acute complications in this group were found in 38.9% of pregnant women (with other acute conditions such as infection). Chronic diseases (such as hypothyroidism) and reproductive diseases (such as miscarriage) were more common in pregnant women with GD. Birth complications such as those with umbilical cord, placenta, or premature rupture of membranes were equally common in both infant groups. Irregular fetal position was more common in infants of mothers with GD. The literature agrees with this.<sup>11</sup> GD is a risk factor for various heart defects and their incidence in infants of such mothers is 6–15% according to some authors.<sup>20</sup> In this study, the incidence of the same was 5.7%. Such results are probably the result of close monitoring of diabetic mothers as well as their infants. Hypoglycemia was statistically significantly more frequent in infants whose mothers had GD. By comparing the total number for both years, the infants of the study group had four times more frequent hypoglycemia. The prevalence of hypoglycemia in neonates whose mothers had GD was 7.6%. The literature cites a percentage between 2.1 and 4.6%.<sup>10</sup> Hypocalcemia was three times more common in neonates whose mothers had GD (5% of all newborns). According to the literature, it is more common in newborns of mothers with diabetes.<sup>21</sup> According to some authors, 1.8% of children of diabetic mothers have this form of the disorder. The neonates of the study group were more often born by cesarean section, and the literature agrees,<sup>2</sup> and more often stayed in the hospital for more than 6 days (four times more often than neonates born by cesarean section of mothers without GD). Those infants whose mothers did not have GD were significantly more likely to remain in the hospital for up to 3 days after delivery. The need for mechanical ventilation was 25% more frequent in neonates of mothers with GD (4.6% versus 3.4%). According to the literature, 34% of neonates of diabetic mothers have respiratory complications and require some form of mechanical ventilation and oxygenation.<sup>18</sup> In this study, the need for oxygenation was 26.7%. There was also an important difference in the need for oxygen. About 11% more neonates in the first group needed oxygen therapy after delivery.

## Conclusions

Cesarean deliveries, both elective and emergency, were significantly more common in pregnant women with GD. Children of mothers with GD are significantly more likely to be macrosomic than those of mothers

without GD. There were almost twice as many premature infants in the group whose mothers had GD. Complications during pregnancy (infections, preeclampsia and polyhydramnion) were more common in the group of mothers with GD. Hypoglycemia was four times more frequent in children of mothers with GD, and hypocalcemia was three times more frequent when compared with control group. The newborns of mothers with GD were more often longer hospitalized after cesarean section.

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## RANI NEONATALNI ISHOD U ŽENA S GESTACIJSKIM DIJABETESOM

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*Izvorni članak*

*Ključne riječi:* gestacijski dijabetes, perinatalni ishod, novorođenče, komplikacije u trudnoći

**Sažetak.** Gestacijski dijabetes je jedan od najčešćih metaboličkih komplikacija u trudnoći. Trudnice s GD, češće imaju komplikacije trudnoće. *Cilj istraživanja* je bio usporediti maternalni i perinatalni ishod u trudnica s gestacijskim dijabetesom. *Metode i ispitanici.* Provedeno je istraživanje parova u KBC-u Osijek tijekom 2 godine (2015. i 2018.). U skupini trudnica s gestacijskim dijabetesom i u kontrolnoj skupini je bilo po 262 ispitanica. Kontrolnu skupinu činile su zdrave trudnice i njihova novorođenčad. *Rezultati.* U dvogodišnjem razdoblju rođeno je 6,4% novorođenčadi od trudnica s GD-om. Majke s GD češće su imale komplikacije trudnoće (infekcije, preeklampsiju, eklampsiju, polihidramnij) te kronične bolesti, kao i komplikacije u porođaju u odnosu na kontrolnu skupinu. Novorođenčad rođena od majki s GD-om su češće bila hipertrofična, hipoglikemična i hipokalcemična, češće su imala potrebu za oksigenacijom i duljom hospitalizacijom, češće se porođena elektivnim i hitnim carskim rezom. *Zaključak.* Boljom antenatalnom skrbi GD-a trudnica značajno je smanjen maternalni i perinatalni morbiditet.