Clinical and Experimental Obstetrics & Gynecology

Clin. Exp. Obstet. Gynecol. **2022**; 49(4): 81
https://doi.org/10.31083/j.ceog4904081

Original Research

Real-life experience with antenatal glucocorticoid administration in premature pregnancies complicated by diabetes mellitus

Anca-Gabriela Dumitrescu[1], Teodor Salmen[2,*], Florentina Furtunescu[3], Costin Berceanu[4], Corina Grigoriu[5,6,*], Roxana-Elena Bohîlțea[5,7,*], Simona Daniela Popescu[8]

[1]Faculty of Medicine, 'Carol Davila' University of Medicine and Pharmacy, 020021 Bucharest, Romania
[2]Department of Diabetes, Nutrition and Metabolic Diseases, "Prof. Dr. N.C.Paulescu" National Institute of Diabetes, Nutrition and Metabolic Disorders, 020475 Bucharest, Romania
[3]Department of Public Health and Management, Faculty of Medicine, 'Carol Davila' University of Medicine and Pharmacy, 050474 Bucharest, Romania
[4]Department of Obstetrics and Gynecology, University of Medicine and Pharmacy of Craiova, 200349 Craiova, Romania
[5]Department of Obstetrics and Gynecology, 'Carol Davila' University of Medicine and Pharmacy Bucharest, 050474 Bucharest, Romania
[6]Department of Obstetrics and Gynecology, University Emergency Hospital Bucharest, 050098 Bucharest, Romania
[7]Department of Obstetrics and Gynecology, "Filantropia" Clinical Hospital, 011171 Bucharest, Romania
[8]Department of Neonatology, 'Carol Davila' University of Medicine and Pharmacy, 050474 Bucharest, Romania
*Correspondence: teodor.salmen@gmail.com (Teodor Salmen); corigri@gmail.com (Corina Grigoriu); r.bohiltea@yahoo.com (Roxana-Elena Bohîlțea)
Academic Editor: Michael H. Dahan
Submitted: 9 December 2021 Revised: 21 January 2022 Accepted: 22 January 2022 Published: 2 April 2022

Abstract

Background: Diabetes mellitus (DM) in pregnancy is associated with an increased risk of premature birth, which therefore increases the risk of acute respiratory distress syndrome (ARDS) of the neonate and is associated with high morbidity and mortality of the newborn. The administration of glucocorticoids to the mother before premature birth decreases the risk of neonatal complications. However, the data regarding the administration of this therapy to mothers with DM is limited. Clinical guidelines recommend treating them in the same manner as the non-DM women, even if there is no recent data to support the benefit in this subpopulation. The aim of this study is to evaluate the real-life effects of glucocorticoid administration on the maternal and fetal prognosis of pregnancies complicated with DM. **Material and methods**: A retrospective study was conducted on 67 pregnant females who were admitted to the Obstetrics & Gynecology Department of The Emergency University Hospital of Bucharest between December 2016–March 2021, and who received corticosteroid before prematurely giving birth to 70 newborns. There was a group of 33 mothers with DM and a second group with 34 non-DM pregnant women selected for control of glucocorticoids' real-life administration in the high risk for premature birth population. **Results**: The administration of glucocorticoids was not restricted by the presence of DM; 78% of the mothers with DM and 79.41% of the mothers without DM received one course of antenatal glucocorticoids for fetal lung maturation ($p = 0.6$). The incidence of ARDS differs between groups was statistically insignificant: 35.29% in the DM group versus 30.55% in the control group ($p = 0.8$). There were similar cases of maternal complications such as pregnancy-induced hypertension (PIH), or preeclampsia in the two groups. These findings suggest that glucocorticoid therapy is effective for premature newborns from pregnancies with DM and does not negatively impact the complication rate of the mothers, sustaining their administration in these cases. **Conclusions**: The administration of antenatal glucocorticoids before premature birth is not influenced by the presence of DM regarding Apgar score at 1 and 5 minutes, the incidence of ARDS, but there were differences such as more large for gestational age (LGA) newborns and neonatal hypoglycemia in the DM group. Considering the low number of patients enrolled from a single-center, future multicentric studies are needed. It is important to emphasize that this study's findings reflect the local practice and cannot be generalized.

Keywords: glucocorticoids; corticosteroids; diabetes mellitus; neonatal outcome; premature birth; acute respiratory distress syndrome

1. Introduction

In 2017, Romania was placed amongst the countries with the highest prevalence of diabetes mellitus (DM). More than 9% of the 18–99 years old population was estimated to suffer from DM [1]. Pregnant women suffering from DM or gestational DM (GDM) are at increased risk of premature birth, with an incidence of 10% and complications that can affect them or the fetus/neonate [1]. The majority of guidelines recommend screening for all pregnant women between 24th and 28th week of gestation with 75-g 2-hour oral glucose tolerance test and all recommend that all women with GDM should undergo a glycemic test at around 6 to 12 weeks after delivery, that breastfeeding is important; in case of future pregnancies, preconception screening should be undergone [2]. Pregnancy-induced hypertension (PIH), preeclampsia, eclampsia, and other metabolic disorders are frequently found in mothers with DM and are associated with an unfavorable progression of pregnancy and poor neonatal outcomes [3]. Newborns of mothers with DM are at great risk of being large for gestational age (LGA), developing neonatal hypoglycemia and hypocalcemia and acute respiratory distress syndrome (ARDS) [4]. Antena-

tal glucocorticoids represent the standard of care for pregnant women at risk of premature birth at gestational ages between 24 and 34/36 weeks of gestation [5,6]. There isn't a uniform consensus about the timing, because the National Institute for Health and Care Excellence and the World Health Organization (WHO) recommendations are for 24 + 0 until 34 + 0 weeks, the American College of Obstetricians and Gynecologists (ACOG) recommendation are for 24 + 0 until 36 + 6 weeks, while the Society of Obstetricians and Gynaecologists of Canada (SOGC) recommendations are for 24 + 0 until 34 + 6 weeks of gestation, even though, the gestational age should be known and the pregnant women should be in spontaneous preterm labor, respectively repeatedly regular uterine contractions associated with significant cervical changes. The way of administration has a uniform recommendation, respectively intramuscular dexamethasone or betamethasone [7]. This therapy is associated with a significant decrease in neonatal mortality, the incidence of ARDS, and intraventricular hemorrhage in the neonatal period [8].

Endogenous corticosteroids exert maturational effects on different organs via cellular glucocorticoid and mineralocorticoid receptors. Synthetic corticosteroids like dexamethasone and betamethasone interact only with glucocorticoid receptors [9]. Both of them pass the placenta in their active form and they are resistant to the action of β-hydroxysteroid dehydrogenase type 2, an enzyme that degrades glucocorticoid hormones coming from the mother [10]. Glucocorticoid receptors are ubiquitous, found in the nucleus of the cell, and play an important role in moderating the genic expression. The complexity of the signaling mechanism via glucocorticoid receptors in the developing fetus has not been yet studied in depth [11]. The best described biochemical effect is on type 1 and 2 pneumocytes and surface epithelial cells of the alveoli. Glucocorticoids stimulate cellular development and surfactant production, therefore preparing the fetus for extrauterine life [12]. Besides the effect on surfactant synthesis, glucocorticoids increase pulmonary compliance and pulmonary total capacity and reduce the passage of proteins from alveolar capillaries to the alveoli, thus contributing to the elimination of pulmonary secretions after birth [13].

Concerning the substance to administer, a multicentric study conducted in 2019 found no difference between dexamethasone and betamethasone in terms of safety and efficiency on decreasing the neonatal complications, and also the morbidity and mortality in the neonatal period [14].

It is important to mention that the subgroup of women with DM was excluded from most clinical studies concerning antenatal glucocorticoid therapy because of the concerns regarding glycemic management [15]. Clinical guidelines recommend treating these women in the same manner as the non-DM women even though there is no recent data to prove the benefit of the therapy in these patients. It is unknown whether these recommendations are applied in clinical practice [16]. This study is a retrospective analysis whose purpose is to evaluate the real-life administration of antenatal glucocorticoids in pregnant women with DM and to analyze the maternal and neonatal prognostic factors, comparing this population with women without DM who gave birth prematurely.

2. Materials and methods

This study comprises data from 67 pregnant women, 33 with DM and 34 non-DM matches by maternal age, parity, body mass index, residence, and ethnicity, who received corticosteroid before prematurely birth in the second largest maternity of Bucharest (approximatively 3500 births/year), in 4 years, respectively between December 2016 and March 2021 and their 70 newborns. Advanced maternal age, rural origin, and primiparity are associated with poor neonatal outcome [17–19] and could have acted as confounding variables, affecting the study's results, therefore, the match was carefully selected. Group 1 (control) was formed by 34 non-DM pregnant women, respectively 50.75% of the total and their 36 newborns; group 2, comprised of 33 mothers with DM, respectively 49.75% of the total, who gave birth to 34 newborns. The women in the second group suffered from gestational diabetes mellitus (GDM) diagnosed by 75-g 2-hour oral glucose tolerance testing 78.78% cases, diet-controlled type 2 DM in 15.15% of cases, and 1 case of insulin-treated type 1 DM, respectively 3.03% of cases. 5 twin pregnancies were present in both groups, 2 in group 1 and 3 in group 2. 2 twin pregnancies of the second group were complicated by intrauterine death of one fetus. Therefore, the 33 women from the second group gave birth to 34 viable newborns and the 34 women from the first group gave birth to 36 viable newborns.

Maternal variables taken into account were: admission blood glucose levels, the presence of obesity or excessive weight gain during pregnancy–considered regarding the body mass index before pregnancy as WHO recommended, the presence of complications (PIH, preeclampsia), and the administration of glucocorticoids. For the newborns, we considered: gestational age at birth, absolute birth weight and birth weight relative to gestational age (normal weight, LGA, small for gestational age (SGA)), Apgar score at 1 and 5 minutes, neonatal complications (ARDS, intracranial hemorrhage, hypoglycemia, hypocalcemia) and neonatal deaths.

The cumulative and comparative analysis of all the neonatal and obstetrical parameters of the cases in the two groups and the statistical analysis regarding the significant difference or the frequency of the complications have been analyzed by the chi-square test. The results were interpreted according to the obtained p-value; $p < 0.05$ was considered to be statistically significant.

The analyzed data were collected from the observation charts of the Obstetrics and Gynecology Departments of the Emergency University Hospital of Bucharest and the

Statistics Department of the hospital, with the permission of the Ethics Committee (73317/02.12.2021).

3. Results

3.1 Maternal characteristics

In both groups, mothers' ages followed Gaussian distribution, with values inside an interval between 20–40 years for group 1 and 20–44 years for group 2. The mean age for group 1 was 32.26 ± 5.04 years old (95% confidence interval (CI); 30.50–34.02), while for group 2 it was 33.73 ± 6.10 years old (95% CI; 31.56–35.89). There were no significant differences between the groups (p = 0.39), therefore they could be compared. Regarding the living area, 50% of participants from de first group and 51.51% of participants from the second one have come from the urban areas. The difference between the groups is not significant (p = 0.54). Concerning parity, the distribution in the two groups was satisfying, with no significant difference (p = 0.35). In the first group, there were 16 (47.05%) primiparous women and 18 (54.54%) in the second group. The mean blood glucose was expectantly higher in the second group [93.63 ± 27.42 mg/dL (95% CI; 83.91–103.36)], compared to the first group [83.38 ± 12.55 mg/dL (95% CI; 79–87.76)] (Fig. 1), but the medians were not significantly different (80 mg/dL for the first group and 90 mg/dL for the second group) (p = 0.14).

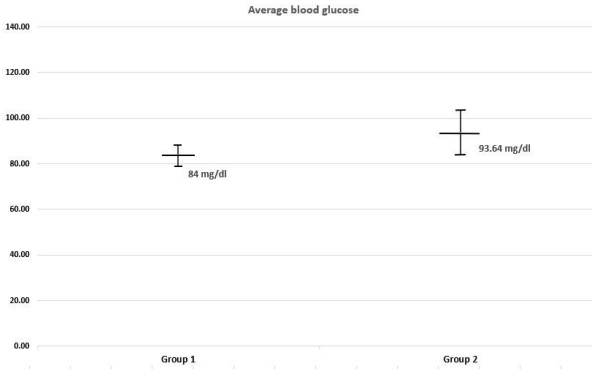

Fig. 1. Mean admission blood glucose.

Obesity and excessive weight gain during pregnancy were more frequent in group 2 and the difference was statistically significant (p = 0.03 for obesity; $p < 0.001$ for excessive weight gain); 9 patients (27.27%) in group 2 were obese and 19 (57.57%) gained excessive weight during pregnancy, while in the control group only 1 patient (2.94%) was obese and 3 (8.82%) gained more weight than normal during pregnancy (Fig. 2). Maternal characteristics are synthesized in Table 1.

There were no significant differences between the two groups regarding the number of cases of PIH or preeclampsia. There were 6 cases of PIH in each of both groups (p = 0.6), 4 cases of preeclampsia in the first group, and 6 in the second one (p = 0.3).

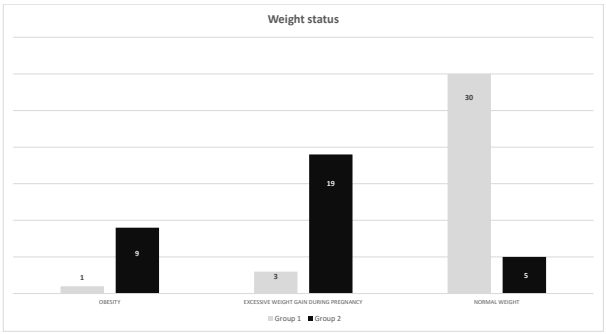

Fig. 2. Weight status of the subjects.

With respect to the administration of antenatal glucocorticoid therapy, there were no significant differences between the groups: 27 (79.41%) women from the first group and 26 (78.78%) women from the second group received the treatment (p = 0.03). In both groups, there was a substantial number of women who received the treatment between 34 and 36 gestational weeks (12 in group 1 and 16 in group 2).

In our study, there were only a few cases of PIH and preeclampsia. This aspect facilitates a better comparison of neonatal outcomes after the administration of antenatal glucocorticoids.

Our study had similar results to the literature reported data, obesity and excessive weight gain during pregnancy being more frequent in the DM group.

3.2 Neonatal characteristics

The mean gestational age for the groups was 33.23 ± 3.08 (95% CI; 32.15–34.31) for the first and 34.75 ± 1.92 weeks (95% CI; 34.07–35.43) for the second. Median ages (34.50 weeks for group 1, 35.00 weeks for group 2) were not statistically different (p = 0.26). Most patients gave birth between 35–37 weeks of gestation (19 in the first group and 24 in the second group). The least births happened at less than 28 weeks of gestation. The newborns in the second group had significantly higher birth weights (p = 0.009), with an average of 2643.82 ± 696.06 g, compared to 2025.28 ± 670.20 g in the first group. There was a difference of 618.55 g between the two groups (Fig. 3). The medians were 2675 g for group 2 and 2225 g for group 1. Minimum and maximum weights for the control group were 650 g and 3050 g, and for DM group were 850 and 3950 g, respectively.

In the first group, there were 66.66% newborns with normal weight, 9 (25%) SGA, and 3 (8.33%) LGA. In the second group, most newborns had normal weights, but there was a bigger number of LGA newborns, respective 15 (44.11%) and only 3 (8.82%) SGA. There were no significant differences regarding the number of SGA (p = 0.11).

Table 1. Maternal characteristic synthesis.

Maternal characteristics		Group 1	Group 2	*p* value
Age (years)		32.26 ± 5.04	33.73 ± 6.10	0.396
Living area	Rural	17 (50.00%)	16 (48.48%)	0.862
	Urban	17 (50.00%)	17 (51.51%)	0.862
Parity	Primiparous	16 (47.05%)	18 (54.54%)	0.8
	Multiparous	18 (52.94%)	15 (45.45%)	0.8
Admission blood glucose (mg/dL)		83.38 ± 12.55	93.63 ± 27.42	0.13
Obesity		1 (2.94%)	9 (27.27%)	<0.001
Excessive weight gain during pregnancy		3 (8.82%)	19 (57.57%)	<0.001
Pregnancy induced hypertension		6 (17.64%)	6 (18.18%)	0.013
Preeclampsia		4 (11.76%)	6 (18.18%)	0.145
Glucocorticoids administration		27 (79.41%)	26 (78.78%)	0.015
Glycated hemoglobin (%)			6.44 ± 1.41	

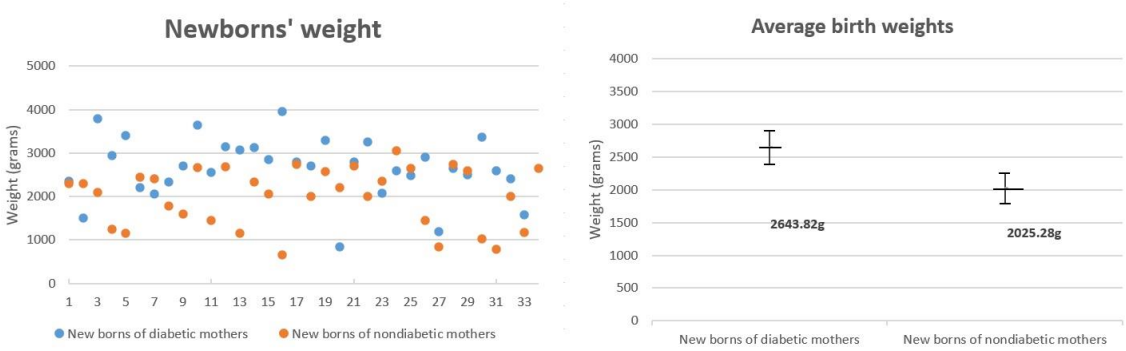

Fig. 3. Birth weights distribution on the two groups and average birth weights.

Newborns from group 2 had significantly higher weights at birth, with an average of 2643.82 g, and a difference of 618.55 g between them and the non-DM group ($p = 0.009$). The difference between groups regarding the number of LGA was statistically significant ($p = 0.001$) (Fig. 4).

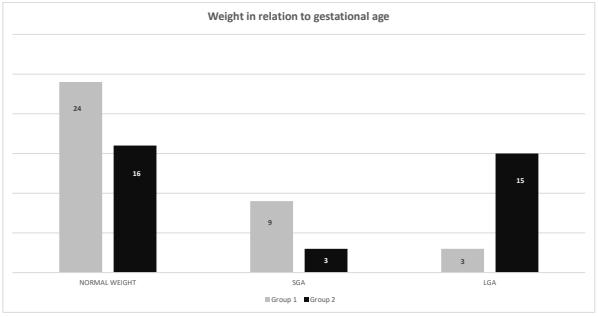

Fig. 4. Weight of premature newborn relative to gestational age, in the two groups.

There were no significant differences with regard to the Apgar score ($p > 0.05$). For group 1, the 1-minute average was 7.11 ± 2.35, while for the second group it was 7.44 ± 1.58. The 5 minutes Apgar average was 8.14 ± 1.53 for group 1 and 8.56 ± 0.75 for group 2. Unexpectedly, the lowest scores were registered in the first group. Regarding ARDS, 30.55% of newborns from group 1 and 35.29% from group 2 developed this complication after birth, with no significant difference between the two groups ($p = 0.8$). Intracranial hemorrhage was encountered more frequently in the control group [6 cases (16.66%), versus only 2 cases (5.88%) ($p = 0.6$)]. There were 16 cases (47.06%) of neonatal hypoglycemia in group 2 and only 5 (13.89%) in group 1 ($p = 0.004$). Neonatal hypocalcemia was also more frequent in the DM group (20.58% versus 8.33%), but the difference was not statistically significant ($p = 0.18$). There were 3 (8.82%) neonatal deaths in group 2 and only 1 (2.77%) in group 1, but the number was too low to achieve statistical significance (Fig. 5). Neonatal characteristics are synthesized in Table 2.

4. Discussion

According to the American Association of Diabetes, the incidence of PIH and preeclampsia increases propor-

Table 2. Neonatal characteristics synthesis.

Neonatal characteristics		Group 1	Group 2
Gestational age at birth		33.23 ± 3.08	34.75 ± 1.92
Birth weight		2025.28 ± 670.20	2643.82 ± 696.06
Birth weight relative to gestational age	Normal weight	24 (66.66%)	16 (47.05%)
	Large for gestational age	3 (8.33%)	15 (44.11%)
	Small for gestational age	9 (25%)	3 (8.82%)
Apgar score	1 minute	7.11 ± 2.35	7.44 ± 1.58
	5 minutes	8.14 ± 1.53	8.56 ± 0.75
Neonatal complications	Acute respiratory distress syndrome	11 (30.55%)	12 (35.29%)
	Intracranial hemorrhage	6 (16.66%)	2 (5.88%)
	Hypoglycemia	5 (13.89%)	16 (47.06%)
	Hypocalcemia	3 (8.33%)	7 (20.58%)
Deaths		1 (2.77%)	3 (8.82%)

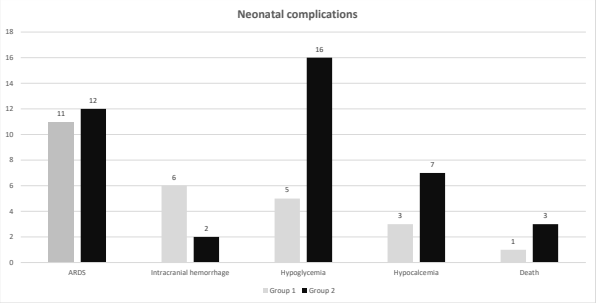

Fig. 5. Neonatal complications manifested in the two study groups.

tionally to the increase in glycated hemoglobin [20,21]. Compared to a low incidence of preeclampsia in non-DM women (2–7%), this complication is diagnosed in 15–20% of pregnancies associated with type one DM and in 10–14% of pregnancies associated with type 2 DM [22]. DM and preeclampsia share multiple risk factors as maternal age, parity, multiple gestations, ethnicity, and obesity. GDM is frequently cited as a risk factor for preeclampsia, although many studies had limitations, not taking into account the common risk factors. A retrospective study conducted in Germany evaluated the association between GDM and preeclampsia, controlling for the common risk factors. The study included 647392 pregnancies. The authors' conclusion was that the risk for preeclampsia is higher in pregnancies with DM and that DM represents an independent risk factor for the development of preeclampsia [23,24]. Another retrospective study conducted in the USA, Washington, had similar results. The pregnant women were divided into 5 groups: PIH, moderate preeclampsia, severe preeclampsia, eclampsia, and one control group with none of these complications. After adjusting for confounding variables (body mass index, age, ethnicity, parity), GDM was associated with a 1.5-fold higher risk of moderate and severe preeclampsia and a 1.4-fold higher risk of PIH when compared to the control group [22].

Obesity is a key risk factor for GDM and at the same time represents an independent risk factor for pregnancy complications. Weight above the superior limit of normality is frequently associated with dyslipidemia and hypertension, anomalies that increase the risk of complications during pregnancy [25,26]. Moreover, maternal obesity plays an important role in the birth of an LGA neonate. In an observational prospective study, the association between obesity and GDM was analyzed. Obesity was more frequent amongst pregnant women with GDM, compared to non-DM patients (70% versus 42.6%, $p < 0.001$) [27].

Corticosteroids administered to the mother prior to the premature birth decrease the morbidity and mortality of the premature newborns [6,28]. However, the data regarding pregnant women with DM is limited. Clinical guidelines recommend treating them in the same manner as the non-DM women, even if there is no recent data to support the benefit in this subpopulation [16]. Following data analysis, there were no significant differences between the two groups with respect to corticosteroids administration, a considerable number of patients receiving the therapy. The presence of DM does not seem to affect the physicians' decision on prescribing glucocorticoids for fetal lung maturation. These results are similar to those of a recent study conducted in New Zealand, which found that there is no difference in the manner of administration between the two populations of pregnant women; 25% of the patients received the treatment at a gestational age above 35 weeks, even though the national guideline of New Zealand recommends glucocorticoids up to this gestational age [16]. ACOG recommends the therapy for women at risk of premature birth between 34 0/7 and 36 6/7 weeks only if they had not received a prior course of glucocorticoids [28]. The Society for Maternal-Fetal Medicine supports the use of glucocorticoids in this group of patients, as 70% of preterm births oc-

cur in this period [13]. The Antenatal Late Preterm Steroids Trial, conducted by National Institute of Child Health and Human Development, a randomized double-blind study, involved pregnant women with singleton pregnancies at risk of premature birth between 34 0/7 and 36 6/7 gestational weeks. After administration of glucocorticoids for fetal lung maturation, it showed a drop in the need for surfactant administration and respiratory support in newborns during the first 72 hours after birth [29]. The Obstetrics and Gynecology Society from Romania recommends in its guideline from 2019 to use glucocorticoid therapy up to 34 weeks of gestation [6]. In our study, glucocorticoids were administered between 34–36 weeks of gestation in many cases of both groups (12 cases in group 1 and 16 cases in group 2), consistent with ACOG guidelines.

Numerous studies suggest that the risk for premature birth is higher for pregnant women with DM than for those non-DM [3,5,30,31], Sibai *et al*. [3] sustaining higher rates of premature births prior to 35 weeks of gestation in women with DM. However, in other studies that compared the average length of pregnancy in women with DM versus non-DM women, the average length was significantly higher in mothers with DM ($p < 0.001$) [32]. In our study the majority of patients (19 from group 1 and 24 from group 2) gave birth between 35 and 37 weeks; 18 deliveries from group 1 and 12 from group 2 took place under 35 weeks.

Kevin P Yeagle [33] conducted a retrospective study in 2019 to compare the Apgar score at 1 and 5 minutes between a group of pregnant women with DM and a group of non-DM pregnant women. He found no differences between the two groups. Our results are similar, with no significant differences between the two groups regarding the Apgar score ($p > 0.05$).

Fetal macrosomia is the most common complication of DM, and is associated with poor management of maternal DM and adverse neonatal outcomes. The concept of excessive fetal growth is expressed by means of two terms: macrosomia and LGA. Also, the fetal growth curve is monitored after the 12th week of gestation, when the biometric measurement begins. The LGA corresponds to a weight above the 90th percentile for gestational age, thus it allows the identification of premature newborns with excessive weight gain [34]. Studies report a high rate of macrosomia or LGA in subjects with DM [35]. 15–45% of newborns of mothers with DM are LGA [36]. A prospective study has compared the neonatal outcomes of 2 groups of pregnant women with DM. One group received an intensive plan of glycemic management while the other received the standard treatment. It seems that even after a strict glycemic control, there were no significant differences with regard to the percent of LGA between the 2 groups [37]. We also found that newborns of mothers with DM are prone to being LGA.

During pregnancy, besides DM, obesity represents an independent risk factor for giving birth to an LGA baby [27]. In the present study, only 5 LGA newborns from group 2 had mothers with normal weight, while the other 10 have been born from obese or overweight women. Therefore, poorly controlled DM may not be the only factor that contributes to excessive fetal growth; it seems that maternal obesity plays an important role too.

DM is a well-known risk factor for neonatal hypoglycemia [4]. In our study, both neonatal hypoglycemia and hypocalcemia were encountered significantly more frequent in the DM group. However, the study that compared neonatal outcomes of mothers following an intensive plan of glycemic management versus the standard therapy found no significant differences between the groups ($p = 0.195$), with high incidences of neonatal hypoglycemia in both of them (8.7% in the intensive treatment group; 14% in the standard treatment group) [37].

Prematurity represents an important risk factor for ARDS, due to incomplete fetal lung maturation. In 1976 Robert *et al*. [38] showed that DM is an independent risk factor for ARDS. Newborns of mothers with DM are 5.6 times more likely to develop ARDS than those of non-DM mothers [38]. A meta-analysis conducted in 2019 supports these findings. The analysis included 24 studies and concluded that maternal DM, pre-gestational or GDM, is associated with both prematurity and neonatal ARDS [39]. Intracranial hemorrhage was also associated with both prematurity and DM and antenatal glucocorticoids therapy reduces the risk for these complications in premature newborns [40]. Our results find a similar incidence of ARDS in both groups. Regarding intracranial hemorrhage, there were more cases in group 1, but out of the 6 newborns, 2 were born at 27 gestational weeks and 3 at 28 gestational weeks. Taking into account the fact that births that take place under 28 weeks of gestation are at the highest risk for this complication and 5 out of 6 newborns in group 1 were in this situation, the results are hard to compare.

Premature neonates are at a higher risk of death during the neonatal period and the first year of life compared to those born at term and the rate of mortality increases proportionally with the decrease of gestational age and birth weight [41]. Maternal DM is also associated with a higher mortality rate during the neonatal period than the general population [35]. The 4 neonatal deaths of our study affected premature newborns of 27, 29, 34, and respectively 36 gestational weeks.

The study limitations are the small number of included patients reported to the period of inclusion and the lack of risk of bias assessment.

5. Conclusions

The administration of antenatal glucocorticoids was not hampered by the presence of maternal DM. In both groups, a considerable number of women received glucocorticoids between 34–36 weeks of gestation, consistent with ACOG recommendations. There were no significant differences regarding Apgar score at 1 and 5 minutes, and

the incidence of ARDS was comparable and low in both groups. These findings could suggest that glucocorticoid therapy has the same efficacy in patients with DM. The frequency of LGA newborns and neonatal hypoglycemia was higher in the DM group, but these results might have been influenced not only by poor glycemic control but also by the excess weight and other metabolic anomalies encountered mainly in patients with DM. Considering the low number of patients enrolled in this study and the lack of more specific data regarding the glycemic control of participants with DM, future studies are needed in order to unequivocally prove the benefit of the antenatal glucocorticoid therapy for fetal lung maturation in pregnant women with DM. It is important to emphasize that this study's findings reflect the local practice and cannot be generalized.

Author contributions

REB designed the research study. AGD and CG collected the data. FF and TS performed the data analysis. AGD and REB performed origibal draft preparation. TS, REB and CG performed the review editing. CB and SDP performed the investigation and validation. FF and SDP performed visualization and funding. All authors read and approved the final manuscript.

Ethics approval and consent to participate

All subjects gave their informed consent for inclusion before they participated in the study. The study was conducted in accordance with the Declaration of Helsinki, and the protocol was approved by the Ethics Committee of Emergency University Hospital of Bucharest (number 73317/02.12.2021).

Acknowledgment

Thanks to all the peer reviewers for their opinions and suggestions.

Funding

This research received no external funding.

Conflict of interest

The authors declare no conflict of interest. REB is serving as one of the Guest editors of this journal. We declare that REB had no involvement in the peer review of this article and has no access to information regarding its peer review. Full responsibility for the editorial process for this article was delegated to MHD.

References

[1] Ministerul Sănătății. Ziua mondială a diabetului, Analiză de situație 2019. 2020. Available at: https://www.dsptimis.ro/promovare/zm_dz_19_analiza.pdf (Accessed: 8 December 2021).

[2] Tsakiridis I, Giouleka S, Mamopoulos A, Kourtis A, Athanasiadis A, Filopoulou D, *et al*. Diagnosis and Management of Gestational Diabetes Mellitus: an Overview of National and International Guidelines. Obstetrical & Gynecological Survey. 2021; 76: 367–381.

[3] Sibai BM, Caritis SN, Hauth JC, MacPherson C, VanDorsten JP, Klebanoff M, *et al*. Preterm delivery in women with pregestational diabetes mellitus or chronic hypertension relative to women with uncomplicated pregnancies. The National institute of Child health and Human Development Maternal-Fetal Medicine Units Network. American Journal of Obstetrics and Gynecology. 2000; 183: 1520–1524.

[4] Barnes-Powell LL. Infants of diabetic mothers: the effects of hyperglycemia on the fetus and neonate. Neonatal Network. 2007; 26: 283–290.

[5] Köck K, Köck F, Klein K, Bancher-Todesca D, Helmer H. Diabetes mellitus and the risk of preterm birth with regard to the risk of spontaneous preterm birth. The Journal of Maternal-Fetal & Neonatal Medicine. 2010; 23: 1004–1008.

[6] Ministerul Sănătății, Comisia de Obstetrică și Ginecologie. Nașterea prematura. 2019. Available at: http://www.ms.ro/wp-content/uploads/2021/01/Anexa-nr.-3-Ghid-privind-na%C8%99terea-%C3%AEnainte-de-termen.docx (Accessed: 8 December 2021).

[7] Tsakiridis I, Mamopoulos A, Athanasiadis A, Dagklis T. Antenatal Corticosteroids and Magnesium Sulfate for Improved Preterm Neonatal Outcomes: a Review of Guidelines. Obstetrical & Gynecological Survey. 2020; 75: 298–307.

[8] Jobe AH, Goldenberg RL. Antenatal corticosteroids: an assessment of anticipated benefits and potential risks. American Journal of Obstetrics and Gynecology. 2018; 219: 62–74.

[9] Agnew EJ, Ivy JR, Stock SJ, Chapman KE. Glucocorticoids, antenatal corticosteroid therapy and fetal heart maturation. Journal of Molecular Endocrinology. 2018; 61: R61–R73.

[10] Sameshima H. Preterm Labor and Delivery. Springer: Singapore. 2020.

[11] Kemp MW, Newnham JP, Challis JG, Jobe AH, Stock SJ. The clinical use of corticosteroids in pregnancy. Human Reproduction Update. 2016; 22: 240–259.

[12] Bonanno C, Wapner RJ. Antenatal corticosteroid treatment: what's happened since Drs Liggins and Howie? American Journal of Obstetrics and Gynecology. 2009; 200: 448–457.

[13] Booker WA, Gyamfi-Bannerman C. Antenatal Corticosteroids. Clinics in Perinatology. 2018; 45: 181–198.

[14] Crowther CA, Ashwood P, Andersen CC, Middleton PF, Tran T, Doyle LW, *et al*. Maternal intramuscular dexamethasone versus betamethasone before preterm birth (ASTEROID): a multicentre, double-blind, randomised controlled trial. The Lancet Child and Adolescent Health. 2019; 3: 769–780.

[15] Amiya RM, Mlunde LB, Ota E, Swa T, Oladapo OT, Mori R. Antenatal Corticosteroids for Reducing Adverse Maternal and Child Outcomes in Special Populations of Women at Risk of Imminent Preterm Birth: A Systematic Review and Meta-Analysis. PLoS ONE. 2016; 11: e0147604.

[16] Tuohy J, Bloomfield FH, Harding JE, Crowther CA. Patterns of antenatal corticosteroid administration in a cohort of women with diabetes in pregnancy. PLoS ONE. 2020; 15: e0229014.

[17] Abdel-Latif ME, Bajuk B, Oei J, Vincent T, Sutton L, Lui K. Does rural or urban residence make a difference to neonatal outcome in premature birth? A regional study in Australia. Archives of Disease in Childhood-Fetal and Neonatal Edition. 2006; 91: F251–F256.

[18] Cnattingius S, Forman MR, Berendes HW, Graubard BI, Isotalo L. Effect of age, parity, and smoking on pregnancy outcome: a population-based study. American Journal of Obstetrics and Gynecology. 1993; 168: 16–21.

[19] Lawlor DA, Mortensen L, Nybo Andersen A. Mechanisms underlying the associations of maternal age with adverse perinatal outcomes: a sibling study of 264 695 Danish women and their

firstborn offspring. International Journal of Epidemiology. 2011; 40: 1205–1214.
[20] American Diabetes Association. Management of Diabetes in Pregnancy: Standards of Medical Care in Diabetes—2020. Diabetes Care. 2020; 43: S183–S192.
[21] Sandu C, Bica C, Salmen T, Stoica R, Bohiltea R, Gherghiceanu F, *et al*. Gestational diabetes-modern management and therapeutic approach (Review). Experimental and Therapeutic Medicine. 2021; 21: 81.
[22] Bryson CL, Ioannou GN, Rulyak SJ, Critchlow C. Association between Gestational Diabetes and Pregnancy-induced Hypertension. American Journal of Epidemiology. 2003; 158: 1148–1153.
[23] Bohîlțea RE, Zugravu CA, Neacsu A, Navolan D, Berceanu C, Nemescu D, *et al*. The prevalence of Vitamin D deficiency and its obstetrical effects. A prospective study on Romanian patients. Revista de Chimie. 2019; 70: 1228–1233.
[24] Weissgerber TL, Mudd LM. Preeclampsia and Diabetes. Current Diabetes Reports. 2015; 15: 9.
[25] Bohiltea RE, Zugravu CA, Nemescu D, Turcan N, Paulet F, Gherghiceanu F, *et al*. Impact of obesity on the prognosis of hypertensive disorders in pregnancy. Experimental and Therapeutic Medicine. 2020; 20: 2423–2428.
[26] O'Malley EG, Reynolds CME, Killalea A, O'Kelly R, Sheehan SR, Turner MJ. Maternal obesity and dyslipidemia associated with gestational diabetes mellitus (GDM). European Journal of Obstetrics & Gynecology and Reproductive Biology. 2020; 246: 67–71.
[27] Ijäs H, Koivunen S, Raudaskoski T, Kajantie E, Gissler M, Vääräsmäki M. Independent and concomitant associations of gestational diabetes and maternal obesity to perinatal outcome: A register-based study. PLoS ONE. 2019; 14: e0221549.
[28] Committee on Obstetric Practice. Committee Opinion No. 713 Summary: Antenatal Corticosteroid Therapy for Fetal Maturation. Obstetrics and Gynecology. 2017; 130: e102–e109.
[29] Gyamfi-Bannerman C, Thom EA, Blackwell SC, Tita AT, Reddy UM, Saade GR, *et al*. Antenatal Betamethasone for Women at Risk for Late Preterm Delivery. New England Journal of Medicine. 2016; 374: 1311–1320.
[30] Melamed N, Chen R, Soiberman U, Ben-Haroush A, Hod M, Yogev Y. Spontaneous and indicated preterm delivery in pregestational diabetes mellitus: etiology and risk factors. Archives of Gynecology and Obstetrics. 2008; 278: 129–134.
[31] Turcan N, Bohiltea RE, Ionita-Radu F, Furtunescu F, Navolan D, Berceanu C, *et al*. Unfavorable influence of prematurity on the neonatal prognostic of small for gestational age fetuses. Experimental and Therapeutic Medicine. 2020; 20: 2415–2422.
[32] Bental Y, Reichman B, Shiff Y, Weisbrod M, Boyko V, Lerner-Geva L, *et al*. Impact of Maternal Diabetes Mellitus on Mortality and Morbidity of Preterm Infants (24–33 Weeks' Gestation). Pediatrics. 2011; 128: e848–e855.
[33] Yeagle KP, O'Brien JM, Curtin WM, Ural SH. Are gestational and type II diabetes mellitus associated with the Apgar scores of full-term neonates? International Journal of Women's Health. 2018; 10: 603–607.
[34] Mitanchez D, Yzydorczyk C, Simeoni U. What neonatal complications should the pediatrician be aware of in case of maternal gestational diabetes? World Journal of Diabetes. 2015; 6: 734.
[35] Yang X, Hsu-Hage B, Zhang H, Zhang C, Zhang Y, Zhang C. Women with Impaired Glucose Tolerance during Pregnancy have Significantly Poor Pregnancy Outcomes. Diabetes Care. 2002; 25: 1619–1624.
[36] Kammana KC, Shakya S, Zhang H. Gestational Diabetes Mellitus and Macrosomia: a Literature Review. Annals of Nutrition and Metabolism. 2015; 66: 14–20.
[37] Garner P, Okun N, Keely E, Wells G, Perkins S, Sylvain J, *et al*. A randomized controlled trial of strict glycemic control and tertiary level obstetric care versus routine obstetric care in the management of gestational diabetes: a pilot study. American Journal of Obstetrics and Gynecology. 1997; 177: 190–195.
[38] Robert MF, Neff RK, Hubbell JP, Taeusch HW, Avery ME. Association between Maternal Diabetes and the Respiratory-Distress Syndrome in the Newborn. New England Journal of Medicine. 1976; 294: 357–360.
[39] Li Y, Wang W, Zhang D. Maternal diabetes mellitus and risk of neonatal respiratory distress syndrome: a meta-analysis. Acta Diabetologica. 2019; 56: 729–740.
[40] Harrison MS, Goldenberg RL. Global burden of prematurity. Seminars in Fetal and Neonatal Medicine. 2016; 21: 74–79.
[41] Behrman A, Butler S. Institute of Medicine (U.S.), and Committee on Understanding Premature Birth and Assuring Healthy Outcomes, Preterm birth: causes, consequences, and prevention. National Academies Press: Washington DC. 2007.