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Antenatal Corticosteroids for Women with Pregestational and Gestational Diabetes: What Do we Do Now?

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Abstract

Background: Antenatal corticosteroids (ACS) treatment, before 34 weeks, has been one of the most important medical progress in the management of preterm births.

One of the main complication of prematurity is respiratory morbidity. This respiratory morbidity is more important for infants born to diabetic women, even at a later gestational age.

For diabetic women at risk of preterm birth between 24 - 34 weeks, it is now established that, pregestational and gestational diabetes is not a contraindication for ACS treatment, because the benefits outweigh the risks [1].

However, when it comes to diabetic women at risk of late preterm birth or having a planned term cesarean birth, there is very little medical evidence and the available guidelines are few and sometimes contradictory.

Aim: 1) To review the maternal and neonatal outcomes after ACS treatment in the late preterm period and before a term cesarean section and to review the specificities of ACS treatment in these periods for diabetic women. 2) To resume the available guidelines relative to the use of ACS administration for women with PGD and GD at risk of delivery in the late preterm period or having a term planned cesarean section.

Methods: An electronic search in the Pubmed, MEDLINE, Embase and Google scholar databases. The references of the articles retrieved were also used, with no limit of time.

Conclusion: ACS administration is recommended for the treatment of diabetic women at risk of preterm birth before 34 weeks. Even though, many studies have found beneficial neonatal outcomes of ACS treatment for women at risk of late preterm delivery or having an early term cesarean section (between 37-38^{6} weeks), diabetic women were mostly excluded from these studies. The safety and benefit of ACS treatment for diabetic women and their infants is not yet established for these indications.

Guidelines concerning ACS treatment for diabetic women are scarce and sometimes contradicting. In general, for women with diabetes, most guidelines recommend using antenatal corticosteroids for the same indications and at the same gestational age as for women without diabetes.

Because of the increasing incidence of diabetes in the population, large prospective controlled trials are necessary to further investigate the neonatal and maternal outcomes, as well as, the possible benefits and safety of ACS administration in later gestation for diabetic women.

Keywords: Antenatal corticosteroids; Gestational diabetes; Pregestational diabetes; Late preterm; Cesarean section

Abbreviations: ACS: Antenatal Corticosteroids; PGD: Pregestational Diabetes; GD: Gestational Diabetes; T1D: Type 1 Diabetes; T2D: Type 2 Diabetes; RDS: Respiratory Distress Syndrome; BMI: Body Mass Index; RR: Relative Risk; CI: Confidence Interval; TTN: Transient tachypnea of the newborn; ALPS: Antenatal Late Preterm Steroids; RCT: Randomized Controlled Trial; BGC: Blood Glucose Concentration; GRADE: Grading of Recommendations Assessment, Development and Evaluation; LOE: Level of Evidence; ACOG: American College of Obstetricians and Gynecologists; NICE: National Institute for Health and Care Excellence; PPROM: Preterm Premature Rupture of Membranes; FIGO: International Federation of Gynecology and Obstetrics; WHO: World Health Organization; NICU: Neonatal Intensive Care Unit; ASTECS: Antenatal Steroids for Term Elective Cesarean Section**;** CNS: Central Nervous System; RCOG: Royal College of Obstetricians and Gynaecologists; SGOC: The Society of Obstetricians and Gynecologists of Canada; SMFM: Society for Maternal-Fetal Medicine; ADIPS: Australasian Diabetes in Pregnancy Society

Introduction

Diabetes during pregnancy can either be pregestational or gestational. Pregestational diabetes (PGD) is present before pregnancy and includes type 1 diabetes (T1D), type 2 diabetes (T2D) and other specific types of diabetes.

T1D occurs mostly during childhood and adolescence. It results from the destruction of the beta cells of the pancreas, leading to insulin deficiency.

T2D is the most common type of diabetes. It occurs mostly during adulthood and is characterized by varying degree of insulin resistance, hyperglycemia and a relative lack of insulin.

The other specific types of diabetes are due to underlying pathologies or conditions, such as, genetic defects, exocrine pancreatic defects or endocrinopathies.

Gestational diabetes (GD) corresponds to a varying degree of glucose intolerance during pregnancy. The screening and diagnostic criteria of GD are still controversial [2]. Women with GD have a nearly ten-fold higher risk of developing T2D later in life compared to women presenting no diabetes during pregnancy [3].

Epidemiology of Diabetes during Pregnancy

Based on a 2019 report of the International Diabetes Federation, 16,8 % of pregnancies are affected by diabetes. 86,4 % of diabetes during pregnancy is represented by GD, while PGD represents 13,4 % of the cases [4].

The prevalence of T1D in the U.S adult population, in 2016, was 0,55 %, while 8,6 % of the U.S adult population had diagnosed T2D [5].

Over the past decades, there has been a constant increase in the prevalence of diabetes in the population, mainly T2D, due to the increase in the prevalence of obesity, the modification of dietary habits and modification of diagnostic threshlolds [6].

As a result, there is an increase in the number of women with diabetes during pregnancy because of the growing proportion of obesity in women in the childbearing age [7].

The incidence and prevalence of GD depends greatly on the population studied and the diagnostic criteria [8]. The prevalence of GD in Europe varies between 2% and 10% [9], while in mainland China, the total incidence of GD is 14,8% [10].

Complications of Diabetes during Pregnancy

An optimal control of the maternal glycemia is essential in order to improve the pregnancy outcomes. However, even with an optimal glycemic control, neonatal morbidity and mortality and perinatal complications remain more important than in the non diabetic population [6].

The fetal complications, result from the hyperglycemia rather than the type of maternal diabetes.

During the first trimester, it is necessary to have an optimal control of maternal glycemia as glucose is teratogenic and there is a strong association between maternal glycemia and congenital malformations [11]. Later in gestation, maternal hyperglycemia, through umbilical transfer of glucose, induces fetal hyperinsulinemia. This hyperinsulinemia is associated with an increased fetal growth rate, large for gestational age, macrosomia, as well as, neonatal hypoglycemia at birth [7].

Maternal complications, on the other hand, tend to differ depending on the type of diabetes. The risk of severe hypoglycemia and retinopathy is more important for women with T1D, while T2D is more often associated with obesity and social deprivation [7].

Table 1 summarizes the maternal, fetal and perinatal complications due to PGD and GD during pregnancy.

Maternal diabetes during pregnancy is also associated with an increase in neonatal respiratory morbidity. Neonates of diabetic women are more likely to suffer from respiratory distress syndrome (RDS), at more advanced gestational age, than infants of non diabetic women [16].

In 2019, a meta-analysis [17] evaluated the association between maternal diabetes and neonatal RDS. This analysis included 20 cohort and 4 case-control studies. The results suggested that maternal DM, including GD and PGD, is associated with an increased risk of neonatal RDS. The pooled OR (odds ratio) risk of neonatal RDS was 1.47 (95% CI 1.24–1.74) with maternal diabetes, 1.57 (95% CI 1.28–1.93) with GD and 2.66 (95% CI 2.06–3.44) with PGD. The gestational age range varied substantially between the included studies, but when adjusted for gestational age, the OR risk of neonatal RDS was still 1.27 (95% CI 0.93 to 1.73, I^2= 86.7, P < 0.001) with maternal diabetes. In this analysis, most of the included studies had adjusted for the potential confounders. However, this meta-analysis has a high heterogeneity. A possible contributing factor is that the diagnostic criteria of neonatal RDS and maternal diabetes among the studies were not completely consistent.

When it comes to infants born to diabetic women, the neonatal respiratory morbidity seems to be more important in case of PGD compared to GD [18]. However, GD remains an independent risk factor for neonatal RDS for late preterm and term births [6,19].

This increased respiratory morbidity is probably due to a combination of multiple factors, namely, the increased incidence of preterm spontaneous and induced births, as well as, the increased risk of cesarean delivery in diabetic women [20]. Furthermore, diabetes is associated with a delay in fetal lung maturation due, namely, to an insufficient and inadequate production of surfactant [21].

Aim of the Study

1)To review the maternal and neonatal outcomes after ACS treatment in the late preterm period and before term cesarean sections and review the specificities of ACS treatment in these periods for diabetic women.

2)To resume the available guidelines relative to the use of ACS administration for women with PGD and GD at risk of delivery in the late preterm period or having a term planned cesarean section.

Methods

The Pubmed, Google scholar, Embase and MEDLINE databases were searched with the terms ‘antenatal corticosteroids’ and ‘late preterm’ or ‘cesarean section’ and ‘gestational diabetes’ or ‘pregestational diabetes’ and ‘guidelines’. When possible, systematic reviews, meta-analysis, randomized controlled trials (RCT), large sized

Table 1: Maternal, fetal and perinatal complications of PGD and GD.

Maternal complications associated with GD	Maternal complications associated with PGD [12]	Maternal complications associated with both GD and GD [12-14]	Fetal and perinatal complications [12-14]
Long term risk of T2D [13,14]	Miscarriage	Hypertensive disorders and preeclampsia	Congenital malformations: heart, CNS (associated with PGD) [14]
Risk of GD recurrence in subsequent pregnancy [14]	Progression of microvascular complications: retinopathy, nephropathy	Preterm labour	Large for gestational age or macrosomia
	Macrovascular complications: myocardal infarction	Infections (e.g pyelonephritis)	IUD/Stillbirth
	Complications related to glycemic control: hypoglycemic episodes.	Polyhydramnios	FGR
		Diabetic ketoacidosis (less frequent in GD) [15]	Prematurity
		Induction of labour or cesarean section	Shoulder dystocia and birth trauma
		Traumatic vaginal delivery and instrumental delivery	Neonatal hypoglycemia
		Post-partum hemorrhage	Hypocalcemia
			Hyperbilirubinemia
			RDS
			Perinatal death
			Long term risk of diabetes, metabolic syndrome, higher BMI [14]

CNS: Central Nervous System IUD: Intra-Uterine Death RDS: Respiratory Distress Syndrome FGR: Fetal Growth Restriction T2D: Type 2 diabetes BMI: Body Mass Index

retrospective studies were studied. The reference lists of the chosen articles were checked to identify cited articles not captured by the electronic search. There was no limit of time applied to the research.

Antenatal corticosteroids therapy for diabetic pregnant women

Women with diabetes during pregnancy tend to receive more ACS treatment. However, it is not clear if it is because of the increased rate of preterm births in these pregnancies or because the neonates are more likely to develop complications after birth [16].

When it comes to the indications of ACS for diabetic pregnant women, it is now well established that in case of a risk of preterm birth between 24 - 34 weeks ACS can be administered [1,22] because the benefits are more important than the potential risks related to the treatment.

The maternal glycemia must be closely monitored after the treatment, since steroids tend to induce an increase in glycemia. If necessary insulin must be initiated or increased, according to an agreed protocol, in order to maintain an optimal glycemic control [1].

Late preterm birth

Late prematurity refers to births occurring between 34^0 and 36^6 weeks. Prematurity is a major health problem and is associated with important neonatal morbidity and mortality. ACS therapy for women at risk of preterm birth before 34 weeks was a major medical progress in order to reduce neonatal morbidity and mortality due to prematurity.

In 2006, a Cochrane review [23] of 21 RCTs evaluated the effects of ACS administration, to women at risk of preterm birth, on the fetal and neonatal morbidity and mortality. This study involved 3885 women and 4269 infants and the gestational age ranged up to 36^6 weeks. This review found an overall reduction of neonatal death (RR (relative risk) 0.69, 95% CI (confidence interval) 0.58 to 0.81), RDS (RR 0.66, 95% CI 0.59 to 0.73), cerebroventricular hemorrhage (RR 0.54, 95% CI 0.43 to 0.69) and necrotizing enterocolitis (RR 0.46, 95% CI 0.29 to 0.74). This review had a large sample size, a good methodology and included only RCTs. However, the method of randomization was unclear or not stated for twelve studies. Furthermore, eight of the included studies allowed weekly repeat courses of corticosteroids in their protocol, which could be a possible source of bias.

When it comes to infants born in the late preterm period, even though they present a lower incidence and severity of neonatal complications, they still have an increased neonatal morbidity compared to term births.

In 2011, a systematic review [24] including 22 cohort studies (2,368,471 late preterm infants and 27,007,204 term infants), tried to evaluate the short and long term morbidity of late preterm infants compared to term infants. Infants born in the late preterm period presented more short term complications, including RDS (RR 17.3, 95% CI 9.8 to 30.6), intraventricular hemorrhage grade I-IV (RR 4.9, 95% CI 2.1 to 11.7), and death < 28 days (RR 5.9, 95% CI 5.0 to 6.9). After the neonatal period, they were more likely to die in the first year (RR 3.7, 95% CI 2.89 to 4.64) and to suffer from cerebral palsy (RR 3.1, 95% CI 2.3 to 4.2). This study evaluated the outcomes on a very large sample and in multiple populations. However, it cannot be excluded that an excess of neonatal morbidity, for the late preterm infants, could be due to the pregnancy complications (preeclampsia, IUGR etc) leading to the premature delivery. A subgroup analysis was not possible because of the limited number of eligible studies. Furthermore, the the late preterms infants were not selected based on the sex, maternal BMI, or mode of delivery, probably explaining why some outcomes had a high heterogeneity (I^2 >75%).

In order to find possible solutions for reducing the neonatal morbidity of late preterm births, the ALPS (Antenatal Late Preterm Steroids) study [25], a multicenter double-blind RCT, tried to determine whether betamethasone, administered to women at risk of late preterm delivery, decreased the risk of neonatal morbidities. Women at risk of preterm birth between 34^0 and 36^5 weeks, were included and 1427 women were assigned to receive betamethasone and 1400 to receive placebo. This study found a significant reduction in the primary outcome (a composite end point of the need for respiratory support within 72 hours after birth and the number of stillbirth or neonatal deaths within 72 hours after delivery), in the treatment group compared to the placebo group (P = 0,02). They also found a significant reduction in the incidence of severe respiratory complications, in the treatment group (P < 0,001) [21]. There was, however, a significative increase in the incidence of neonatal hypoglycemia in the ACS treatment group (p<0,001). This study had a good methodology and few possible sources of bias, but patients with PGDs were excluded.

Many studies have further tried to assess the neonatal outcomes after ACS treatment for women at risk of late preterm delivery. The Saccone et al 2016 systematic review [26] included three RCTs (n = 3200) and evaluated the effectiveness of ACS treatment for women at risk late preterm. They found that infants of mothers who received antenatal betamethasone had a significantly lower incidence of TTN (transient tachypnea of the newborn) (RR 0.72, 95% CI 0.56 to 0.92), severe RDS (RR 0.60, 95% CI 0.33 to 0.94), and use of surfactant (RR 0.61, 95% CI 0.38 to 0.99), but higher neonatal hypoglycemia (RR 1.61, 95% CI 1.38 to 1.87). Most of the outcomes of this review had low heterogeneity (I^2 <10). However, the majority (2800 out of 3200) of the women at risk of late preterm delivery, came from the ALPS study and data lacked on the long term outcomes. Two of the studies excluded diabetic women and one study had only 5 diabetic participants.

In 2021, the Deshmukh et al systematic review [27] including 7 RCTs also evaluated the neonatal outcomes after ACS treatment in the late preterm period. In the ACS treatment group there was a reduced need for respiratory support (RR 0.68, 95% CI 0.47to 0.98, p = 0.04) LOE (level of evidence):Moderate) but a higher risk of neonatal hypoglycemia (RR 1.61 95% CI 1.38 to 1.87, p<0.00001, LOE: High). Furthermore, neonates exposed to ACS had reduced need for resuscitation at birth (RR 0.63, 95% CI 0.42 to 0.95, p = 0.03, LOE: Low). The incidence of RDS, TTN and surfactant therapy did not differ significantly. This review had a robust methodology, a large sample size and used the GRADE (Grading of Recommendations Assessment, Development and Evaluation) guidelines to summarize the level of evidence. However, like in the previous review, the pooled results were largely influenced by the large sample size of the ALPS study and none of the included studies reported long-term developmental follow up.

Over these last few years, several scientific committees have started recommending the use of ACS after 34 weeks. Based on the ALPS study, the ACOG (American College of Obstetricians and Gynecologists) recommended, in 2016, ACS therapy between 34^0 and 36^6 weeks in case of high risk of preterm birth, for women who had received no previous course of ACS [28].

In 2019, the FIGO (International Federation of Gynecology and Obstetrics) recommended a single course of ACS between 34^0 and 36^6 for women at risk of preterm birth within 7 days and who had not previously received corticosteroids [29].

However, when it comes specifically to diabetic pregnant women at risk of late preterm birth, very few studies or guidelines are available in the literature. No prospective trial has studied the potential benefits or risks of ACS in the late preterm period.

In 2016, a systematic review [30] failed to determine the effectiveness and safety of corticosteroids for diabetic women at risk of preterm birth. No eligible studies, namely RCTs or cohort studies, comparing ACS treatment versus placebo or no treatment, were found. Furthermore, many studies on the safety of ACS for reducing adverse neonatal outcomes have excluded diabetic women [23].

The 2018 retrospective cohort study of Krispin et al [31] tried to determine the association between ACS treatment and neonatal complications in diabetic mothers delivering after 34 weeks. The study included 2262 women with singleton pregnancies, diagnosed with GD, receiving ACS before 34^0 weeks and delivering, either in the late preterm period, or at term. The cohort was divided according to gestational age at delivery. 161 mothers delivered in the late preterm period and 30% of them received ACS. Besides a lower rate of nulliparity in the treatment group (p=0,001), there were no other differences in the baseline characteristics compared to the women of the control group. No reduction in respiratory complications was found between the treatment group and the control group, whether delivery occurred in the late preterm period or at term. The strength of this study is that it analyzed specifically diabetic women and was conducted in a large tertiary medical center with consistent management protocols for GD. However, the data precising whether GD was treated by diet or with medication could not be retrieved and the neonatal outcomes could not be adjusted accordingly. Furthermore, the exact time period elapsed between ACS treatment and delivery was not controlled.

Without strong medical evidence, the guidelines available for management of diabetic women at risk of late preterm delivery, are mainly based on expert recommendations.

In 2015, the World Health Organization (WHO) [1] strongly recommended, based 'on very low-quality evidence', to consider ACS after 34 weeks for women with poorly controlled diabetes, if there was laboratory evidence of fetal lung immaturity.

The 2020 RCOG (Royal College of Obstetricians and Gynaecologists) guidelines [22], recommend following the NICE guidance for women with PGD and GD. This means considering ACS after 34 weeks and up to 35^6 weeks in case of a risk of preterm delivery.

The 2018 SOGC (The Society of Obstetricians and Gynecologists of Canada) clinical practice guidelines[32], recommend ACS for women with GD and PGD, at the same dosage, for the same indications and at the same gestational age as non diabetic women. This implies giving one course of ACS, between 24^0 and 34^6 weeks, for women at risk of preterm delivery within the next 7 days. The balance of risks and benefits does not support the routine administration of ACS after 35 weeks. However, ACS can be used between 35^0 and 36^6 weeks only in selected cases, after counseling with the woman and the pediatric team. Screening for gestational diabetes should be postponed for at least seven days after ACS.

The Australian and New Zealand (RANZCOG) guidelines [33] recommend that, in the absence of trials studying ACS use in diabetic patients, the indications for treatment should be the same as in non diabetic patients. ACS therapy can be administered up to 34^6 weeks in case of risk of preterm birth within the next 7 days.

The 2021 SMFM (Society for Maternal-Fetal Medicine) guidelines [34] recommend against the use of late preterm corticosteroids in pregnant women with PGD, given the risk of worsening neonatal hypoglycemia (Grade 1c).

The 2020 ADIPS (Australasian Diabetes in Pregnancy Society) guideline for pre-existing diabetes and pregnancy [35] states that there is lack of evidence for use of ACS therapy after 34 weeks for women with PGD, as these women were excluded from the studies.

Term cesarean section

Cesarean birth is a known risk factor for respiratory morbidity. Labor provides mechanical and hormonal stimuli facilitating fluid resorption from fetal lungs. Infants born by cesarean section before labour are at increased risk of respiratory morbidity because of the absence of these stimuli [36,37].

The Li et al. 2019 meta-analysis [38], evaluated the association between cesarean section and RDS. It included a total of 26 observational (cohort or case–control) studies, (n= 810,454). This analysis found an increased risk of neonatal RDS after cesarean birth [OR of 1.76 (95% CI 1.48–2.09)]. The risk of neonatal RDS was increased for emergency cesarean section [OR 1.85 (95% CI 1.34–2.56)], as well as, elective cesarean section [OR 2.38 (95% CI 1.89–2.99)]. This meta-analysis included a large population and almost all the studies adjusted the potential confounders (gestational age, birth weight, maternal disease etc). However, the influence of ACS could not be analyzed due to the absence of relevant informations. Furthermore, high heterogeneity was found in this meta-analysis, but after excluding studies having a significant impact on the between-study heterogeneity, the results were not substantially changed and heterogeneity was reduced.

Many studies have tried to evaluate whether ACS treatment before a term cesarean section could reduce neonatal respiratory morbidity. A 2018 Cochrane review [39] including four RCTs (3956 women and 3893 neonates), found that prophylactic ACS treatment appeared to decrease the risk of RDS (RR 0.48; 95% CI 0.27 to 0.87; low-quality evidence), TTN (RR 0.43; 95% CI 0.29 to 0.65; low-quality evidence), admission to the NICU for respiratory morbidity (RR 0.42; 95% CI 0.22 to 0.79), and admission to neonatal special care (all levels) for respiratory complications (RR 0.45; 95% CI 0.22 to 0.90; low-quality evidence). ACS treatment also appeared to reduce the length of stay in NICU by 2.70 days (MD -2.70; 95% CI -2.76 to -2.64). The quality of evidence, as assessed using GRADE was low for the outcomes of RDS, TTN and admission to NICU for respiratory morbidity, indicating that the true effect could potentially be substantially different from the estimated effect. Furthermore, the long term outcomes were not reported in the studies, and potential long term harms remain unknown.

When it comes to interventions to reduce respiratory morbidity related to cesarean section, data available in the literature now generally recommends avoiding elective cesarean before 39 weeks of gestation if possible [1,40,41]. Delaying cesarean section is probably the main factor that could reduce respiratory morbidity.

The neonatal respiratory morbidity relative to gestational age at delivery was assessed during the ASTECS (Antenatal Steroids for Term Elective Cesarean Section) trial [42]. This was a multi-center RCT evaluating whether ACS treatment reduced RDS in infants born by elective cesarean section at term. The study included 998 women and 503 were randomized to receive betamethasone prior to cesarean section. Antenatal betamethasone reduced admissions to special care baby units with RDS after elective cesarean section at term (RR 0.46, 95% CI 0.23 to 0.93, P = 0.02). A logistic regression model predicted the probability of admission to special care unit with RDS according to the gestational age at birth. The predicted probability of admission at 37 weeks was 11.4% in the control group vs 5.2% in the treatment group, at 38 weeks 6.2% vs 2.8%, and at 39 weeks 1.5% vs 0.6%, respectively, confirming an important reduction in respiratory morbidity when birth is delayed to 39 weeks gestation.

However, for women with diabetes during pregnancy, delaying cesarean birth is seldom possible. Furthermore, infants born to diabetic women by cesarean section, even at term, are at increased risk of respiratory morbidity, firstly because of the increased risk associated with cesarean birth, but also because diabetes during pregnancy is associated with increased respiratory morbidity [17]. However, the studies evaluating the neonatal outcomes after ACS treatment prior to term cesarean births are rare and of small size.

In 2019, Paul et al [43] conducted a retrospective study to evaluate the neonatal outcomes after ACS treatment for diabetic women, prior to term elective cesarean section. Between 2011 and 2016, 30 women met the inclusion criteria. Each identified women was matched 1:1 to a woman who did not receive ACS, based on ethnicity, emergency or elective cesarean and year of delivery. The percentage of NICU

admission for respiratory complications was significantly lower in the treatment group compared to the control group (3,3 % vs. 20%, P = 0,046). The mean nadir glucose level in babies was significantly lower in the ACS group compared to those in the control group (2.37 mmol/L vs 2.79 mmol/L; P = 0.014). The incidence of neonatal hypoglycemia was, however, non significatively higher in the corticosteroid group compared to the control group (60.0% vs 36.7%, P = 0.07).

Furthermore, a 2020 retrospective study [44] included102 diabetic women who underwent cesarean between 37^0 and 38^6 weeks. 33 women (32.4%) received ACS treatment before cesarean delivery. Neonates of mothers treated with ACS were significatively more admitted to NICU for hypoglycemia (24,2 % vs 4,4 %, P=0,003). RDS, including TTN, was not significatively higher in the treatment group (15.2% vs. 7.2%, P = 0.209).

Another retrospective study [45] included 160 women with PGD between 2010 and 2015, of which 27 (17%) received ACS treatment prior to cesarean section at term. This study found no decrease in respiratory morbidity for women with PGD receiving ACS.

Besides the fact that these retrospective studies all have small sample sizes, the contradicting neonatal respiratory outcomes make these results very difficult to apply to our medical practice.

Very few guidelines are available concerning the administration of ACS before a term cesarean section for women with diabetes.

The 2015 Australian and New Zealand (RANZCOG) guidelines [33] state that ACS can be used 48h prior to planned cesarean birth beyond 34^6 weeks, for women with diabetes during pregnancy or GD, if there is known fetal lung immaturity. If ACS is used, monitor maternal BGC (blood glucose concentration) and treat if elevated.

The 2018 SGOC guidelines [32] recommend ACS for women with GD and PGD, at the same dosage, for the same indications and at the same gestational age as non diabetic women. This implies not to routinely administer ACS therapy to women undergoing pre-labour cesarean section at term gestation (including at 37 and 38 weeks).

The 2020 ADIPS guidelines [35] states that after >37 weeks, ACS therapy should be administered depending on the individual clinical situation, the local guidelines, discussion with the woman and the medical team.

Potential adverse effects of antenatal corticosteroids after 34 weeks

ACS treatment after 34 weeks is associated with potential side-effects. One possible short-term side effect, is neonatal hypoglycemia. Many studies have found an increased risk of neonatal hypoglycemia following ACS administration to women at risk of late preterm birth [25-27].

In the ALPS study [25], the length of hospital stay of the infants with hypoglycemia was, however, not longer compared to those without hypoglycemia, which suggests that the condition was self-limited. Although this seems to be reassuring, neonatal hypoglycemia can be a severe complication associated with long term consequences including neurological damage that may result in mental retardation, developmental delay and recurrent seizure activity. Furthermore, studies tend to show that even transient and treated neonatal hypoglycemia can lead to negative childhood outcomes [46].

Following the ALPS, the Euglycemia after Antenatal Late Preterm Steroids (E-ALPS) Study [47], an ongoing randomized open label trial has for objective to evaluate whether screening for and treatment of steroid-induced hyperglycemia in women treated with betamethasone in the late preterm period can decrease the rate of fetal hyperinsulinemia, and thus, reducing neonatal hypoglycemia in order to improve short-term neonatal outcomes. However, women with PGD and GD are yet again excluded from this study.

The major unknown of ACS treatment in later gestation remains the potential long term side effects. Corticosteroids can have long term adverse effects on the brain and it is now established that it's use in the postnatal period, for the prevention of chronic lung disease, is associated with abnormal neurological development and cerebral palsy. This is compatible with a direct toxic effect of steroids on the developing CNS (Central Nervous System) [48].

Furthermore, in animal studies, exposure to ACS has been associated with a delay in brain growth and development [49-52] and with persistent changes in the hypothalamic–pituitary–adrenal (HPA) axis [53-56].

Later gestation is a critical phase of important neurological development. The long-term follow-up after the ASTECS trial showed that children in the corticosteroids treatment group were more likely to be rated in the lower quartile of academic ability, by their school, at age 8 to 15 [57].

In 2020, a Finnish population-based retrospective cohort study [58] (n=670 097 singleton children), evaluated if ACS treatment was associated with mental and behavioral disorders in children born at term and preterm. The median length of follow-up was 5.8 years. The disorders were diagnosed using the ICD-10 codes (International Statistical Classification of Diseases and Related Health Problems, Tenth Revision). Of the 14 868 (2.22%) ACS treated children, 6730 (45.27%) were born at term and 8138 (54.74%) were born preterm. Exposure to ACS was significantly associated with higher risk of mental and behavioral disorder in the entire cohort of children, (HR (adjusted hazard ratio) 1.33, 95% CI 1.26 to 1.41), as well as, in the term born children (HR, 1.47 [95% CI, 1.36 to 1.69). In the preterm born children, the cumulative incidence rate of mental and behavioral disorder was significantly higher for the ACS treated children, but the HR was not significantly higher (absolute difference, 3.38% [95% CI, 2.95% to 4.87%]; HR, 1.00 [95% CI, 0.92 to 1.09]). These associations persisted within sib-pair comparisons among the term children, suggesting that unmeasured familial confounding factors could not explain these results. However, the birth register used to retrieve information used for the study did not include report of the number or timing of ACS treatments.

When it comes to women with diabetes, ACS treatment is associated with an increase in maternal glycemia and this can result in an increased incidence of neonatal hypoglycemia. The retrospective cohort study of Tuohy et al [59] described the maternal and neonatal glycemic control following ACS administration to women with diabetes in pregnancy. Between 2006-2016, ACS was administered to 647 out of 7317 women with diabetes (8.8%). After an initial course of ACS, the blood glucose concentrations was > 7 mmol/L for 92% women and > 10 mmol/L for 52% of the women. The median peak blood glucose concentration, approximately 10 mmol/L, occurred 9 hours after ACS administration and hyperglycemia lasted about 72 hours. Women with T1D had the highest peak of BGC (13.4 mmol/L) and the highest incidence of hypoglycemia, both before (49%) and after (58%) ACS treatment. Furthermore, infants of women who were hyperglycemic within 24 hours of birth were more likely to develop hypoglycemia (< 2.6 mmol/L, OR 1.51 [95% CI 1.10–2.07], p = 0.01) and severe hypoglycemia (≤ 2.0 mmol/L, OR 2.00 [95% CI 1.41–2.85], p < 0.0001) than babies of non-hyperglycemic mothers. Although the sample size was large, the main limitations of this study are related to its retrospective nature, because many variables could not be controlled, such as, the BGC testing schedules, the steroid administered, the time between ACS administration to birth and this limited the ability of this study to fully assess the effect of ACS treatment on maternal and neonatal glycemia.

Strengths and Limitations

This study gives an overview of the recent literature related to

the benefits and possible risks of ACS treatment in the late preterm period and before a term cesarean section. Futhermore, it treats of the understudied subject of the maternal and neonatal impacts of ACS treatment for diabetic women in the late preterm and at term. Even though, the data and studies in this article have been presented as objectively as possible, the main limitation of this literature review is related to its narrative nature and the various degree of subjectivity related to this research method.

Conclusions

In general, ACS therapy in late preterm and at term remains a controversial subject especially when it concerns women with diabetes. Because of the constantly increasing incidence of diabetes in the population, high quality prospective controlled studies on maternal, neonatal and long-term child outcomes after ACS treatment are essential. Studies should evaluate the incidence of neonatal RDS, neonatal hypoglycemia, maternal hyperglycemia and the optimal post-steroid treatment protocol to maintain maternal euglycemia, as well as, the long-term child neurodevelopmental disorders.

In the meantime, because of the absence of evidence to guide clinical practice, clinicians must consider the individual characteristics of each woman and fetus, such as glycemic control, planned mode of birth, and the risk of maternal complications, when considering ACS treatment.

References

1. WHO. WHO recommendations on interventions to improve preterm birth outcomes. 978 92 4 150898 8. 2015; 98.
2. Benhalima K, Mathieu C, Damm P, Van Assche A, Devlieger R, Desoye G, et al. A proposal for the use of uniform diagnostic criteria for gestational diabetes in Europe: an opinion paper by the European Board & College of Obstetrics and Gynaecology (EBCOG). Diabetologia. 2015; 58:1422-9.
3. Vounzoulaki E, Khunti K, Abner SC, Tan BK, Davies MJ, Gillies CL. Progression to type 2 diabetes in women with a known history of gestational diabetes: systematic review and meta-analysis. BMJ. 2020; 369:1361.
4. IDF. International Diabetes Federation. IDF Diabetes Atlas, 9th edn. Brussels, Belgium: International Diabetes Federation, 2019. [Internet]. 2019.
5. Bullard KM. Prevalence of Diagnosed Diabetes in Adults by Diabetes Type — United States, 2016. MMWR Morb Mortal Wkly Rep [Internet]. 2018; 67.
6. Mortier I, Blanc J, Tosello B, Gire C, Bretelle F, Carcopino X. Is gestational diabetes an independent risk factor of neonatal severe respiratory distress syndrome after 34 weeks of gestation? A prospective study. Arch Gynecol Obstet. 2017; 296:1071-1077.
7. Ali S, Dornhorst A. Diabetes in pregnancy: health risks and management. Postgrad Med J. 2011; 87:417-27.
8. Lawrence RL, Wall CR, Bloomfield FH. Prevalence of gestational diabetes according to commonly used data sources: an observational study. BMC Pregnancy Childbirth. 2019; 19:349.
9. Buckley BS, Harreiter J, Damm P, Corcoy R, Chico A, Simmons D, et al. Gestational diabetes mellitus in Europe: prevalence, current screening practice and barriers to screening. A review. Diabet Med. 2012; 29:844-54.
10. Gao C, Sun X, Lu L, Liu F, Yuan J. Prevalence of gestational diabetes mellitus in mainland China: A systematic review and meta-analysis. J Diabetes Investig. 2019; 10:154-62.
11. Chen C-P. Congenital Malformations Associated with Maternal Diabetes. Taiwan J Obstet Gynecol. 2005; 44:1-7.
12. American College of Obstetricians and Gynecologists' Committee on Practice Bulletins—Obstetrics. ACOG Practice Bulletin No. 201: Pregestational Diabetes Mellitus. Obstet Gynecol. 2018; 132:e228-48.
13. Denney JM, Quinn KH. Gestational Diabetes. Obstet Gynecol Clin North Am. 2018; 45:299-314.
14. Johns EC, Denison FC, Norman JE, Reynolds RM. Gestational Diabetes Mellitus: Mechanisms, Treatment, and Complications. Trends Endocrinol Metab. 2018; 29:743-54.
15. Sibai BM, Viteri OA. Diabetic Ketoacidosis in Pregnancy. Obstet Gynecol. 2014; 123:167-78.
16. Tuohy JF, 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. Li Y, Wang W, Zhang D. Maternal diabetes mellitus and risk of neonatal respiratory distress syndrome: a meta-analysis. Acta Diabetol. 2019; 56:729-40.
18. Kawakita T, Bowers K, Hazrati S, Zhang C, Grewal J, Chen Z, et al. Increased Neonatal Respiratory Morbidity Associated with Gestational and Pregestational Diabetes: A Retrospective Study. Am J Perinatol. 2017; 34:1160-8.
19. Fung GPG, Chan LM, Ho YC, To WK, Chan HB, Lao TT. Does gestational diabetes mellitus affect respiratory outcome in late-preterm infants? Early Hum Dev. 2014; 90:527-30.
20. Remsberg KE, McKeown RE, McFarland KF, Irwin LS. Diabetes in pregnancy and cesarean delivery. Diabetes Care. 1999; 22:1561-7.
21. Gewolb IH, O'Brien J. Surfactant secretion by type II pneumocytes is inhibited by high glucose concentrations. Exp Lung Res. 1997; 23:245-55.
22. RCOG. Guidance for maternal medicine services in the evolving coronavirus (COVID-19) pandemic. 2020; 44.
23. Roberts D, Dalziel SR. Antenatal corticosteroids for accelerating fetal lung maturation for women at risk of preterm birth. Cochrane Database Syst Rev [Internet]. 2006 [cité 19 août 2021]; 3.
24. Teune MJ, Bakhuizen S, Gyamfi Bannerman C, Opmeer BC, van Kaam AH, van Wassenaer AG, et al. A systematic review of severe morbidity in infants born late preterm. Am J Obstet Gynecol. 2011; 205:374.e1-374.e9.
25. Gyamfi-Bannerman C, Thom EA, Blackwell SC, Tita ATN, Reddy UM, Saade GR, et al. Antenatal Betamethasone for Women at Risk for Late Preterm Delivery. N Engl J Med. 2016; 374:1311-20.
26. Saccone G, Berghella V. Antenatal corticosteroids for maturity of term or near term fetuses: systematic review and meta-analysis of randomized controlled trials. BMJ. 2016; 355:i5044.
27. Deshmukh M, Patole S. Antenatal corticosteroids for impending late preterm (34-36+6 weeks) deliveries—A systematic review and meta-analysis of RCTs. PLOS ONE. 2021; 16:e0248774.
28. Committee on Obstetric Practice. Committee Opinion No. 713: Antenatal Corticosteroid Therapy for Fetal Maturation. Obstet Gynecol. 2017; 130:e102-9.
29. Good clinical practice advice: Antenatal corticosteroids for fetal lung maturation. Int J Gynecol Obstet. 2019; 144:352-5.
30. 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. Rubens C, éditeur. PLOS ONE. 2016; 11:e0147604.
31. Krispin E, Hochberg A, Chen R, Wiznitzer A, Hadar E, Borovich A. Neonatal outcome in gestational-diabetic mothers treated with antenatal corticosteroids delivering at the late preterm and term. Arch Gynecol Obstet. 2018; 298:689-95.
32. Skoll A, Boutin A, Bujold E, Burrows J, Crane J, Geary M, et al. No. 364-Antenatal Corticosteroid Therapy for Improving Neonatal Outcomes. J Obstet Gynaecol Can. 2018; 40:1219-39.
33. Antenatal corticosteroids given to women prior to birth to improve fetal, infant, child and adult health: Clinical Practice Guidelines. Auckl N Z Liggins Inst Univ Auckl. 2015; 481.
34. Reddy UM, Deshmukh U, Dude A, Harper L, Osmundson SS. Society for Maternal-Fetal Medicine Consult Series #58: Use of antenatal corticosteroids for individuals at risk for late preterm delivery: Replaces SMFM Statement #4, Implementation of the use of antenatal corticosteroids in the late preterm birth period in women at risk for preterm delivery, August 2016. Am J Obstet Gynecol.

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35. Rudland VL, Price SAL, Hughes R, Barrett HL, Lagstrom J, Porter C, et al. ADIPS 2020 guideline for pre-existing diabetes and pregnancy. Aust N Z J Obstet Gynaecol. 2020; 60:E18-52.

36. Tutdibi E, Gries K, Bücheler M, Misselwitz B, Schlosser RL, Gortner L. Impact of Labor on Outcomes in Transient Tachypnea of the Newborn: Population-Based Study. Pediatrics. 2010; 125:e577-83.

37. Gerten KA, Coonrod DV, Bay RC, Chambliss LR. Cesarean delivery and respiratory distress syndrome: does labor make a difference? Am J Obstet Gynecol. 2005; 193:1061-4.

38. Li Y, Zhang C, Zhang D. Cesarean section and the risk of neonatal respiratory distress syndrome: a meta-analysis. Arch Gynecol Obstet. 2019; 300:503-17.

39. Sotiriadis A, Makrydimas G, Papatheodorou S, Ioannidis JP, McGoldrick E. Corticosteroids for preventing neonatal respiratory morbidity after elective caesarean section at term. Cochrane Database Syst Rev. 2018; 8:CD006614.

40. Tita ATN, Landon MB, Spong CY, Lai Y, Leveno KJ, Varner MW, et al. Timing of elective repeat cesarean delivery at term and neonatal outcomes. N Engl J Med. 2009; 360:111-20.

41. American College of Obstetricians and Gynecologists' Committee on Obstetric Practice, Society for Maternal– Fetal Medicine. Committee Opinion No.677: Antenatal Corticosteroid Therapy for Fetal Maturation. Obstet Gynecol. 2016; 128:e187-194.

42. Stutchfield P, Whitaker R, Russell I. Antenatal Steroids for Term Elective Caesarean Section (ASTECS) Research Team. Antenatal betamethasone and incidence of neonatal respiratory distress after elective caesarean section: pragmatic randomised trial. BMJ. 2005; 331:662.

43. Paul R, Murugesh C, Chepulis L, Tamatea J, Wolmarans L. Should antenatal corticosteroids be considered in women with gestational diabetes before planned late gestation caesarean section. Aust N Z J Obstet Gynaecol. 2019; 59:463-6.

44. Gupta K, Rajagopal R, King F, Simmons D. Complications of Antenatal Corticosteroids in Infants Born by Early Term Scheduled Cesarean Section. Diabetes Care. 2020; 43:906-908.

45. Thevathasan I, Walker SC, Leung L, Unterscheider J, Said J. Antenatal corticosteroid administration for fetal lung maturation prior to elective caesarean section at term in women with pre-gestational diabetes - more harm than good? Am J Obstet Gynecol. 2017.

46. Groom KM. Antenatal corticosteroids after 34 weeks' gestation: Do we have the evidence? Semin Fetal Neonatal Med. 2019; 24:189-96.

47. University of North Carolina, Chapel Hill. Fetal Metabolic Consequences of Late Preterm Steroid Exposure [Internet]. clinicaltrials.gov; 2021. Report No.: NCT03076775.

48. Barrington KJ. The adverse neuro-developmental effects of postnatal steroids in the preterm infant: a systematic review of RCTs. BMC Pediatr. 2001; 1:1.

49. Huang WL, Beazley LD, Quinlivan JA, Evans SF, Newnham JP, Dunlop SA. Effect of corticosteroids on brain growth in fetal sheep. Obstet Gynecol. 1999; 94:213-8.

50. Whitelaw A, Thoresen M. Antenatal steroids and the developing brain. Arch Dis Child Fetal Neonatal Ed. 2000; 83:F154-157.

51. Uno H, Lohmiller L, Thieme C, Kemnitz JW, Engle MJ, Roecker EB, et al. Brain damage induced by prenatal exposure to dexamethasone in fetal rhesus macaques. I. Hippocampus. Brain Res Dev Brain Res. 1990; 53:157-67.

52. Rittenschober-Böhm J, Rodger J, Jobe AH, Kallapur SG, Doherty DA, Kramer BW, et al. Antenatal Corticosteroid Exposure Disrupts Myelination in the Auditory Nerve of Preterm Sheep. Neonatology. 2018; 114:62-8.

53. Kemp MW, Newnham JP, Challis JG, Jobe AH, Stock SJ. The clinical use of corticosteroids in pregnancy. Hum Reprod Update. 2016; 22:240-59.

54. Braun T, Challis JR, Newnham JP, Sloboda DM. Early-life glucocorticoid exposure: the hypothalamic-pituitary-adrenal axis, placental function, and long-term disease risk. Endocr Rev. 2013; 34:885-916.

55. Reynolds RM. Programming effects of glucocorticoids. Clin Obstet Gynecol. 2013; 56:602-9.

56. Moisiadis VG, Matthews SG. Glucocorticoids and fetal programming part 1: Outcomes. Nat Rev Endocrinol. 2014; 10:391-402.

57. Stutchfield PR, Whitaker R, Gliddon AE, Hobson L, Kotecha S, Doull IJM. Behavioural, educational and respiratory outcomes of antenatal betamethasone for term caesarean section (ASTECS trial). Arch Dis Child Fetal Neonatal Ed. 2013; 98:F195-200.

58. Räikkönen K, Gissler M, Kajantie E. Associations Between Maternal Antenatal Corticosteroid Treatment and Mental and Behavioral Disorders in Children. JAMA. 2020; 323:1924-33.

59. Tuohy JF, Bloomfield FH, Crowther CA, Harding JE. Maternal and neonatal glycaemic control after antenatal corticosteroid administration in women with diabetes in pregnancy: A retrospective cohort study. PLOS ONE. 2021; 16:e0246175.