Review Article

Glycemic Management after Antenatal Corticosteroid Therapy

Sanjay Kalra, Bharti Kalra[1], Yashdeep Gupta[2]

Departments of Endocrinology, [1]Obstetrics and Gynecology, Bharti Hospital, Karnal, Haryana, [2]Medicine, Government Medical College and Hospital, Chandigarh, India

Abstract

Antenatal corticosteroids (ACS) are recommended for use in antenatal mothers at risk of preterm delivery before 34 weeks. One common side-effect of these drugs is their propensity to cause hyperglycemia. A PubMed search was made using terms 'steroid,' 'dexamethasone,' 'betamethasone' with diabetes/glucose. Relevant articles were extracted. In addition, important cross-reference articles were reviewed. This review, based upon this literature search, discusses the available evidence on effects on glycemic status as well as management strategies in women with pre-existing diabetes, gestational diabetes mellitus, as well as normoglycemic women after ACS use in pregnancy.

Keywords: Antenatal corticosteroid therapy, Betamethasone, Diabetes, Dexamethasone, Gestational diabetes mellitus, Pregnancy

Address for correspondence: Dr. Sanjay Kalra, Department of Endocrinology, Bharti Hospital, Kunjpura Road, Karnal, Haryana -132 001, India.
E-mail: brideknl@gmail.com

Introduction

Glucocorticoids are drugs, which have multiple effects on carbohydrate, protein, and lipid metabolism, as well as other aspects of homeostasis. They are also potent anti-inflammatory and immunosuppressive molecules. One common side-effect of these drugs is their propensity to cause hyperglycemia. These drugs are used in pregnancy to accelerate lung maturity in the preterm fetus.

Antenatal corticosteroids were first recommended for use in the National Institutes of Health (NIH) Consensus Development Conference statement 1995.[1] Use of glucocorticoids, i.e., dexamethasone or betamethasone, in antenatal mothers at risk of preterm delivery, prevents respiratory distress and lowers the risk of hyaline membrane disease in their preterm infants. Glucocorticoids increase alveolar surfactant, improve pulmonary compliance, and expand maximal lung volume in the fetus. This occurs due to induction of protein synthesis in surfactant-producing type II cells in the fetal lung.[2]

Access this article online

Quick Response Code:

Website: www.najms.org

DOI: 10.4103/1947-2714.127744

Rationale of Antenatal Corticosteroid Treatment (ACS) in Diabetes

The need for ACS in threatened preterm pregnancies is being felt in modern obstetric medicine. In women with diabetes, this need is even more pronounced. Antenatal women with diabetes are at higher risk of experiencing various obstetric and medical complications. Fetal lung maturity is delayed in pregnancies where euglycemia is not achieved. These facts imply that ACS may be required to improve neonatal survival in preterm pregnancies complicated by diabetes. ACS therapy is absolutely contraindicated in systemic maternal infections such as tuberculosis, and advised with caution in chorio-amnionitis.[3] These medical aspects have to be considered before prescribing ACS in immuno-compromised states like uncontrolled diabetes.

Use of antenatal corticosteroid prophylaxis for threatened preterm labor has become more prevalent in recent years. Gestational diabetes is not considered a relative contraindication for ACS. In fact, women with gestational

diabetes were more likely (odds ratio 1.21; 95% confidence interval 1.05-1.40) to receive ACS in a study conducted in British Columbia, Canada.[4]

Points to Ponder

As the prevalence of gestational diabetes mellitus (GDM) increases, queries arise as to the

1. Indications for ACS in pre-existing, overt or GDM complicated by threatened preterm delivery
2. Effects of ACS on glycemia
   - in previously euglycemic antenatal women
   - in women with GDM
   - in women with pre-existing diabetes (T1DM and T2DM)
3. Glycemia monitoring in
   - all women receiving ACS
   - patients with GDM receiving ACS
   - patients with pre-existing or overt diabetes
4. Glycemic management after ACS administration

Answers to these questions can be gleaned from recommendations and guidelines proposed by the National Institutes of Health (NIH), on use of ACS in 1995, and on repeated courses of ACS in 2000;[1,5] the Royal College of Obstetricians and Gynecologists (RCOG) in 2010;[6] the Cochrane reviews on this topic,[7-9] as well as the WAPM.[3] Recent studies on the subject, though few in numbers, also provide valuable guidelines. Yet, some questions still remain unanswered. This review tries to explore the lacunae in our knowledge of ACS in diabetes, and proposes solutions based on the concept of logical empiricism.

Issue 1: Indications for ACS in GDM Complicated by Threatened Preterm Delivery

In general, the indications for ACS are driven by obstetric and perinatal, rather than medical, factors. Indications remain the same, irrespective of glycemic status. The NIH Consensus Development Panel of 1995 firmly conducted that it was reasonable to use ACS in diabetes, though the experts could not find sufficient data for the use of ACS in pregnancy complicated by diabetes.[1]

World Association of Perinatal Medicine (WAPM) clearly recommends ACS in antenatal women with diabetes. It calls for "close monitoring and treatment by an experienced obstetrical team" to guarantee diabetic control" and "to avoid the possibility of severe transient hyperglycemia."[3]

A similar suggestion is made by the Fifth International Workshop – Conference on Gestational Diabetes Mellitus (2007). The recommendation acknowledges that the frequency of preterm delivery is higher in women with untreated GDM. It recommends following normal indications for the use of ACS, albeit with "intensified monitoring of maternal glucose levels" and "temporary addition or increase of insulin doses."[10]

However, the National Institute of Health and Clinical Excellence (NICE) have published a clinical guideline for diabetes in pregnancy that states that 'diabetes should not be considered a contra-indication to antenatal corticosteroids.'[11]

The conventional antenatal corticosteroid regimes: Betamethasone 12 mg IM q24h x 2 doses, or dexamethasone 6 mg IM q12h x 4 doses, can be used in diabetes. Unpublished data from our hospital shows that three doses of betamethasone 8 mg, given at 12 hourly intervals, lead to less hyperglycemia than the conventional dosage regimes. Though the total steroid dose remains the same, the lower boluses of dexamethasone lead to lower glycemic peaks in patients with GDM or pre-existing diabetes.

It must be remembered that strict maternal glycemic control *per se* reduces the incidence of respiratory distress syndrome in neonates of mothers with diabetes.

Suggestion

In consonance with all international guidelines, ideally, all women with threatened preterm should receive ACS as per routine obstetric practice, irrespective of diabetes status.

The decision of prescribing ACS should be individualized, based on the benefit: risk rates in the particular clinical situation. Lack of expertise in managing diabetes, for example, may be a relative contraindication for ACS in borderline patients. The availability of neonatal care will also have a bearing upon obstetric decision making. In doubtful cases, a team-based shared decision-making approach, involving all members of the perinatal care team- the endocrinologist, obstetrician, and neonatologist, should be followed.

In extreme cases, where ACS may jeopardize maternal health, e.g., in diabetic ketoacidosis or fulminant infection, maternal health should take precedence over fetal prophylaxis.

Issue 2: Effects of ACS on Glycemia

Long-term steroid therapy and GDM

The increased risk of GDM receiving long-term glucocorticoid therapy is well-known,[12,13] but the effect

of a few doses of corticosteroids on glucose metabolism is less documented, especially in a cohort of persons already at high risk of glucose intolerance. In general, the glycemic effect of steroids begins about 12 hours after the first dose and lasts up to 5 days.[3]

ACS in women without pre-existing diabetes

In 10 healthy pregnant women volunteers, acting as a control group, betamethasone in a dose of 12 mg twice daily for one day was shown not to induce hyperglycemia. However, this study by Ramirez-Torres *et al*. monitored only fasting and post-prandial blood glucose.[14]

In a retrospective study involving laboratory recorded records of 3396 patients, Fisher *et al*. analyzed the incidence of diagnosed GDM in patients receiving ACS. Patients who received ACS for threatened preterm delivery (n = 50) were more likely to have abnormal one hour post-glucose challenge values (60% vs. 25%, $P < 0.001$) and abnormal 3 hour glucose tolerance tests (23.8% vs. 4.0%; $P < 0.001$%) than controls (n = 1985) who were not exposed to ACS.[15]

In apparently healthy women, though fasting and post-prandial glucose levels may remain normal after ACS, 50 g glucose challenge test may provide false-positive reports (Gurbuz *et al*). Plasma glucose values measured one hour after administration of 50 g glucose were higher at 24 hours after ACS administration, as compared to the tests done prior to ACS, ($P < 0.001$) in non-diabetic women at risk of preterm labor. However, there was no difference observed at 72 hours (P = 0.96) and 7 days (P = 0.99) after ACS therapy. Screening results were positive in 42.5%, 10%, and 5% of subjects, at 24 hours, 72 hours, and 7 days.[16]

In another study, using continuous glucose monitoring (GDM), Refuerzo *et al*. identified a 16% to 33% increase in glucose levels in pregnant women without diabetes, at 20, 44, and 68 hours after receiving the first dose of ACS. A higher risk of 33% to 48% was noticed at the same time periods in woman with diabetes. CGM is thus able to identify short, but significant, episodes of hyperglycemia after ACS, which may be missed with conventional monitoring.[17]

ACS in women with diabetes

In a retrospective study of 55 patients with diabetes who received ACS, the impact on fasting and 2 hour post-prandial glucose was measured. Fasting glucose levels were elevated >95 mg% in over 90% of women on day 2 and day 3 after ACS administration. At least one post-prandial glucose value was elevated (>120 mg %) in 81%-98% of women on days 1 through 3.[18]

Suggestion

There is no recommendation by any international professional body to check blood glucose prior to prescription of ACS. However, we strongly recommend checking casual blood glucose before administering corticosteroids to any person. This is indicated in view of the high prevalence of GDM, and fits well with the concept of targeted screening in high-risk persons. The results also help inform decisions regarding the need for further maternal surveillance, including ketonuria and glycemia, the need for medical nutrition therapy, and the possibility of insulin therapy. Most importantly, this simple, economical investigation helps determine the etiology and temporal profile of hyperglycemia, so that dysglycemia detected later on in pregnancy or the postpartum period is not attributed iatrogenic causes (ACS) by the patient and her family.

Steroid use should warrant more aggressive screening for GDM, above and beyond routine recommendations.[19]

Issue 3: Glycemia Monitoring in Peri-ACS Period

Recommendations for screening for gestational diabetes mellitus are a subject of great controversy. None of the various recommendations specifically suggest screening methods for women receiving ACS.

As described earlier, 50 g glucose challenge test may provide false-positive reports immediately after ACS. Studies imply that screening tests for GDM should not be performed for up to 1 week after ACS administration.[16]

Suggestion

Euglycemic women should undergo screening for GDM as per routine obstetric practice. However, steroid use should warrant more aggressive screening for GDM, above and beyond routine recommendations. Blood glucose estimation must be done prior to administration of ACS. Regular frequent feto-maternal surveillance must be carried out in the patient-ward for at least 5 days after ACS administration.

Frequency and nature of monitoring required will vary with the nature of diabetes. The need for monitoring in various types of diabetes is listed in descending order, as follows: Pre-existing type 1 diabetes mellitus, pre-existing type 2 diabetes mellitus, gestational diabetes mellitus on insulin, and gestational diabetes mellitus on medical nutrition therapy.

Ideal frequency of monitoring in antenatal women with diabetes is a 7 point profile, including 3 pre- meal

estimations, 3 post-meal estimations, and a 3 am value. This is concordant with recommendation for routine management of gestational diabetes mellitus.[10] Urine ketone estimation and continuous glucose monitoring may be considered in select patient populations.

Issue 4: Glycemic Management in Women with Diabetes after ACS Administration

The challenges in management of glycemia after ACS are well documented. No simple, one-size-fits-all solution is available for this clinical challenge. An individualized approach is necessary, because of the wide inter-individual and intra-individual variability noted in degree and duration of hyperglycemia after steroid injections.

The NICE guideline recommends that diabetic women receiving steroids should have additional insulin according to an agreed protocol.[11] The national Indian guidelines on indoor management of diabetes recommend a 20% increase in the dose of insulin in persons with diabetes who receive steroid therapy.[20]

In the study by Ramirez-Torres,[14] patients with GDM, treated by diet alone, required insulin *de novo* in 40% cases, which those already on insulin needed an increase of 39% to 112% in the daily insulin dose. An increased requirement of 26% to 64% was documented in women with pre-existing type 2 diabetes mellitus on insulin therapy. The greatest changes occurred on the 2nd, 3rd, and 4th day after ACS therapy. This finding highlights the need for regular glycemic monitoring during this period, and a proactive increase in insulin doses, if clinically indicated.

In another retrospective study of 55 patients with diabetes who received ACS, insulin had to be started in 11 of 19 women earlier controlled on diet, and in 3 of 6 patients earlier controlled with glyburide.[18] Kaushal *et al*. published a nurse-driven protocol to manage diabetes and prevent hyperglycemia after the use of intramuscular dexamethasone in antenatal women. They continued subcutaneous insulin and diet and added intravenous insulin infusion from the first dexamethasone dose until 12 h after the second. Titration was based on hourly blood glucose measurements, using any of four-graded sliding scales, selected according to the patient's current subcutaneous insulin dose and modified as per blood glucose values. The median amount of supplementary intravenous insulin required was 74 U (range 32-88 U).[21]

A proactive approach to insulin dose modification may help control glycemia after ACS and avoid deleterious effects to both mother and fetus. An increase in dose of 16% to 40% has been recommended by various authors.[18,22]

Suggestion

Medical nutrition therapy should be reinforced in all patients receiving ACS, irrespective of prior glycemic status. High calorie foods should be avoided for up to 5 days after ACS administration.

Insulin therapy may be required for a short period, after ACS therapy, in women who were previously well controlled on medical nutrition therapy. Both the patient and the health care provider should be prepared for such a possibility.

In patients already on insulin, an increase in dosage or a change in insulin regime may be mandated. If glycemic control is not achieved by increasing the dose of insulin by 20-30%, it may be advisable to increase the number of injections per day. This can be done by adding rapid acting insulin by substituting pre-mixed insulin with rapid acting insulin or by changing basal insulin to pre-mixed or basal bolus regime [Table 1]. In rare cases, intravenous insulin may be needed to achieve glycemic control. Indications for intravenous insulin include ketoacidosis, highly uncontrolled glycemia not responding to subcutaneous insulin, and fetal or maternal distress deemed due to hyperglycemia.

Regular glycemic monitoring is necessary with intensive insulin therapy and is the basis of insulin dose adjustment. Hyperglycemia and hypokalemia both, which are side-effects of aggressive insulin therapy, are linked with intrauterine death and must be avoided. Feto-maternal surveillance should continue along with routine obstetric care.

The national Indian guidelines, which recommend a 20% increase in dose, seem a reasonable suggestion. A small subset of patients, however, may require more aggressive up titration.

Summary

ACS has proven benefits for neonatal survival in antenatal women with threatened preterm labor, many of whom may have co-existing diabetes. All women with threatened preterm should receive ACS as per routine obstetric practice irrespective of diabetes status. Exceptions will include medical conditions that may worsen with steroid therapy.

Blood glucose estimation must be done prior to administration of ACS. Regular frequent fetomaternal surveillance must be estimated on indoor basis for at

Table 1: Strategies for glycemic control after antenatal corticosteroid (ACS) therapy

Therapy	Suggested therapy after ACS	
Glycemic status Current Regimen of patient	Well controlled glycemia	Poorly controlled glycemia
Medical nutrition therapy (MNT)	Strict MNT	Rapid acting insulin
Basal Insulin	Dose optimization of basal insulin	Intensify basal insulin to either pre-mixed insulin or basal bolus regime
Pre-mixed insulin	Dose optimization of pre-mixed insulin Addition of rapid acting insulin to pre-mixed insulin: either a Mix — Rapid — Mix or a Rapid- Rapid-Mix regime can be followed with three meals.	Intensify pre-mixed insulin to basal bolus regime Addition of rapid acting insulin to pre-mixed insulin, either a Mix- Rapid — Mix or a Rapid- Rapid-Mix regime can be followed. Intravenous insulin
Basal bolus insulin	Dose optimization Addition of correction doses of rapid acting insulin	Addition of subcutaneous correction doses Intravenous Insulin

MNT = Medical nutrition therapy

least 5 days after ACS administration. Frequency and nature of monitoring required will vary with the nature of diabetes.

Medical nutrition therapy should be reinforced in all patients receiving ACS irrespective of prior glycemic status. Supplementary insulin should be added, using a proactive approach, to minimize the negative impact of hyperglycemia upon mother and fetus. However, individualization of therapy is needed to ensure optimal management.

There is a great need for further research in this important, yet relatively neglected, field of obstetric diabetology.

References

1. Effect of Corticosteroids for Fetal Maturation on Perinatal Outcomes. NIH Consens Statement 1994;12:1-24.
2. Ballard PL, Ballard RA. Scientific basis and therapeutic regimens for use of antenatal glucocorticoids. Am J Obstet Gynecol 1995;173:254-62.
3. Miracle X, Di Renzo GC, Stark A, Fanaroff A, Carbonell-Estrany X, Saling E; Coordinators Of World Associatin of Perinatal Medicine Prematurity Working Group. Guideline for the use of antenatal corticosteroids for fetal maturation. J Perinat Med 2008;36:191-6.
4. Kazem M, Hutcheon JA, Joseph KS. A population-based study of antenatal corticosteroid prophylaxis for preterm birth. J Obstet Gynaecol Can 2012;34:842-8.
5. Antenatal corticosteroids revisited: Repeat courses. NIH Consens Statement 2000;17:1-18.
6. Roberts D, Dalziel SR. Antenatal corticosteroids for accelerating fetal lung maturation for women at risk of preterm birth. Cochrane Database Syst Rev 2006;3:CD004454.
7. Crowther CA, Harding JE. Repeat doses of prenatal corticosteroids for women at risk of preterm birth for preventing neonatal respiratory disease. Cochrane Database Syst Rev 2007;3:CD003935.
8. Brownfoot FC, Crowther CA, Middleton P. Different corticosteroids and regimens for accelerating fetal lung maturation for women at risk of preterm birth. Cochrane Database Syst Rev 2008;4:CD006764.
9. Royal College of Obstetricians and Gynaecologists (RCOG). Antenatal corticosteroids to reduce neonatal morbidity and mortality. London (UK): Royal College of Obstetricians and Gynaecologists (RCOG); 2010 Oct. 13 p. (Accessed August 4, 2013, at http://www.clinicalguidelines.scot.nhs.uk/National%20Guidelines/RCOG%20No7.pdf).
10. Metzger BE, Buchanan TA, Coustan DR, de Leiva A, Dunger DB, Hadden DR, *et al*. Summary and recommendations of the Fifth International Workshop-Conference on Gestational Diabetes Mellitus. Diabetes Care 2007;30 Suppl 2:S251-60.
11. National Institute for Health and Clinical Excellence. Diabetes in pregnancy: Management of diabetes and its complications from pre-conception to the postnatal period. London: NICE, 2008. (Accessed August 4, 2013, at http://www.nice.org.uk/nicemedia/pdf/CG63NICEGuidelineReissue.pdf).
12. Ha Y, Lee KH, Jung S, Lee SW, Lee SK, Park YB. Glucocorticoid-induced diabetes mellitus in patients with systemic lupus erythematosus treated with high-dose glucocorticoid therapy. Lupus 2011;20:1027-34.
13. Yildirim Y, Tinar S, Oner RS, Kaya B, Toz E. Gestational diabetes mellitus in patients receiving long-term corticosteroid therapy during pregnancy. J Perinat Med 2006;34:280-4.
14. Ramírez-Torres MA, Pérez-Monter SE, Espino y Sosa S, Ibargüengoitia-Ochoa F. Effect of betamethasone in blood glucose levels in pregnant diabetic women at risk of preterm birth. Ginecol Obstet Mex 2011;79:565-71.
15. Fisher JE, Smith RS, Lagrandeur R, Lorenz RP. Gestational diabetes mellitus in women receiving beta-adrenergics and corticosteroids for threatened preterm delivery. Obstet Gynecol 1997;90:880-3.
16. Gurbuz A, Karateke A, Ozturk G, Kabaca C. Is 1-hour glucose screening test reliable after a short-term administration of antenatal betamethasone? Am J Perinatol 2004;21:415-20.
17. Refuerzo JS, Garg A, Rech B, Ramin SM, Vidaeff A, Blackwell SC. Continuous glucose monitoring in diabetic women following antenatal corticosteroid therapy: A pilot study. Am J Perinatol 2012;29:335-8.

18. Kreiner A, Gil K, Lavin J. The effect of antenatal corticosteroids on maternal serum glucose in women with diabetes. Open J Obstet Gynecol 2012;2:112-5.
19. Kitzmiller JL, Block JM, Brown FM, Catalano PM, Conway DL, Coustan DR, *et al*. Managing preexisting diabetes for pregnancy: Summary of evidence and consensus recommendations for care. Diabetes Care 2008;31:1060-79.
20. Bajwa SS, Baruah MP, Kalra S, Kapoor MC. Guidelines on Inpatient Management of Hyperglycemia. In: Muruganathan A, editor. Medicine Update. Vol. 23. Association of Physicians of India; 2013. p. 164-9.
21. Kaushal K, Gibson JM, Railton A, Hounsome B, New JP, Young RJ. A protocol for improved glycaemic control following corticosteroid therapy in diabetic pregnancies. Diabet Med 2003;20:73-5.
22. Mathiesen ER, Christensen AB, Hellmuth E, Hornnes P, Stage E, Damm P. Insulin dose during glucocorticoid treatment for fetal lung maturation in diabetic pregnancy: Test of an algorithm [correction of analgoritm]. Acta Obstet Gynecol Scand 2002;81:835-9

How to cite this article: Kalra S, Kalra B, Gupta Y. Glycemic management after antenatal corticosteroid therapy. North Am J Med Sci 2014;6:71-6.
Source of Support: Nil. **Conflict of Interest:** None declared.