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Antenatal corticosteroids and perinatal outcome in late fetal growth restriction: analysis of prospective cohort

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Short title: Antenatal corticosteroids in late FGR

Keywords: antenatal corticosteroids, fetal lung maturation, fetal growth restriction, late preterm

CONTRIBUTION

What are the novel findings of this work?

Our study shows no benefit of antenatal corticosteroids (ACS) for fetal lung maturation in pregnancies complicated by FGR after 32 weeks in a matched control comparison on short term perinatal outcomes.

What are the clinical implications of this work?

This work supports the lack of evidence that ACS should be recommended routinely for late preterm FGR. At present, in order to provide the best management for these pregnancies, it may be necessary to identify if there is a subgroup of FGR that can benefit from ACS in order to maximize the potential benefits, minimizing risks.

ABSTRACT

Objective: The aim of this study is to evaluate the possible role of antenatal administration of corticosteroids for fetal lung maturation on short term perinatal outcomes in late FGR.

Methods: This cohort study is a secondary analysis of a multicenter prospective observational study, the TRUFFLE-2 feasibility study, conducted between 2017 and 2018 in 33 European perinatal centers. We included women with singleton pregnancy from 32+0 to 36+6 weeks of gestation with a fetus considered at risk for FGR, defined as estimated fetal weight (EFW) or abdominal circumference (AC) <10th centile, or umbilico-cerebral ratio (UCR) >95th centile, or a fall of more than 40 centile points in AC measurement from the 20 weeks scan. The primary adverse outcome was a composite of abnormal condition at birth or major neonatal morbidity.

Results: A total of 86 pregnancies who received antenatal corticosteroids (exposed) were matched with non-exposed pregnancies. Both groups were similar regarding gestational age at inclusion (33 weeks), EFW (1673 g) and UCR (0.68), gestational age at delivery (35.5 weeks) and birth weight (1925 g); the presented values are for both groups combined. No significant differences were observed between exposed and non-exposed for composite adverse outcome (28% vs. 24%; p=0.73) or for any of its elements.

Conclusion: The present data do not show a beneficial effect of steroids on short term outcomes in fetuses with late FGR.

INTRODUCTION

Pregnancies affected by fetal growth restriction (FGR) are at increased risk of adverse obstetric outcomes and particularly iatrogenic preterm delivery. Thus, administration of antenatal corticosteroids (ACS) to accelerate fetal lung maturation is the standard of care in order to reduce perinatal morbidity and mortality[1]. However, the available evidence studying specifically FGR fetuses has not been able to confirm that respiratory distress syndrome (RDS) is reduced in FGR newborns after administration of ACS [2-5]. While it is well established that appropriately grown fetuses at risk of preterm birth should be given a single course of ACS because the benefits exceed the risks[1], it is still uncertain whether antenatal steroid exposure is beneficial, neutral or even detrimental in FGR.

Early studies demonstrated that lung growth and surfactant production are accelerated in FGR fetuses in absence of antenatal glucocorticoid treatment [6] probably as a result of the elevated plasma cortisol levels present in FGR fetuses [7]. Moreover, FGR fetuses are more exposed to maternal steroids through the downregulation of placental 11-beta-hydroxysteroid dehydrogenase type II (11-bHSD II), the enzyme that normally prevents maternal cortisol from crossing the placenta [8]. Papers reporting a similar incidence of RDS in FGR and non-FGR babies [5, 9, 10] are in contrast with others showing an increased risk of RDS in FGR newborns [11]. Currently, it is still under debate if ACS are [12] or are not [13] associated with a beneficial reduction in the complications in FGR newborns. Torrance et al. suggested in 2009 that ACS treatment does not affect either mortality or morbidity in FGR fetuses [14]. In FGR animal models, antenatal steroids have been shown to reduce fetal brain growth, alter cerebral blood flow, and cause brain damage [15, 16] raising the question whether antenatal administration of steroids in late FGR fetuses could be detrimental.

Given these premises, we aimed to investigate the role of steroids on perinatal outcome in pregnancies complicated by late FGR in the setting of the TRUFFLE2 Feasibility study, a prospective multicenter observational cohort [17].

METHODS

This was a secondary analysis of a multicenter prospective observational cohort study conducted between 1st April 2017 and 1st July 2018 in 33 European perinatal centers [17]. Briefly, women were eligible if they had a singleton pregnancy from 32^{+0} to 36^{+6} weeks of gestation with a fetus considered at risk for FGR, defined as estimated fetal weight (EFW) or abdominal circumference (AC) <10th centile, or umbilico-cerebral ratio (UCR) >95th centile, or a fall of more than 40 centile points in AC measurement from the 20 weeks scan. The references for EFW, AC and Doppler parameters were based on local charts. In order to be eligible, the fetus had to have positive umbilical artery end-diastolic flow and a normal computerized cardiotocogram (CTG) with a short term variability (STV) of >3.0 msec. Gestational age was calculated from certain menstrual age and/or ultrasound assessment before 22 weeks of gestation. Women were ineligible if there was known, planned or impending delivery based either on maternal obstetric complications, uterine contractions or rupture of membranes, or there was a fetus with known or suspected structural or chromosomal abnormality. Birth weight Z-scores were calculated using the Hadlock fetal weight chart[18]. Data were collected on a secure cloud-based electronic data capture platform (CASTOR EDC, Amsterdam, The Netherlands). The database carried no personal identifiers. Participants and their infants could only be identified using unique study identifiers that were stored in their recruiting center.

The primary adverse outcome was a composite of abnormal condition at birth, major neonatal morbidity or perinatal death. Abnormal condition at birth was defined as at least one of the following: perinatal death, Apgar score <7 at 5 minutes, umbilical artery pH <7.0 or vein pH <7.1, resuscitation with intubation, chest compressions or medication. Major neonatal morbidity was defined as at least one of the following: neurological abnormality (intracranial haemorrhage grade 3 or 4, periventricular leukomalacia grade 2 or 3, encephalopathy, or seizures necessitating anti-epileptic drug treatment); cardio-vascular abnormality (hypotensive treatment, ductus arteriosus treatment, or disseminated coagulopathy); respiratory morbidity (respiratory support for more than 1 week, or mechanical ventilation, meconium aspiration, persistent pulmonary hypertension); or sepsis (clinical sepsis with positive blood culture, necrotizing enterocolitis [Bell's stage 2 or greater], or meningitis).

For the purpose of the current analysis, we identified women who received steroids to improve fetal lung maturation before delivery (exposed), according to each participating institution's local policy or clinician advice. All units considered a single course of steroids if two doses of betamethasone or dexamethasone 12 mg intramuscular were administered with a 24 h interval. Each exposed pregnancy was matched with one who did not receive ACS (non-exposed), based on gestational age at delivery ± 10 days and birth weight ± 150 g.

Groups were compared two-sided for statistical significance by Kruskal-Wallis test or Fisher's exact test, as appropriate. Data are presented as number, percentage (%), or median and interquartile range (IQR) as required. Statistical calculations were performed using SPSS software (version 25; IBM Corp., New York, NY, USA).

RESULTS

Complete delivery and outcome data were available for 856 newborns without major congenital abnormalities. Of these, 97 received a single course of steroids, 83 (86%) received betamethasone, 14 (14%) received dexamethasone, which was given within 2 weeks before delivery in 57 (61%). Repeated courses were not administered. A total of 86 (exposed) pregnancies were matched with 86 non-exposed ones. There were 11 pregnancies who received steroids but could not be matched to a non-exposed one because gestational age at delivery and EFW were too low (Figure 1).

Demographic, obstetric and fetal Doppler velocimetry characteristics of the women included in the cohort are shown in Table 1. Exposed and non-exposed were similar regarding gestational age at inclusion, EFW and UCR, gestational age at delivery and birth weight. The overall median gestational age at inclusion was 33 weeks and EFW was 1673 g. There was no statistically significant difference in composite adverse outcome (exposed 28%, non-exposed 24%). Women who received ACS within 14 days before delivery had, compared to those with an interval of more than 14 days, significantly higher gestational age at steroid administration (34 vs 32 weeks), lower gestational age at delivery (35 vs 37 weeks), and higher rate of composite adverse outcome (39% vs 14%) (Table 1). The eleven women who could not be matched had a significantly lower EFW and higher UCR at inclusion, and lower birth weight and gestational age at delivery than those who were matched. This explains the inability to find a match for these pregnancies.

Women who received steroids had higher obstetric risk (higher age, BMI and more often hypertensive morbidity), were included at an earlier gestational age, had lower EFW and higher UCR, and delivered earlier with lower birth weight associated with a higher rate of composite adverse outcome than women who did not receive antenatal corticosteroids (Table 1).

Delivery details and perinatal outcome of exposed and non-exposed are further specified in Table 2. The median gestational age at delivery was 35 weeks in in both groups. Exposed pregnancies were delivered more frequently by pre-labour caesarean section. No significant differences were observed between exposed and non-exposed for composite adverse outcome (28% vs. 24%; p=0.73) or for any of its elements. When comparing pregnancies who received steroids within 14 days of delivery with their matched non-exposed pregnancies

there was a higher rate of major morbidity and respiratory morbidity in the ACS group, while other parameters were similar (Table S1). A similar comparison in women who received corticosteroids more than 14 days before delivery versus their matched non-exposed showed no statistically significant differences in perinatal and outcome parameters (Table S2). Figure 2 shows the percentage of adverse composite outcome for infants who received antenatal corticosteroids, specified for interval between corticosteroid administration and delivery.

DISCUSSION

Our study showed no benefit of administration of antenatal corticosteroids for fetal lung maturation or other neonatal morbidity in pregnancies complicated by FGR after 32 weeks. Composite adverse outcome and other delivery and neonatal outcomes were similar between exposed and non-exposed pregnancies. Only 11% of the study population received corticosteroids. The decision to administer corticosteroids was left to the individual clinician and apparently guided by the perception of increased perinatal risk. Women who received corticosteroids had a lower gestational age at inclusion, lower EFW and higher UCR than women who did not get steroids.

The present data did not show a beneficial effect of steroids on short term outcomes in a prospectively selected and appropriately FGR phenotyped cohort. The small sample size and the fact that for those women with the highest risk no matched control could be found, represent a limitation given the possibility that a type II error may still be present, and do not allow definitive conclusions to be drawn regarding benefit or disadvantages of giving steroids in FGR. An adequately powered study to explore significantly and clinically meaningful differences in reducing composite adverse outcome from 21 to 10% would require 225 women per intervention arm (90% power, alpha 0.05 and beta 0.1). However, meaningful conclusions from this analysis can be evaluated to generate the research hypothesis. Another limitation is that the evaluation of the effect of steroids on perinatal outcomes was not the aim of the TRUFFLE-2 Feasibility study, which was rather set up to explore best predictors of outcome to investigate in randomized trial the optimal timing of delivery in late FGR [20]. Additionally, receiving corticosteroids less than 14 days before delivery may be associated with a higher obstetric risk and bias results. In this regard, it must be noted that a non-statistically significant but possibly clinically relevant difference in adverse outcome between exposed and non-exposed was observed both with an interval between corticosteroids and delivery <14 days (39% vs 20%) and > 14 days (14% vs 30%). However, as shown in Figure 2, the relationship between interval and outcome seems to be more complex, and our limited sample size does not allow to investigate it any further.

The main strength of our study is that the effects of steroids on perinatal outcomes of late FGR were evaluated in a selected population of late FGR fetuses followed up prospectively until delivery. By matching on birthweight and gestational age at delivery exposed and non-

exposed pregnancies were similar concerning the two most relevant predictors of adverse perinatal outcome.

In the first trial on the effects of steroids in case of preterm birth a non-significant higher fetal mortality was reported in case of severe maternal hypertension and FGR[22] and consequently FGR was excluded from subsequent trials. Therefore, obstetricians must base clinical practice on observational studies only. The present data on short term outcome are in line with several papers showing no significant beneficial effect of steroids in the context of FGR [5, 13, 14, 19]. However, other studies of early preterm FGR observed a reduction of cerebral hemorrhage [20], a reduced risk of RDS, intraventricular hemorrhage and perinatal death [12] or an increase of survival without disability or handicap at 2 years[23] observed following antenatal corticosteroid administration. Only one of these studies targeted late preterm FGR [19], similar to ours. This study did not observe a decrease of respiratory morbidity by ACS. The reported inconsistencies regarding the effect of steroids on neonatal outcomes in normally grown compared to FGR babies may be due to differences in gestational age or duration of exposure at ACS administration, or effects of glucocorticoids on the development of organ systems.

The role of steroids in the appropriately grown late preterm infants has been extensively studied and benefits have been demonstrated[24] However, the possible effect on the subgroup of fetuses affected by FGR is still under debate. It has been postulated that FGR itself may lead to enhanced fetal lung maturation through different mechanisms: chronic intrauterine stress seems to stimulate production of cortisol by the fetal adrenal gland, and the downregulation of placental 11-bHSD II increases the exposition to maternal steroids for these fetuses [7, 14]. If we assume that FGR fetuses are exposed to increased levels of cortisol, we can hypothesize that even a single course of ACS acts like repeated doses, thus explaining why exogenous administration of glucocorticoids may have no additional benefit in FGR fetuses or possibly be detrimental both in short and long term[25,26].

Recent evidence suggests that the use of glucocorticoids in the perinatal period could be associated with adverse effect on neurodevelopmental outcomes [15, 16, 25-27] . It has also been demonstrated that repeated administration of steroids to mothers at risk of preterm birth can adversely affect fetal growth, induce hypertension and reduce brain growth with delayed myelination [5, 15]. A retrospective study from Bitar et al. on 247 pregnancies with FGR or small-for-gestational age fetuses found that ACS in the late preterm period did not significantly

decrease the need for respiratory support in newborns, while the rate of neonatal hypoglycemia significantly increased after exposure to antenatal corticosteroids [19]. However, following the results of the Antenatal Late Preterm Steroids (ALPS) trial [27] the American College of Obstetricians and Gynecologists and the Society of Maternal Fetal Medicine recommended steroid administration for late preterm pregnancies without prior exposure and at risk of delivery within the next 7 days [28]. Fetal growth restriction is a risk factor for iatrogenic preterm birth, making growth restricted infants more likely to be exposed to both early and late preterm steroids, with possibly no or limited benefit and tangible risks.

Our findings highlight the need for studies focusing on the effect of ACS in late preterm FGR. In order to provide the best prenatal management for these pregnancies, it may be necessary to identify whether there is a subgroup of FGR that can benefit from ACS, and if so to evaluate the best timing of this intervention in order to maximize the potential benefits while minimizing risks. Presently, though, we believe that there is insufficient evidence to recommend antenatal corticosteroids to be given routinely in the context of late preterm FGR.

Disclosure

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REFERENCES

1. Mcgoldrick E, Stewart F, Parker R, Dalziel SR. Antenatal corticosteroids for accelerating fetal lung maturation for women at risk of preterm birth. *Cochrane Database Syst Rev* 2020; **12**: CD004454.
2. Piazze JJ, Maranghi L, Nigro G, Rizzo G, Cosmi EV, Anceschi MM. The effect of glucocorticoid therapy on fetal lung maturity indices in hypertensive pregnancies. *Obstet Gynecol* 1998; **92**: 220–225.
3. Soregaroli M, Bonera R, Danti L, Dinolfo D, Taddei F, Valcamonico A, Frusca T. Prognostic role of umbilical artery Doppler velocimetry in growth-restricted fetuses. *J Matern Fetal Neonatal Med* 2002; **11**: 199–203.
4. Sterne G, Shields LE, Dubinsky TJ. Abnormal fetal cerebral and umbilical Doppler measurements in fetuses with intrauterine growth restriction predicts the severity of perinatal morbidity. *J Clin Ultrasound* 2001; **29**: 146–151.
5. Torrance HL, Mulder EJ, Brouwers HA, Van Bel F, Visser GH. Respiratory outcome in preterm small for gestational age fetuses with or without abnormal umbilical artery Doppler and/or maternal hypertension. *J Matern Fetal Neonatal Med* 2007; **20**: 613–621.
6. Gross TL, Sokol RJ, Wilson MV, Kuhnert PM, Hirsch V. Amniotic fluid phosphatidylglycerol: a potentially useful predictor of intrauterine growth retardation. *Am J Obstet Gynecol* 1981; **140**: 277–281.
7. Economides DL, Nicolaides KH, Linton EA, Perry LA, Chard T. Plasma cortisol and adrenocorticotropin in appropriate and small for gestational age fetuses. *Fetal Ther* 1988; **3**: 158–164.
8. McTernan CL, Draper N, Nicholson H, Chalder SM, Driver P, Hewison M, Kilby MD, Stewart PM. Reduced placental 11beta-hydroxysteroid dehydrogenase type 2 mRNA levels in human pregnancies complicated by intrauterine growth restriction: an analysis of possible mechanisms. *J Clin Endocrinol Metab* 2001; **86**: 4979–4983.
9. Friedman SA, Schiff E, Kao L, Sibai BM. Neonatal outcome after preterm delivery for preeclampsia. *Am J Obstet Gynecol* 1995; **172**: 1785–1788.

10. Tyson JE, Kennedy K, Broyles S, Rosenfeld CR. The small for gestational age infant: accelerated or delayed pulmonary maturation? Increased or decreased survival? *Pediatrics* 1995; **95**: 534–538.

11. Mcintire DD, Bloom SL, Casey BM, Leveno KJ. Birth weight in relation to morbidity and mortality among newborn infants. *N Engl J Med* 1999; **340**: 1234–1238.

12. Bernstein IM, Horbar JD, Badger GJ, Ohlsson A, Golan A. Morbidity and mortality among very-low-birth-weight neonates with intrauterine growth restriction. The Vermont Oxford Network. *Am J Obstet Gynecol* 2000; **182**: 198–206.

13. Elimian A, Verma U, Canterino J, Shah J, Visintainer P, Tejani N. Effectiveness of antenatal steroids in obstetric subgroups *Obstet Gynecol* 1999; **93**: 174–179.

14. Torrance HL, Derks JB, Scherjon SA, Wijnberger LD, Visser GH. Is antenatal steroid treatment effective in preterm IUGR fetuses? *Acta Obstet Gynecol Scand* 2009; **88**: 1068–1073.

15. 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**: 213–218.

16. Miller SL, Chai M, Loose J, Castillo-Meléndez M, Walker DW, Jenkin G, Wallace EM. The effects of maternal betamethasone administration on the intrauterine growth-restricted fetus. *Endocrinology* 2007; **148**: 1288–1295.

17. Stampalija T, Thornton J, Marlow N, Napolitano R, Bhide A, Pickles T, Bilardo CM, Gordijn SJ, Gyselaers W, Valensise H, Hecher K, Sande RK, Lindgren P, Bergman E, Arabin B, Breeze AC, Wee L, Ganzevoort W, Richter J, Berger A, Brodszki J, Derks J, Mecacci F, Maruotti GM, Myklestad K, Lobmaier SM, Prefumo F, Klaritsch P, Calda P, Ebbing C, Frusca T, Raio L, Visser GHA, Krofta L, Cetin I, Ferrazzi E, Cesari E, Wolf H, Lees CC; TRUFFLE-2 Group. Fetal cerebral Doppler changes and outcome in late preterm fetal growth restriction: prospective cohort study. *Ultrasound Obstet Gynecol* 2020; **56**: 173–181.

18. Hadlock FP, Harrist RB, Martinez-Poyer J. In utero analysis of fetal growth: a sonographic weight standard. *Radiology* 1991; **181**: 129–133.

19. Bitar G, Merrill SJ, Sciscione AC, Hoffman MK. Antenatal corticosteroids in the late preterm period for growth-restricted pregnancies. *Am J Obstet Gynecol MFM* 2020; **2**: 100153.

20. Spinillo A, Ometto A, Bottino R, Piazzi G, Iasci A, Rondini G. Antenatal risk factors for germinal matrix hemorrhage and intraventricular hemorrhage in preterm infants. *Eur J Obstet Gynecol Reprod Biol* 1995; **60**: 13–19.

21. Mylrea-Foley B, Thornton JG, Mullins E, Marlow N, Hecher K, Ammari C, Arabin B, Berger A, Bergman E, Bhide A, Bilardo C, Binder J, Breeze A, Brodszki J, Calda P, Cannings-John R, Černý A, Cesari E, Cetin I, Dall'Asta A, Diemert A, Ebbing C, Eggebø T, Fantasia I, Ferrazzi E, Frusca T, Ghi T, Goodier J, Greimel P, Gyselaers W, Hassan W, Von Kaisenberg C, Kholin A, Klaritsch P, Krofta L, Lindgren P, Lobmaier S, Marsal K, Maruotti GM, Mecacci F, Myklestad K, Napolitano R, Ostermayer E, Papageorghiou A, Potter C, Prefumo F, Raio L, Richter J, Sande RK, Schlembach D, Schleußner E, Stampalija T, Thilaganathan B, Townson J, Valensise H, Visser GH, Wee L, Wolf H, Lees CC. Perinatal and 2-year neurodevelopmental outcome in late preterm fetal compromise: the TRUFFLE 2 randomised trial protocol. *BMJ Open* 2022; **12**: e055543.

22. Liggins GC, Howie RN. A controlled trial of antepartum glucocorticoid treatment for prevention of the respiratory distress syndrome in premature infants. *Pediatrics* 1972; **50**: 515–525.

23. Schaap AH, Wolf H, Bruinse HW, Smolders-De Haas H, Van Ertbruggen I, Treffers PE. Effects of antenatal corticosteroid administration on mortality and long-term morbidity in early preterm, growth-restricted infants. *Obstet Gynecol* 2001; **97**: 954–960.

24. Hodyl NA, Crawford TM, Mckerracher L, Lawrence A, Pitcher JB, Stark MJ. Antenatal steroid exposure in the late preterm period is associated with reduced cord blood neurotrophin-3. *Early Hum Dev* 2016; **101**: 57–62.

25. Chang YP. Evidence for adverse effect of perinatal glucocorticoid use on the developing brain. *Korean J Pediatr* 2014; **57**: 101–109.

26. Modi N, Lewis H, Al-Naqeeb N, Ajayi-Obe M, Doré CJ, Rutherford M. The effects of repeated antenatal glucocorticoid therapy on the developing brain. *Pediatr Res* 2001; **50**: 581–585.

27. Gyamfi-Bannerman C, Thom EA, Blackwell SC, Tita ATN, Reddy UM, Saade GR, Rouse DJ, MD, McKenna DS, Clark EAS, Thorp JM, Chien EK, Peaceman, Gibbs RS, Swamy GK, Norton ME, Casey BM, Caritis SN, Tolosa JE, Sorokin Y, VanDorsten JP, Jain L. Antenatal corticosteroids for women at risk of late preterm delivery. *N Engl J Med* 2016; **374**: 1311–1320.

28. Reddy UM, Deshmukh U, Dude A, Harper L, Osmundson SS, Pubs@Smfm.Org SFM-FMSEA. 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* 2021; **225**: B36–B42.

FIGURE LEGENDS

Figure 1: Flowchart of the study cohort.

Figure 2: Percentage of adverse composite outcome for infants who received antenatal corticosteroids, specified for interval between corticosteroid administration and delivery. Number of infants in each week shown in the bars (total 97).

Table 1. Demographic, obstetric and Doppler variables in the study cohort, with specification for women with an interval between corticosteroids and delivery of <14 days, or a longer interval

	Exposed (n=86)				Non-exposed (n=86)	P2#	ACS Not matched (n=11)	P3#	NO ACS* (n=759)	P4#
	Interval <14 days (n=49)	Interval ≥ 14 days (n=37)	P1#	All						
Maternal age	33 .0 (29.5-37.0)	32.0 (28.5-34.0)	0.26	32 (29-36)	32 (28-36)	0.35	33.0 (28.0-35.0)	0.73	31 (28-35)	**0.03**
Nulliparous	32 (65%)	24 (65%)	1.00	56 (65%)	51 (59%)	0.53	9 (82%)	0.39	459 (61%)	0.23
Smoking	1 (2%)	4 (11%)	0.21	5 (6%)	9 (11%)	0.40	0 (---)	0.92	63 (9%)	0.65
Body mass index (kg/m^2)	24.1 (21.0-29.0)	24.2 (19.9-27.1)	0.26	24.2 (20.8-27.6)	22.5 (20.4-25.4)	0.25	24.2 (22.4-26.9)	0.38	22.3 (20.2-25.4)	**0.01**
Pregnancy-induced hypertension	20 (41%)	14 (38%)	0.82	34 (40%)	34 (40%)	1.00	7 (64%)	0.13	78 (10%)	**0.00**
Gestational age at inclusion (weeks)	33.4 (32.4-34.7)	33.0 (32.4-34.2)	0.52	33.1 (32.4-34.5)	33.3 (32.4-34.6)	0.97	32.3 (32.1-32.7)	**0.02**	34.1 (32.9-35.6)	**0.00**
Estimated fetal weight (g)	1684 (1439-1922)	1584 (1377-1899)	0.45	1673 (1392-1905)	1634 (1462-1892)	0.78	1331 (1252-1405)	**0.00**	1920 (1668-2169)	**0.00**
Umbilico-cerebral ratio	0.69 (0.53-0.83)	0.66 (0.47-0.84)	0.73	0.68 (0.51-0.83)	0.62 (0.51-0.75)	0.22	1.02 (0.75-1.95)	**0.00**	0.55 (0.47-0.66)	**0.00**
Gestational age at Corticosteroids	34.4 (33.7-35.8)	31.9 (30.2-33.2)	**0.00**	33.8 (32.2-35.3)	---	---	32.1 (31.3-32.3	0.00	---	---
Corticosteroids days pre-delivery	4 (3-7)	28 (20-45)	**0.00**	8 (3-25)	---	---	10 (2-15)	0.31	---	---

Gestational age at delivery	35.3 (34.2-36.4)	36.9 (34.8-37.8)	**0.01**	35.5 (34.4-37.0)	35.9 (34.9-37.0)	0.34	33.0 (32.3-33.9	**0.00**	38.3 (37.1-39.3)	**0.00**
Birth weight	1880 (1720-2090)	2020 (1760-2250)	0.16	1925 (1714-2200)	1948 (1718-2170)	0.91	1220 (1165-1300)	**0.00**	2544 (2250-2820)	**0.00**
Birth weight Z-score	-2.3 (-2.7 to -1.7)	-2.6 (-3.0 to -2.0)	0.27	-2.5 (-2.9 to -1.8)	-2.6 (-3.0 to -2.0)	0.46	-3.5 (-4.1 - -3.3)	**0.00**	-1.9 (-2.4 to -1.4)	**0.00**
Composite adverse outcome	19 (39%)	5 (14%)	**0.01**	24 (28%)	21 (24%)	0.73	8 (73%)	**0.01**	61 (8%)	**0.00**

Data are given as median (interquartile range) or n (%).

Fisher Exact Test or Kruskal-Wallis Test; P1: 49 exposed interval <14 days versus 37 non-exposed ≥ 14 days in cases; P2: 86 total exposed versus 86 non-exposed; P3: 86 exposed matched versus 11 exposed not matched; P4: 759 complete study cohort except women with corticosteroids versus 97 women with corticosteroids. (p 0.00 = p<0.01)

* Includes controls

Table 2. Delivery details and perinatal outcome in the study cohort.

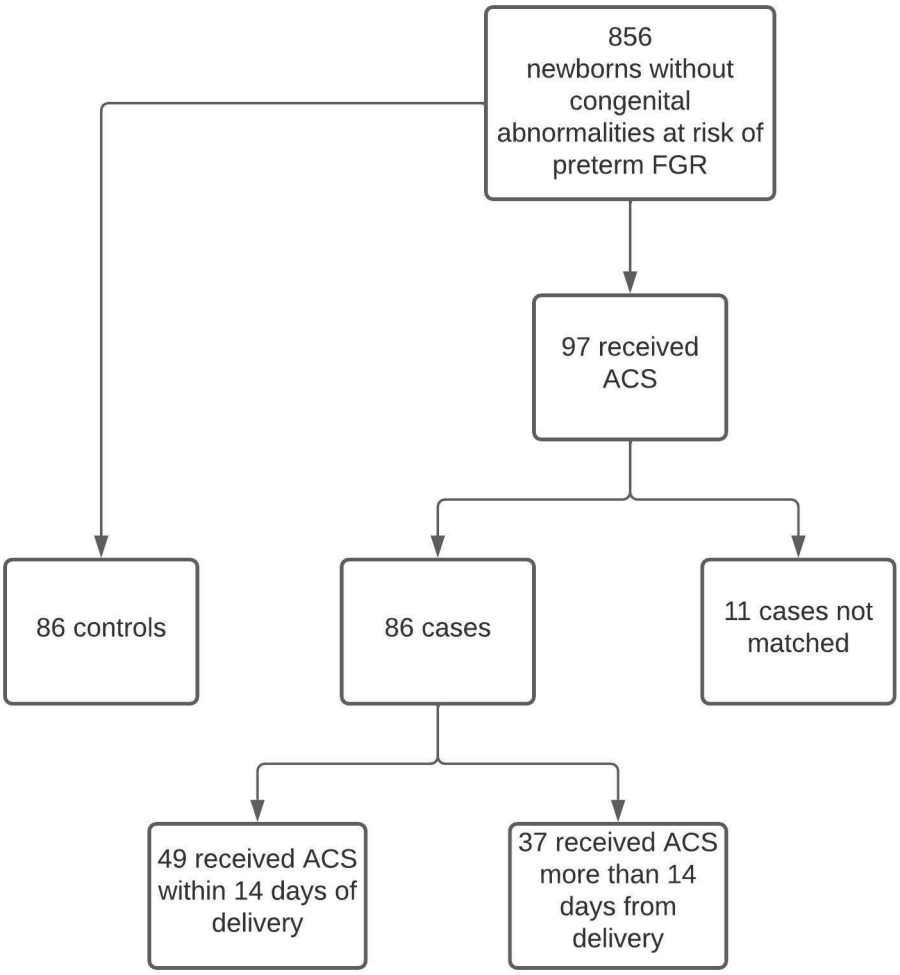
	Exposed (n=86)	Non-exposed (n=86)	P#
Mode of delivery			
Spontaneous labour, vaginal delivery	4 (5%)	14 (12%)	**0.01**
Spontaneous labour, delivery by CS	11 (13%)	3 (4%)	
Induction, vaginal delivery	12 (14%)	17 (20%)	
Induction, delivery by CS	4 (5%)	11 (13%)	
Pre-labour CS	55 (64%)	41 (48%)	
Indication for pre-labour CS			
Fetal (cCTG, Doppler, FGR)	30 (55%)	17 (42%)	0.40
Maternal	11 (20%)	9 (22%)	
Other	14 (26%)	15 (37%)	
Perinatal outcome			
Gestational age at delivery (weeks)	35.5 (34.4-37.0)	35.9 (34.9-37.0)	0.34
Birth weight (g)	1925 (1714-2200)	1948 (1718-2170)	0.91
Birth weight Z-score	-2.5 (-2.9 to -1.8)	-2.6 (-3.0 to -2.0)	0.46
Male sex	39 (45%)	38 (44%)	1.00
Abnormal condition at birth	6 (7%)	6 (7%)	1.00
Major neonatal morbidity*	23 (27%)	18 (21%)	0.47
Cerebral morbidity	0	0	---
Cardiovascular morb.	2 (2%)	4 (5%)	0.68
Infection/sepsis	4 (5%)	3 (4%)	1.00
Respiratory morbidity	20 (23%)	11 (13%)	0.11
Resp. support <1st wk	16 (19%)	8 (9%)	0.12
Resp. support after 1st wk	0 (---)	0 (---)	---
Mechanical ventilation	2 (2%)	0 (---)	0.50
RDS	7 (8%)	3 (4%)	0.33
Other resp. morbidity	1 (1%)	1 (1%)	1.00
Composite adverse outcome	24 (28%)	21 (24%)	0.73

Data are given as median (interquartile range) or n (%).

CS: Cesarean section

* Multiple diagnoses possible

Fisher Exact Test or Kruskal-Wallis Test



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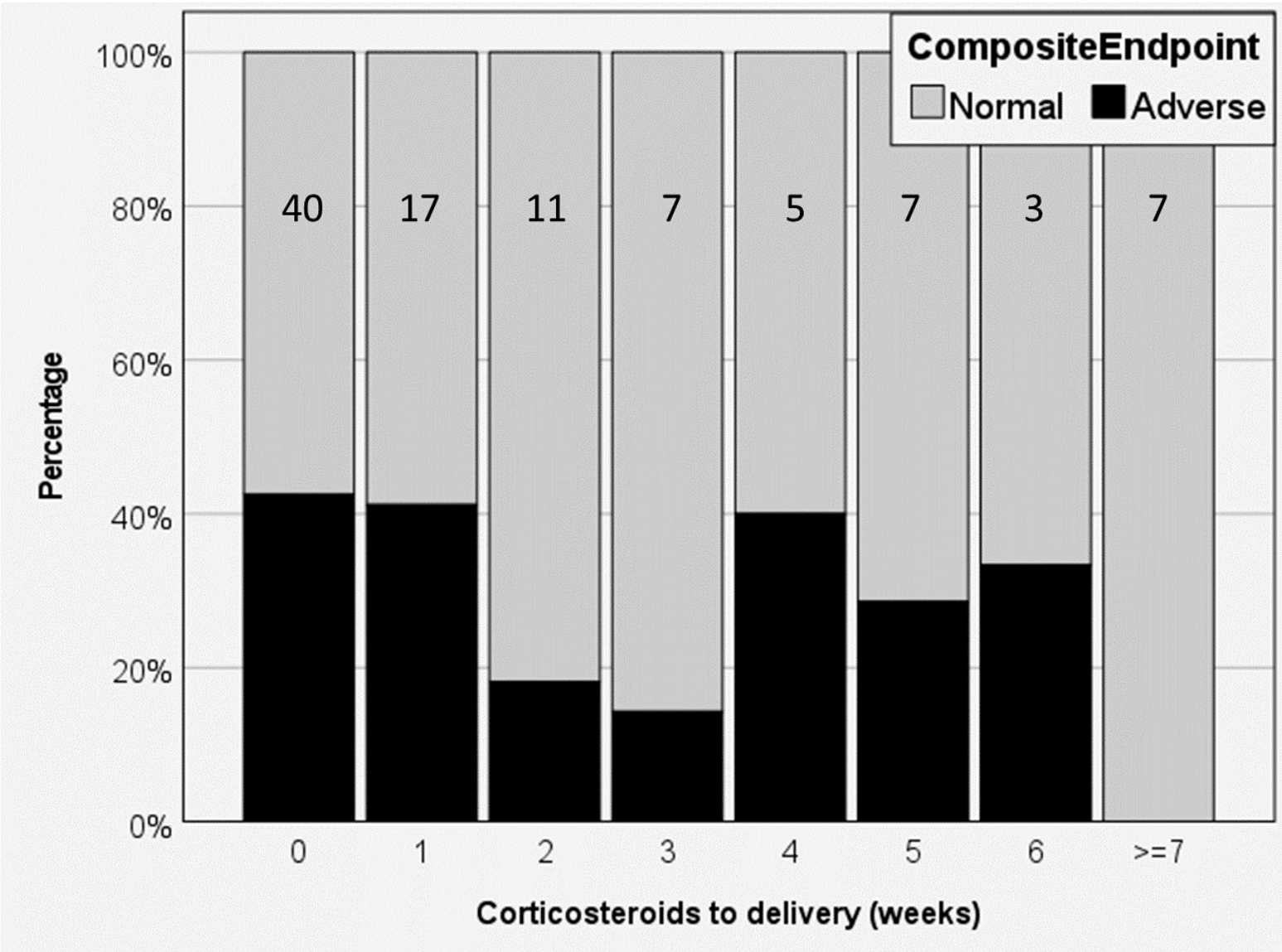

UOG-2022-0568.R1_Figure_2.png