Journal of Paediatrics and Neonatal Disorders
Volume 9 | Issue 1
ISSN: 2456-5482

Research Article Open Access

In Utero Exposure to Steroids and Neonatal Adrenal Insufficiency: A Retrospective Study

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Citation: Khubaib Ahmed, Umberto Piaggio (2024) In Utero Exposure to Steroids and Neonatal Adrenal Insufficiency: A Retrospective Study, J Paedatr Neo natal Dis 9(1): 103

Received Date: October 20, 2024 **Accepted Date:** November 20, 2024 **Published Date:** November 25, 2024

Abstract

Background: Maternal steroid use carries a theoretical risk for neonatal adrenal insufficiency (AI). Most of neonatal units do not recommend short synacthen test (SST) to check AI in babies who were exposed to steroids in utero. Two local units in Yorkshire recommend SST based on certain criteria. One unit uses antenatal dose thresholds of 7.5 mg/day equivalent prednisolone for≥ 28 days while another uses 5 mg/day equivalent prednisolone for same duration as indication for SST.

Aim: To explore the relationship between antenatal steroid use and neonatal AI based on dose and duration set in local guidelines.

Method: Retrospective study in two centres. Cohort identified from laboratory data for SST of babies who met criteria. Results included cortisol levels at 0-minute, 30 and 60 minutes post stimulation. Data review carried out for dose, duration of steroid exposure, symptoms, and the test outcome. Analysis done for correlation between dose, duration of steroid exposure and test results.

Result: Fifty-nine (59) patients identified with an average dose 19.7 mg prednisolone equivalent, and average exposure of 173 days. Forty-eight (48) with full data included in final analysis. Five had abnormal SST, none had clinical symptoms. No statistically significant correlation found between dose or duration of exposure cortisol levels on SST results.

Conclusion: The dose and duration of in utero steroid exposure does not correlate with test outcomes. None of the cohort had clinical AI symptoms. The study recommendation is to avoid SST in term babies born exposed to steroids in utero unless clinically evident.

Keywords: Neonatal Adrenal Insufficiency; Iatrogenic Adrenal Suppression; Antenatal Steroids

Introduction

The effect of medications used during pregnancy on foetus and new-bon baby has always been a subject of interest in medical practice.

Steroids are type of medication that is widely used. It is a synthesized form of the naturally occurring glucocorticoids produced by the adrenal gland under regulation of hypothalamic pituitary axis (HPA).

Physiologically, in the hypothalamus- the paraventricular nucleus- the Corticotrophin-releasing hormone (CRH) is released which in turn stimulates adrenocorticotrophic hormone (ACTH) production from the pituitary glands. ACTH stimulates adrenal cortex to produces cortisol. Levels of cortisol in blood feeds back to receptors in the pituitary and hypothalamus to regulate its secretion [1].

What regulates steroid transport to foetus? Maternal steroid cannot normally reach the foetus in high amounts due to oxidative action of the enzyme 11beta hydroxysteroid dehydrogenase two (11 BHSD2) [2]. This enzyme is produced by placenta which converts cortisol to cortisone, an inactive form. Betamethasone and dexamethasone however are exception, both cross placenta and not fully metabolised by 11BHSD, thus used for foetal indications e.g., enhancing foetal lung maturation in imminent preterm delivery [3].

Theoretically this enzyme could get saturated with higher doses of steroids and/or secondary to prolonged exposure, i.e., consumed. This means, higher amounts of steroids can bypass the enzyme action into baby's circulation. Delivery and abrupt cessation of exogenous steroid (without allowing for gradual hormonal and signalling adaptation) may result in adrenal suppression which can lead to adrenal crisis and potential death [4]. This theory has prompted further exploration for clinical and biochemical evidence which remains controversial to date [5].

Two local neonatal units in south Yorkshire have been using guidelines that test babies born to mother on steroids by performing short synacthen test (SST). SST is performed by checking cortisol level at 0 minute then injecting baby with adrenocorticotropic hormone (ACTH) to stimulate further production of cortisol. Following injection of ACTH, cortisol is measured at 30 minutes and 60 minutes. A response of greater or equal to 430nmol/l and an increment of >200 nmol/l from baseline would be considered appropriate to pass the test (i.e., no adrenal suppression). The guidelines in place use specific cut off at which baby will qualify for the test. This cut off has been decided pragmatically as supraphysiological dose that could affect baby's adrenal gland. One centre is using a cut off antenatal steroid dose of 7.5 mg per day (prednisolone equivalent) for more than or equal 28 days, whilst the other unit uses 5 mg per day (prednisolone equivalent) for same duration [6, 7].

Aim of the Study

This study aims to compare the efficiency of local guidelines in identification of Neonatal adrenal insufficiency, following antenatal exposure to maternal steroid. It also aims to describe the characteristics and number of cases screened by each unit. The description includes the duration and dose of maternal steroids, symptomatology as well as results of neonatal SST.

This is to be able to describe more accurately a potential threshold at which antenatal steroids, either by dose or duration, affect the new-born adrenal gland.

Methodology

Study design: The study is a retrospective cohort study conducted on two centres.

Patients were identified from laboratory data of term babies who had SST over the last 8 years across two large units within south Yorkshire region. The two units combined are looking after the health and care of one and half million people [8].

Inclusion criteria: We included only those who had SST secondary to maternal steroid use. Term babies-with gestation age thirty--seven weeks and above- who had no intrauterine growth restriction (IUGR), had no confirmed or suspected underlying metabolic or endocrine condition.

Exclusions: All preterm babies (less than thirty-seven weeks) were excluded. Babies who were born with suspected congenital conditions were excluded to avoid any confusion in the results that could be related to these conditions rather than adrenal suppression.

Ethical approval: Local approval for service evaluation (SE) was granted based on local standards set by audit/governance teams in both centres. Following SE approval, Ethical approval for the study was granted from University of Leeds ethics committee (UoL approval June 2022).

Up until the first half of 2018, babies born to mothers on steroids in one of the study centres used to undergo three random cortisols levels eight hours apart. The guidelines then stated if cortisol levels were normal, then patient will be considered as having adequate response. If cortisol levels are abnormal then patient will undergo short synacthen test and will be discussed with endocrinology team. Some of the patients went through this pathway in 2018 and before, for that reason those patients were excluded form the study data as the study is based on current guideines which use SST as gold standard without random cortisol levels. this exclusion led the data collection to be limited to five years period (form 2018 up to 2022).

Setting of the study: The study has been conducted as service evaluation in two separate centres. Both units use a similar pathway on their guidelines but use a different cut off/threshold for screening. In one centre, the cut off is 7.5 mg/day prednisolone equivalent for more than or equal 28 days, while in the second centre it is 5 mg/day for same duration. Both units use standard dose short synacthen test of (145mcg/m^2).

Data collection: Following identification of cases from laboratory data, we retrieved and reviewed notes. For some cases maternal notes (Physical and electronic) were reviewed to determine certain information that were not recorded on baby's notes. Data collection included: Type of steroids, Duration of use in days, gestational age at birth, age at the time of test, the standard dose SST results at zero then 30minutes and 60 minutes, and whether baby was Symptomatic vs asymptomatic babies. The clinical outcome of discharge, follow up or medication given were also collected.

Maternal steroids used were due to various reasons. This included rheumatoid arthritis, autoimmune hepatitis; various skin conditions requiring steroids treatment; Systemic lupus erythematosus; inflammatory bowel diseases; etc. different types of steroids were identified. The majority of patients were on prednisolone. Other forms were hydrocortisone, beclomethasone, betnovate creams, dermovate and budosenide. None of the patients were on betamethasone.

For purpose of analysis, doses of all steroids types -other than prednisolone- have been converted to equivalent dose prenisolone per day based on local conversion table set in the local guidelines which then were cross checked through a validated online calculator App (MDcalc) [9].

Outcomes measured: The Cumulative dose of steroid per day and length of usage during pregnancy in comparison to neonatal SST's baseline cortisol and peak response at 60 minutes (which reflects pass and fail status).

Data analysis: Statistical advice for data analysis was sought with support from University of Leeds department of statistics. The analysis target is to assess correlation between dose, and duration of use i.e., in utero exposure time and the SST results.

Results

Table 1: Characteristics of study sample

Total patients	N=59 38 (site one)21 (site two)
Average steroid dose	19.7 mg per day prednisolone equivalent
Minimum dose	5 mg daily
Maximum dose	100 mg daily
Average duration of exposure	173 days (range 31-270 day)
Gestational age	37-41 weeks
Age at time of SST	Range:1-14 daysMean= 4 days
Neonatal co-morbidities	NIL

Total number of patients who met inclusion criteria were fifty-nine (59). Eleven patients excluded due to incomplete data. Forty-eight patients were included for analysis as shown in figure (1)

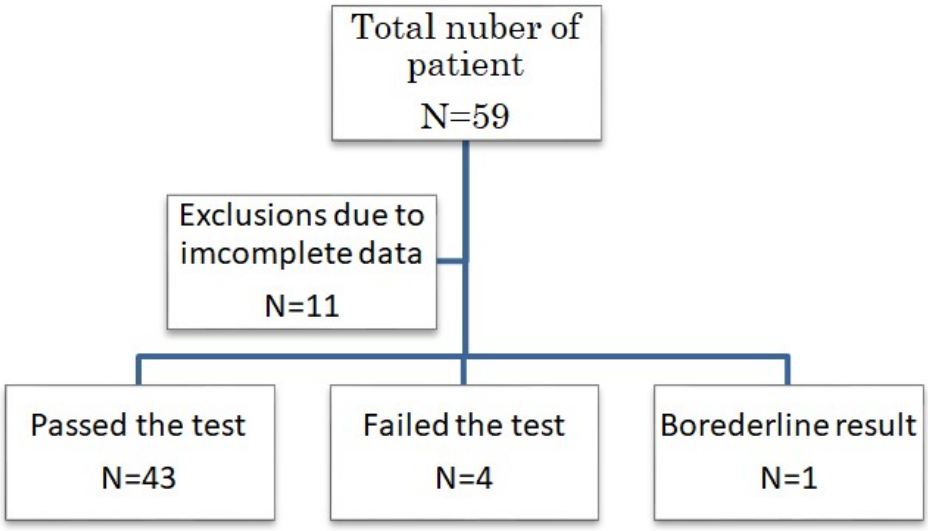

Figure 1: total study sample and analysis pathway:

Spearman correlation coefficient was used for analysis of variables. Each data set has been ranked as there were repeated values (ties) then analysed.

Analysis of Steroid Dose and Basal Cortisol Level:

The association between the steroid dose and basal cortisol level is not statistically significant. $r_s = 0.09557$, p (2-tailed) = 0.52

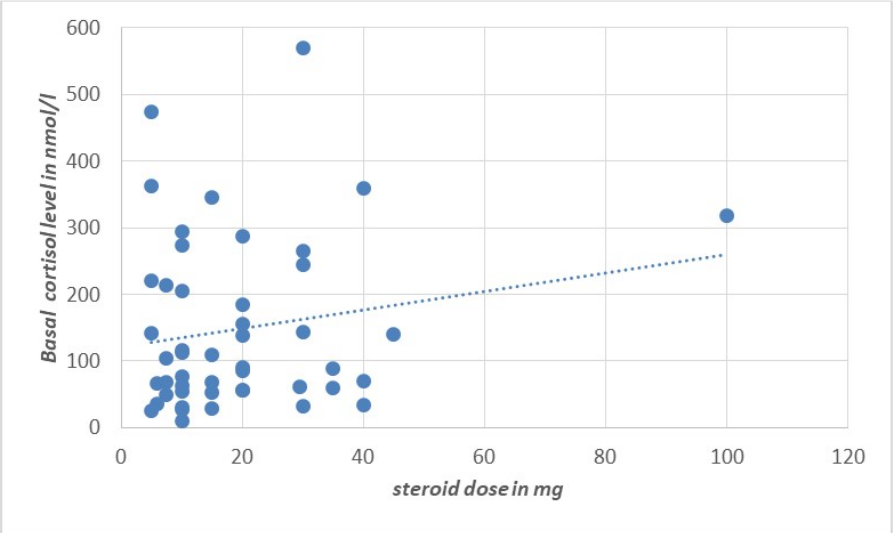

Figure 2: Basal cortisol level and steroid dose correlation graph

Analysis of Steroid duration of exposure and basal cortisol level:

The association between duration of exposure to steroids and basal cortisol level is not statistically significant with r_s =0.11727, p (2-tailed) = 0.4273.

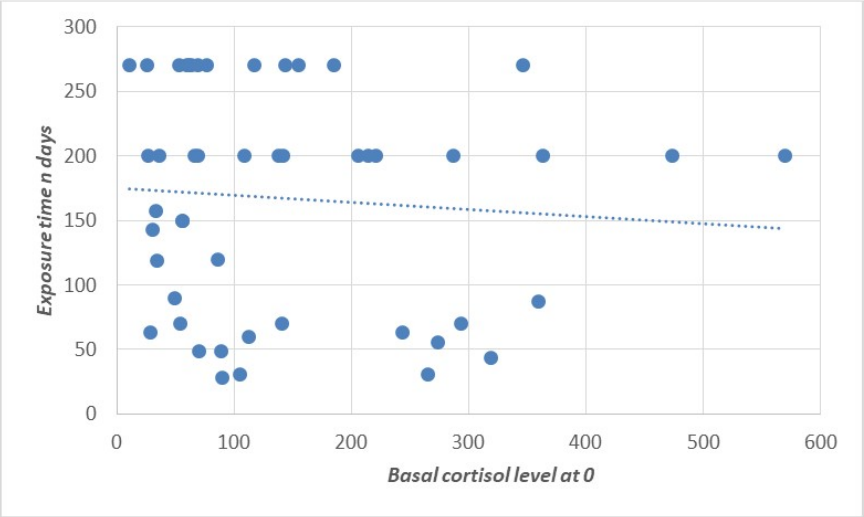

Figure 3: Duration of exposure and basal cortisol correlation graph

Analysis of Steroid dose and peak response at 60 minutes:

Analysis for these variables showed rs = -0.11101, p (2-tailed) = 0.44762.

This indicates the association between the steroid dose and peak test response values is not statistically significant.

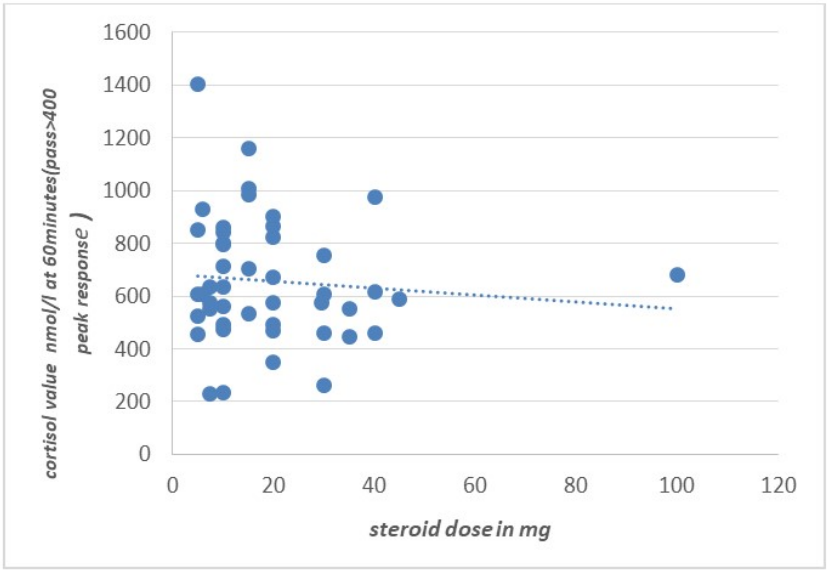

Figure 4: Dose and peak SST response correlation graph

Analysis of Steroid duration of exposure and test peak response at 60 minutes:

Analysis showed rs = 0.22337, p (2-tailed) = 0.12288.

The association between duration of exposure and the peak test response values is not considered statistically significant.

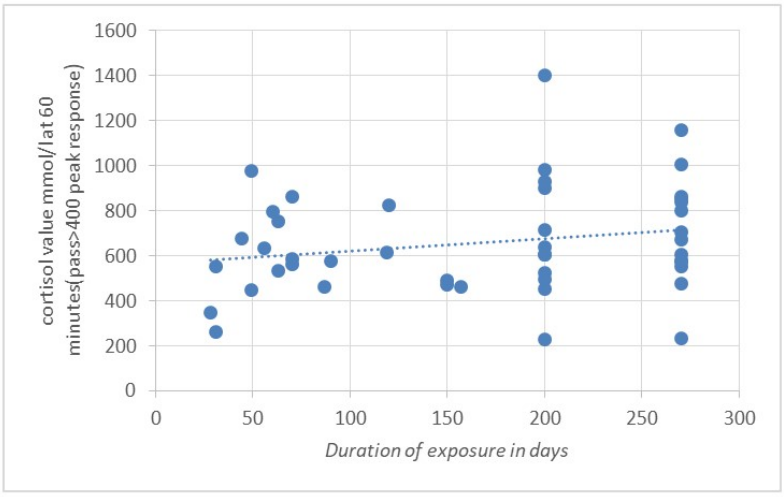

Figure 5: Duration and peak SST response correlation graph

In the study sample, only four patients failed the test and one patient had borderline results. None of those patients have been reported to have clinical symptoms related to adrenal insufficiency and none of them were among the highest steroid dose (Range 7.5 to 30 mg prednisolone equivalent per day), only one with maternal steroid exposure time of 270 days (some patients who passed the test had similar exposure time with higher doses). As per local guidance in the two units, if patient has suboptimal response, i.e., failed SST, should be deemed as having adrenal suppression and should commence on glucocorticoids replacement. Out of the four cases who failed the test, two had no further data with regards to treatment initiation or test repeat.

The other two patients received steroid replacement. Both had test repeated one month and twelve days respectively, medications were stopped and were discharged with no further follow up required. The borderline result patient was planned for repeat test, but also no further data or notes found on the system. None of this group- as far as we know- developed any adverse outcome related to adrenal insufficiency.

Table 2: Characteristics of the five patients failed SST

Antenatal steroid dose	Duration of use during pregnancy	Baseline Cortisol response (0minutes)	cortisol response (60minutes)	Pass/fail	Outcome
30 mg	200 days	-	367	Failed	Started glucocorticoids replacement
30 mg	31 days	265	263	Failed	Discharged, no data on system re medications or follow up
7.5 mg	200 days	214	230	Failed	Discharged, no data on system re medications or follow up
20 mg	28 days	90	348	Borderline	Planned for repeat but nil on the system/notes
10 mg	270 days	11	233	Failed	Started glucocorticoids replacement

There was some variability in age of babies at the time of SST noted. As per the protocol, the baby should have the SST on day two of life based on type of steroid. Seven patients had the test between 20-23 hours of age while other group of patients had the test beyond the 48 hours window.

Discussion

Data analysis concluded no statistically significant correlation between maternal steroid doses and basal cortisol level at 0(steroid level prior to stimulation). There was also no statistically significant correlation between duration of exposure to maternal steroids and basal cortisol level. Lastly, the SST peak response results do not significantly correlate with cumulative dose of steroids or duration of exposure in utero.

These results should be interpreted with caution as it does not necessarily conclude that overall steroid exposure. The results would rather suggest that current cut off and duration of steroid used during pregnancy set in the guidelines would not predict SST values i.e., having adrenal insufficiency or not.

To the best of our knowledge, this is the biggest retrospective cohort study directly focusing on this subject and unlike other studies [10-13], it included various types of steroids used during pregnancy all of which converted to equivalent unified prednisolone dose.

Since only term babies included (37weeks and above) the results obtained may not reflect the same on younger age groups (preterm babies) and cannot be generalised to include them. Preterm babies might be at higher risk compared to term babies. This high risk is not only due to premature hypothalamic-pituitary axis and adrenal glands-, but also the unpredicted activity of the enzyme 11BHSD2 in preterm [14]. Certainly, further studies are required to explore this area.

Most of the studies so far have concluded that adrenal suppression is unlikely to occur following in utero exposure to steroids, [10,11,12,15] Other studies suggested there is transient physiological upregulation or down regulation of the hypothalamic pituitary axis -without clinical manifestation- which will revert to normal state in the first few months of life (5,13). On the other hand, when reviewing available literature, there have been case reports with adrenal suppression with clinical and biochemical findings [16-18]. One of the case reports had antenatal dose of sixty-four (64) mg prednisolone daily and on another case, fifty--

seven (57) mg daily. In both cases the duration was more than a month. Both babies had clinical symptoms/signs manifested as hypoglycaemia and hypotension. Both patients were weaned off medications gradually over the first four months. When comparing those two case reports to our study findings, we can see the values are much higher than the cut off used in our guidelines, however, one of our patients in the study had antenatal dose of up to 100 mg prednisolone equivalent and had no clinical or biochemical evidence of adrenal insufficiency.

The study findings would fit with the current available higher evidence in the literature, as there were no clinical signs or symptoms of adrenal suppression. Our cases who failed the test- asymptomatic-and received medications were taken off treatment shortly after. This would support the presence of transient yet clinically insignificant biochemical dysregulation as suggested previously.

We would anticipate this study to have significant impact on practice at least locally. In addition to the financial cost of the test, the technical difficulties, and resources, we must consider the stress and anxiety imposed on patient and family. We would suggest that current cut-offs set to qualify for SST should be reviewed for term babies given the absence of clear correlation and absence of clinical findings suggestive of AI.

In addition to the above, our recommendation is to have low threshold for SST if clinical assessment reveals any suggestive symptoms like hypoglycaemia or hypotension, as indication for SST in term babies. This echoes the recommendations from previous studies [15]. Our study may trigger further future projects to explore whether in utero exposure to certain amounts of steroid could be set to predict whether adrenal suppression can occur in term or preterm neonates.

Limitations

Small sample size represents an issue in the study. The rarity of the condition is one factor that limited the sample size and subsequently the power of the study. Other factors were the inclusion criteria for the reasons mentioned in methodology section. This did not allow for independent T test between pass and fail groups there were only five patients who did not pass SST.

There was an issue with incomplete data. This included one or combination of missing dose, unknown duration, or lack of one of the three-point test results (0, 30,60 minutes). This issue has further limited the number of cases suitable for analysis.

The variability of gestational age at SST time is raising the question about the accuracy of the test results and whether cortisol levels taken prior to 24 hours of age may reflects maternal level rather than baby's level.

There are other factors that have not been addressed in the study. For instance, maternal co- morbidities were not included in the study. Many of the co-morbidities have been linked to placental pathology which in turn can affect 11BHSD2 activity in a similar way to prematurity [19]. We are not sure if there was maternal comorbidities or placental pathology in any of the patients who failed the test.

Conclusion

Routine screening of neonatal adrenal suppression secondary to antenatal steroid use remains a controversial subject. Our study has supported that adrenal suppression is unlikely to occur -in term babies- as there was no clinical adrenal suppression noted with various doses and duration of exposure to steroids during pregnancy. It has also highlighted the absence of correlation between doses, duration, and SST results. We would recommend revising the need for dose and duration cut-off guidelines on term babies but, keeping low threshold for SST if clinical features were suggestive.

What is known: There is a theoretical risk of neonatal adrenal insufficiency (AI) secondary to maternal steroid use. In practice, the evidence for this remains controversial. The majority, if not all neonatal units in the UK do not routinely test babies born to mothers on steroids for AI.	**What does the study add**: this study has found no correlation between antenatal exposure to steroids- whether cumulative dose or duration- and basal cortisol level or SST peak response respectively. The study suggested that locally implemented guidelines should be revised for term babies given the lack of evidence.

Authors Declaration

No conflict of interest

Funding

No funding received for this study

References

1. McKay LI, Cidlowski JA (2003) Physiologic and Pharmacologic Effects of Corticosteroids. In: Kufe DW, Pollock RE, Weichselbaum RR, et al., editors. Holland-Frei Cancer Medicine. 6th edition. Hamilton (ON): BC Decker.

2. Duthie L, Reynolds R (2013) Changes in the Maternal Hypothalamic-Pituitary-Adrenal Axis in Pregnancy and Postpartum: Influences on Maternal and Foetal Outcomes. Neuroendocrinology, 98:106-115.

3. van Runnard Heimel PJ, Franx A, Schobben AF, Huisjes AJ, Derks JB, Bruinse HW (2005) Corticosteroids, pregnancy, and HELLP syndrome: a review. Obstet Gynecol Surv, 60:57-70.

4. Auriche M, Houang M, Giabicani E, Netchine I, Mitanchez D (2019) Hypothalamo-pituitary-adrenal (HPA) axis in infants exposed to corticosteroids during fetal life. Horm Res Paediatr, 91(suppl 1):1-682.

5. Tegethoff M, Pryce C, Meinlschmidt G (2009) Effects of intrauterine exposure to synthetic glucocorticoids on fetal, newborn, and infant hypothalamic-pituitary-adrenal axis function in humans: a systematic review. Endocr Rev, 30:753-789.

6. JW neonatal guidelines (Accessed through local trust intranet).

7. Neonates of Mothers on Steroids during Pregnancy. DBTH guidelines.

8. Sheffield Children's NHS Foundation Trust.

9. MDCalc - Medical calculators, equations, scores, and guidelines.

10. de Vetten L, van Stuijvenberg M, Kema IP, et al. (2017) Maternal use of prednisolone is unlikely to be associated with neonatal adrenal suppression—a single-center study of 16 cases. Eur J Pediatr, 176:1131-1136.

11. Mesogitis S, Daskalakis G, Papapetrou P, Mavroudis K, Papandroulaki F, Papantoniou N, Antsaklis A (2011) The effect on the fetal pituitary-adrenal axis of dexamethasone administration early in the second trimester of pregnancy. J Maternal-Fetal

Neonatal Med, 24:109-112.

12. Battin MR, Bevan C, Harding JE (2007) Repeat doses of antenatal steroids and hypothalamic-pituitary-adrenal axis (HPA) function. Am J Obstet Gynecol, 197:40.e1-6.

13. Ashwood PJ, Crowther CA, Willson KJ, Haslam RR, Kennaway DJ, Hiller JE, Robinson JS (2006) Neonatal adrenal function after repeat dose prenatal corticosteroids: a randomized controlled trial. Am J Obstet Gynecol, 194:861-867.

14. Hofmann M, Pollow K, Bahlmann F, Casper F, Steiner E, Brockerhoff P (2001) 11β-hydroxysteroid dehydrogenase (11β-HSD-II) activity in human placenta: Its relationship to placental weight and birth weight and its possible role in hypertension. J Perinat Med, 29:23-30.

15. de Vetten L, van Stuijvenberg M, Kema I, et al. (2014) Neonatal Adrenal Suppression After Maternal Corticosteroid Use? A Single-centre Case-study. Arch Dis Child, 99.

16. Kurtoğlu S, Sarıcı D, Akın MA, Daar G, Korkmaz L, Memur Ş (2011) Fetal adrenal suppression due to maternal corticosteroid use: case report. J Clin Res Pediatr Endocrinol, 3:160-162.

17. Homar V, Grosek S, Battelino T (2008) High dose methylprednisolone in a pregnant woman with Crohn's disease and adrenal suppression in her newborn. Neonatology, 94:306-309.

18. Saulnier PJ, Piguel X, Perault-Pochat C, Csizmadia-Bremaud C, Saulnier JP (2010) Hypoglycaemic seizure and neonatal adrenal insufficiency after maternal exposure to prednisone during pregnancy: a case report. Eur J Pediatr, 169:763-765.

19. Kajantie E, Dunkel L, Turpeinen U, Stenman UH, Wood PJ, Nutila M, Andersson S (2003) Placental 11β-hydroxysteroid dehydrogenase-2 and fetal cortisol/cortisone shuttle in small preterm infants. J Clin Endocrinol Metab, 88:493-500.