Arch Gynecol Obstet (2017) 296:1091–1096
DOI 10.1007/s00404-017-4543-1

MATERNAL-FETAL MEDICINE

Timing of antenatal steroids exposure and its effects on neonates

Hester C. Q. Lau[1] · Janice S. Z. Tung[1] · Tiffany T. C. Wong[1] · P. L. Tan[2] · Shephali Tagore[3]

Received: 21 May 2017 / Accepted: 11 September 2017 / Published online: 25 September 2017

Abstract
Objective Antenatal corticosteroid (ACS) has long been regarded as the standard of care for women at risk of preterm labour. There are, however, varying practices and regimes in ACS administration. It is unclear if "a window of efficacy" truly exists and if the benefits of ACS would diminish after 7 days from the first dose. The objective of this study is to determine if the time interval between antenatal corticosteroids and delivery influences the neonatal outcomes in preterm deliveries from 23^{+5} to 36^{+6} weeks' gestation.
Methods This is a retrospective analysis of 302 women and 352 infants who delivered from 23^{+5} to 36^{+6} weeks' gestation in KK Women's and Children's Hospital from 1st November 2014 to 31st January 2015. The timings of the first two doses of corticosteroids and the delivery were retrieved. Neonatal outcomes were compared between those delivering within 7 days and those delivering beyond 7 days of first dose of ACS.
Results 61.2% of preterm infants received at least one dose of antenatal corticosteroids, of which 23.6% received it within the window of efficacy. Overall incidence of respiratory distress asyndrome in our study is 17.6%. Significantly, neonates with ACS exposure beyond 7 days were seven times more likely to have RDS as compared to those exposed to ACS within the window of efficacy (RR 0.535, 95% CI 0.166–1.72), after adjusting for potential confounders.
Conclusion The results of this study support the current practice among obstetricians to aim to administer ACS within 7 days of delivery.

Keywords Antenatal corticosteroids · Neonatal respiratory distress syndrome · Preterm labour · Window of efficacy · Neonatal outcomes

Introduction

Preterm labour, defined as birth before 37 weeks of gestation, complicates about 9.5% of pregnancies in Singapore [1]. It can occur as indicated deliveries due to maternal or foetal complications in 30–40%, or occur spontaneously as preterm labour and preterm pre-labour rupture of membrane (PPROM) in the remaining 60–70%.

One of the serious complications of preterm birth is Neonatal Respiratory Distress Syndrome (RDS). As lung maturation usually occurs between 28 and 35 weeks gestation, preterm infants have less alveoli, and qualitative and quantitative deficiency in surfactant. Without surfactant, the surface tension of alveoli increases, leading to atelectasis during expiration. Subsequently, intrapulmonary shunting and ventilation perfusion inequalities occur, causing respiratory failure. RDS is a serious complication of preterm birth and the primary cause of early neonatal morbidity and mortality worldwide. Those preterm infants who do survive the neonatal period are also at an increased risk of long-term neurological complications and disability [2].

In 1972, Liggins and Howie were the first to show that glucocorticoid administration to pregnant mothers accelerates lung maturation and reduces the incidence of RDS in

✉ Hester C. Q. Lau
hester.lau@mohh.com.sg

[1] Department of Obstetrics and Gynaecology, KK Women's and Children's Hospital, 100 Bukit Timah Road, Singapore 229899, Singapore

[2] Department of Neonatology, KK Women's and Children's Hospital, Singapore 229899, Singapore

[3] Department of Maternal-Fetal Medicine, KK Women's and Children's Hospital, Singapore 229899, Singapore

premature babies delivered within 7 days of corticosteroid therapy [3]. Corticosteroids increase protein production, biosynthesis of phospholipids and hence increase surfactant in foetal lungs. Since then, many studies have confirmed these findings. The most recent Cochrane review on antenatal corticosteroids (ACS) [4] showed that a single course of ACS significantly reduced the incidence of RDS of average 34% (risk ratio (RR) 0.66, 95% confidence interval 0.56–0.77; 28 studies, 7764 participants). The reduction in RDS risk also benefits patients with suspected chorioamnionitis [5]. Other beneficial effects included reduction in neonatal death, intraventricular haemorrhage (IVH), necrotising enterocolitis (NEC), need for respiratory support and neonatal intensive care unit (NICU) admission. Corticosteroids have since become the standard of care for women at risk of preterm labour worldwide.

However, it is still unclear whether the benefits of a complete course of ACS would diminish after 7 days from the first dose as first suggested in Liggins & Howie's paper. The optimal treatment–delivery interval for administration of ACS proposed by the Royal College of Obstetrics and Gynaecology (RCOG) is more than 24 h and before 7 days after the completion of a course of ACS. There are current studies that showed that infants delivering more than 7 days after initial ACS exposure have a higher frequency of RDS than those who were delivered within a week [6–9]. These question the need for a repeated dose of ACS if delivery did not occur within 7 days of first ACS exposure. Yet, there are concerns regarding the safety of repeated doses of ACS [10–12]. The National Institute of Health and Care Excellence (NICE) guidelines (NG25) "Preterm labour and birth" [13] does not recommend rescue doses of ACS, and to consider it if the initial course was given less than 26^{+0} weeks of gestation.

Furthermore, there are many differing practices and regimes in the administration of ACS [14, 15] which may influence efficacy. The ACS regime practiced in KK Women & Children's Hospital (KKH) in Singapore involves administration of IM Dexamethasone 12 mg every 12 h for two doses to women at risk of preterm delivery from 23^{+5} (48 h before viable gestation) up to 35^{+6} weeks' gestation. This study aims to determine if the time interval between the first dose of IM Dexamethasone 12 mg and delivery affects neonatal outcomes in preterm deliveries from 23^{+5} to 36^{+6} weeks' gestation.

Methodology

This is a retrospective analysis of women who delivered from 23^{+5} to 35^{+6} weeks' gestation in our centre within the duration of 1st November 2014 to 31st January 2015. Data were retrieved from pre-existing computerised databases. One study investigator extracted data from the databases while a second investigator did a quality assurance review of 10% of the data and found discrepancies in less than one percent of all data variables collected.

The maternal data included the demographics, delivery details, indication for antenatal corticosteroids administration, maternal obstetrics and past medical history, antenatal history for current pregnancy, and details of antenatal corticosteroids admission. The presence of RDS is the main foetal outcome in this study. Other foetal outcomes collected include length of stay in Neonatal Intensive Care Unit (NICU), mortality rate, need for surfactant therapy, duration of ventilation, presence of IVH, proven neonatal sepsis and NEC.

RDS is diagnosed by the neonatologist based on the following clinical parameters:

1. Respiratory rate of more than 60 per minute.
2. Respiratory distress in evidence of dyspnoea (grunting, sternal, subcostal and intercostal retraction).
3. Occurring within 4–6 h of delivery.
4. Oxygen requirement (any percentage) to prevent cyanosis.
5. Chest X-ray changes (homogenous reticulogranular) [16].

IVH is diagnosed by cranial ultrasound on day three of life and graded according to the classification by Papile et al. [17]. NEC is diagnosed according to Bell staging criteria [18].

The window of efficacy for ACS in this study is defined as delivery within 48 h to 7 days from first dose of ACS. Neonatal outcomes were compared between the group of neonates that were delivered within 7 days and those delivering beyond 7 days of first dose of ACS.

The data collected were analysed via Statistical Package for the Social Sciences (SPSS) version 22. Pearson Chi-square test was performed for categorical variables. For continuous variables, normality was checked using Kolmogorov–Smirnov test. For normally distributed variables, *T* test was performed. For non-normally distributed variables, Mann–Whitney *U* test was performed. Multinomial logistic regression analyses were performed to estimate the odds of RDS in newborns after administration of antenatal corticosteroids, adjusting for covariates with significant effects greater than 10% on outcome of interest with inclusion and then exclusion from adjusted analysis. Adjusted analysis was not performed for individual morbidities with low frequencies, less than 10 observations for category for other outcomes. Comparisons with association $p < 0.05$ and 95% confidence interval not inclusive of null value of one were considered statistically significant differences.

Results

A total of 352 infants were delivered prematurely to 301 women in the study period with 249 singleton, 50 twins and one triplet deliveries. All records were available and retrieved within the study period. As seen from Fig. 1, only 216 (61.2%) infants were exposed to dexamethasone antenatally. Out of which, only 51 (23.6%) received ACS during the window of efficacy, 66 (30.6%) received them more than 1 week before delivery and 99 (45.8%) received it less than 48 h of delivery. There were no infants who received a rescue dose or a repeat course of ACS.

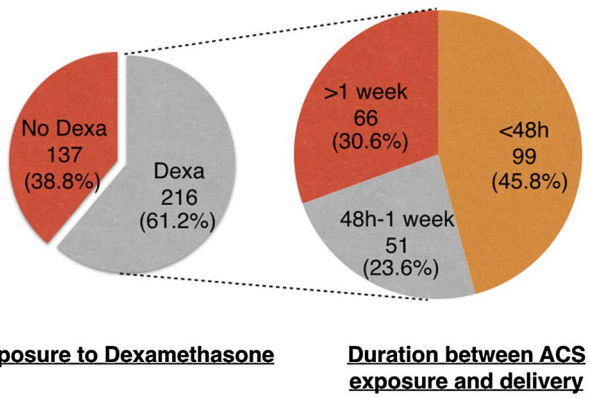

Fig. 1 Proportion of neonates who was exposed to Dexamethasone (Dexa) antenatally and the duration between ACS exposure and delivery

There was a significant association between birth weight and ACS exposure to delivery among the 3 groups (within 48 h, 48 h to 7 days and beyond 7 days). There were no statistically significant difference between the groups in terms of gestational age, type of preterm birth, gestation, mode of delivery and indication for ACS (Table 1).

The overall incidence of RDS in our study is 17.6%. As seen from Fig. 2, lesser gestational age at delivery (OR 2.124, 95% CI 0.411–0.571), PPROM (OR 7.7, 95% CI 1.892–25) and preterm labour (OR 5.895, 95% CI 1.557–22.323) were found to be associated with RDS independent of ACS exposure.

A total of three (0.90%) NEC occurred among the 352 neonates studied. There were no cases of NEC among neonates who received steroids. There were 16 (4.7%) cases of IVH among the neonates studied. Mortality rate (inclusive of stillborn and neonatal death) within the 3 months study period was 4.0%. There was no statistically significant difference in NEC, IVH and mortality rate among neonates who received ACS within 48 h, within window of efficacy or beyond a week.

As seen from Table 2, when compared to those neonates without ACS, those who had ACS exposure were less likely

Table 1 Neonatal characteristics according to timing of ACS exposure

Neonatal characteristics	Less than 48 h	48 h to 7 days	Beyond 7 days	Total, *n*	*p* value
Total, *n* (%)	99 (45.8)	51 (23.6)	66 (30.6)	216	–
Gestational age (weeks), mean (SD)	33.62 (0.265)	32.45 (0.460)	33.45 (0.378)	–	0.056
Birth weight (kg), mean (SD)	2.17 (0.060)	1.87 (0.086)	2.11 (0.077)	–	**0.025**
Method of conception, *n* (%)					0.171
Spontaneous, *n* (%)	62 (43.1)	32 (22.2)	50 (34.7)	144	
Iatrogenic, *n* (%)	37 (51.4)	19 (26.4)	16 (22.2)	72	
Gestation					0.139
Single, *n* (%)	71 (49.0)	36 (24.8)	38 (26.2)	145	
Multiple, *n* (%)	28 (39.4)	15 (21.1)	28 (39.4)	71	
Mode of delivery					0.069
Vaginal delivery, *n* (%)	33 (47.8)	10 (14.5)	26 (37.7)	69	
Caesarean section, *n* (%)	66 (44.9)	41 (27.9)	40 (27.2)	147	
Diagnosis					0.099
Preterm labour	39 (50.0)	14 (17.9)	25 (32.1)	78	
Preterm premature rupture of membranes	21 (43.8)	11 (22.9)	16 (33.3)	48	
Hypertension (including Pre-eclampsia and eclampsia)	21 (53.8)	11 (28.2)	7 (17.9)	39	
Antepartum haemorrhage	2 (11.1)	7 (38.9)	9 (50.0)	18	
Foetal factors: intrauterine growth restriction (IUGR), oligohydramnios, non-reassuring foetal status (NRFS)	5 (33.3)	6 (40.0)	4 (26.7)	15	
Elective caesarean section	6 (60.0)	2 (20.0)	2 (20.0)	10	
Others	4 (57.1)	0 (0.0)	3 (42.9)	7	

Bold indicates statistically significant results

to have RDS and oxygen therapy regardless of the time interval between ACS exposure to delivery. The other neonatal outcomes (NICU stay and length of stay, surfactant therapy, IVH, NEC, APGAR score at 5 min, cord pH and proven neonatal sepsis) were not found to be significantly different when the 3 groups were compared.

Table 3 shows the incidence of RDS for neonates who were exposed to ACS within 48 h, from 48 h to 7 days and beyond 7 days. Those with ACS exposure beyond 7 days were 7.02 times more likely to get RDS (95% CI 1.54–32.07), after adjusting for confounders including gestational age, birth weight and indication for ACS. When compared with neonates with ACS exposure within the window of efficacy (48 h to 1 week), neonates given within 48 h were 0.53 times less likely to get RDS (95% CI 0.17–1.72) although this did not achieve statistical significance.

Discussion

Administration of antenatal corticosteroids (ACS) is a widely accepted practice for preterm deliveries to decrease the incidence of neonatal respiratory distress syndrome (RDS). However, the timing of ACS administration in relation to the delivery is controversial. It remains unknown if the efficacy of ACS beyond a week from initial exposure is

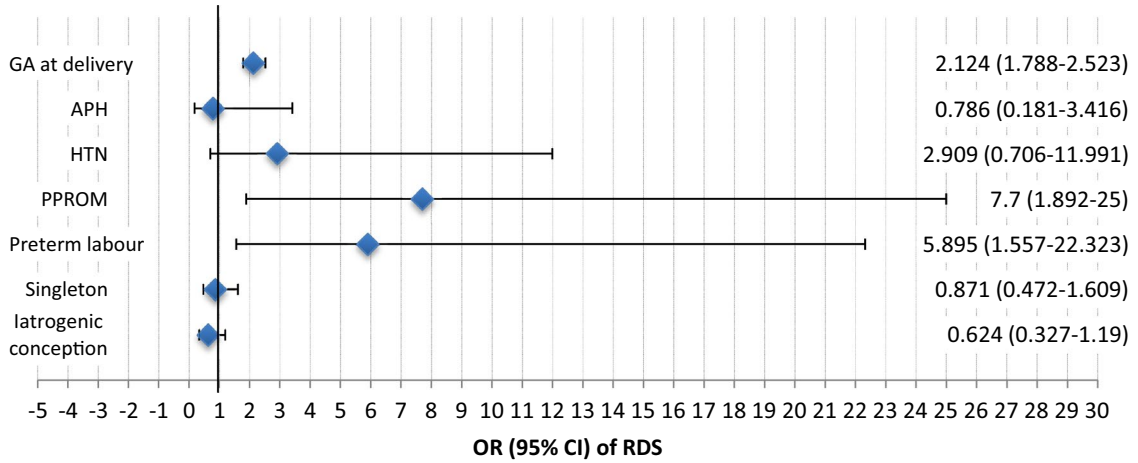

Fig. 2 Multivariate analysis of the association between neonatal characteristics with incidence of RDS, independent of ACS exposure

Table 2 Multivariate analysis of the association between the time intervals of ACS exposure to birth with adverse neonatal outcomes

Outcome	Adjusted OR (95% CI) according to timing of antenatal corticosteroids*			
	No ACS	Less than 48 h	48 h to 7 days	Beyond 7 days
RDS	Reference	**<0.001 (< 0.001–0.139)**	**<0.001 (< 0.001–0.152)**	**0.001 (< 0.001–0.398)**
Oxygen therapy	Reference	**0.001 (< 0.001–0.184)**	**0.001 (< 0.001–0.211)**	**0.003 (< 0.001–0.446)**
Surfactant therapy	Reference	0.083 (< 0.001–252.637)	0.105 (< 0.001–239.076)	0.149 (< 0.001–182.233)
Resuscitation needed^	Reference	234.943 (0.507–108,818.017)	240.747 (0.636–91,186.478)	27.813 (0.125–6203.785)

Bold indicates statistically significant results

* Adjusted for gestational age of dexamethasone given, birth weight and indication for ACS

^Resuscitation include Bag and Mask, and endotracheal intubation

Table 3 Multivariate analysis of the association between the time intervals of ACS exposure to birth with incidence of RDS

Outcome	Less than 48 h	48 h–7 days	Beyond 7 days
Incidence of RDS (%)	21 (42.0)	17 (34.0)	12 (24.0)
Adjusted OR (95% CI) according to timing of ACS*	0.53 (0.17–1.72)	Reference	**7.02 (1.54–32.07)**

Bold indicates statistically significant results

* Adjusted for gestational age, birth weight and indication for ACS

indeed limited, necessitating a repeat dose of ACS. It also begs the question of how important is it for obstetricians to judge the timing of ACS administration relative to the likelihood of preterm delivery within the next 7 days.

Main findings

Our results showed that ACS exposure in preterm neonates significantly reduce the incidence of RDS and oxygen therapy requirement. There was a benefit of administrating corticosteroids (IM Dexamethasone 12 mg 12 h apart) within 7 days of delivery as infants with ACS exposure beyond 7 days are seven times more likely to have RDS as those with ACS exposure within this window period. This result is similar to that in some other studies as well. In a retrospective cohort study performed by Ring et al. [9], time interval of more than 14 days since ACS exposure is associated with increased risk of ventilator support and surfactant use. Waters et al. [6] found that delivery more than a week after ACS exposure is associated with higher frequency of RDS among neonates born at 30–33^{+6} weeks, but no association is found with use of surfactant therapy. Our results also suggested benefit of administering ACS within 48 h of delivery.

Strength and limitations

Strengths of our study include a large number of preterm deliveries with a significant incidence of RDS for analysis, from a clinically diverse cohort of women presenting at the largest obstetric centre and perinatal unit in Singapore. We also included all preterm neonates within the study period, including those late preterm babies (34^{+0} to 36^{+6} weeks gestation). The study contributes to the literature on neonatal outcomes associated with an antenatal corticosteroid regime of two doses of intramuscular Dexamethasone 12 mg 12 h apart for women presenting with preterm labour up to 35^{+6} weeks.

We acknowledge that there are several limitations to our study. Our study is a retrospective review which limits the analysis on cause and effect relationship between the factors and outcomes. The low incidence of severe complications: stillbirth, neonatal death, IVH and NEC within the study period did not allow us to examine them. Both Peaceman et al. [19] and Ring et al. [8] failed to show a significant difference in the IVH incidence between neonates exposed to ACS within 7 days and beyond 7 days. The number of neonates ($n = 10$) involved in this subgroup analysis was too small, a problem similar to what these previous studies faced. Similarly, the incidence of NEC is also too low to be correlated with timing of ACS. Peaceman et al. [19] found no significant correlation between NEC and timing of ACS. It is hypothesised that ACS aids in the maturation of organs with glucocorticoid receptors such as the brain, thyroid and gastrointestinal tract, thus reducing the incidence of IVH and NEC [20–22]. Hence, it may be worthwhile to analyse these correlations in future larger studies.

Interpretation

It is possible that the results of this study may be partly due to the different ACS regime in our centre and the inclusion of late preterm neonates. In our centre, antenatal corticosteroid regime involves intramuscular Dexamethasone 12 mg every 12 h for two doses, given to mothers with preterm labour up to 35 + 6 weeks. Previous studies mentioned above involved an ACS regime of 24-hourly dosage instead of a 12-hourly one. There are, however, evidence to suggest that a 12-h interval may be equivalent to standard 24-h interval [14]. Our study included late preterm babies (34 + 0 to 36 + 6 weeks gestation). In the Cochrane Review on ACS in 2006, RDS was found to be decreased when steroids were administered at 33^{+0} to 34^{+6} weeks (RR 0.52, 95% CI 0.31–0.91, two studies, 434 infants) but not at 35^{+0} to 36^{+6} weeks (RR 0.61, 95% CI 0.11–3.26, one study, 189 infants) [2]. In the updated Cochrane Review on ACS in 2017 [4], there appears to be no evidence that the gestational age at trial entry resulted in difference in RDS rates [GA $\leq$ 35 + 0 weeks RR 0.65 (0.58–0.73) vs. GA $\geq$ 34 + 0 weeks RR 0.71 (0.56–0.91)]; both groups had decreased rate of RDS. A recent study by Gyamfi-Bannerman et al. [23] also reported positive results showing benefit of betamethasone for late preterm birth in a multicentre, placebo-controlled, randomised trial in which 2831 women at high risk of delivery between 34^{+0} and 36^{+5} weeks' gestation. The study showed significantly lower risk of the composite primary outcome (stillbirth or neonatal death before 72 h or need for respiratory support by 72 h of age) in the betamethasone group than in the placebo group. The estimated number of women who would need to be treated to avoid one infant requiring respiratory support was 35 (95% CI 19–259).

Conclusion

In summary, our study reinforced the rationale behind the common practice of giving antenatal corticosteroids in preterm birth and also demonstrated significant decrease in RDS for those who were delivered within 7 days of ACS. This supports the current practice among obstetricians to aim to administer ACS within the window of efficacy. There may also be added benefit to the infant to administer at least a dose of ACS in late preterm labour. Our study also revealed that only 61.2% of preterm foetuses were exposed to ACS. It is imperative to keep a regular audit of this intervention for preterm birth, educate patients to allow earlier presentation,

and encourage the timely administration of ACS before preterm delivery occurs in order to benefit.

Author contributions JSZT and HCQL: Development of the research design, analysis strategy, data collection, statistical analysis, interpretation of results, manuscript writing; co-first authors of this manuscript. TTCW: Data collection, statistical analysis, and manuscript writing. TPL: Development of research study and analysis strategy. ST: Development of research design and analysis strategy, editorial guidance. All authors approved this version of manuscript for submission.

Compliance with ethical standards

Conflict of interests The authors report no conflict of interest. There was no financial support.

Ethical approval This study received ethical approval from SingHealth Centralised Institutional Review Board (CIRB Ref: 2012/157/D). The study was conducted in KK Women's and Children's Hospital, Singapore.

References

1. Eveline Gan (2015) Premature births on the rise in Singapore. TODAY **(in press)**
2. Roberts D, Dalziel SR (2006) Antenatal corticosteroids for accelerating fetal lung maturation for women at risk of preterm birth. Cochrane Database Syst Rev. 3:CD004454. doi:10.1002/14651858.CD004454.pub2
3. Liggins GC, Howie RN (1972) A controlled trial of antepartum glucocorticoid treatment for prevention of the respiratory distress syndrome in premature infants. Pediatrics 50:515–525
4. Roberts D, Brown J, Medley N, Dalziel SR (2017) Antenatal corticosteroids for accelerating fetal lung maturation for women at risk of preterm birth. Cochrane Database Syst Rev 3:CD004454. doi:10.1002/14651858.CD004454.pub3
5. Miyazaki K, Furuhashi M, Ishikawa K, Tamakoshi K, Hayashi K, Kai A et al (2015) Long-term outcomes of antenatal corticosteroids treatment in very preterm infants after chorioamnionitis. Arch Gynecol Obstet 292:1239–1246. doi:10.1007/s00404-015-3762-6
6. Waters TP, Mercer B (2009) Impact of timing of antenatal corticosteroid exposure on neonatal outcomes. J Matern Fetal Neonatal Med 22:311–314
7. Vis JY, Wilms FF, Kuin RA, Reuvers JM, Stam MC, Pattinaja DAPM et al (2011) Time to delivery after the first course of antenatal corticosteroids: a cohort study. Am J Perinatol 28:683–688
8. Boesveld M, Heida KY, Oudijk MA, Brouwers HAA, Koenan SV, Kwee A (2014) Evaluation of antenatal corticosteroid prescribing patterns among 984 women at risk for preterm delivery. J Matern Fetal Neonatal Med 27(5):516–519
9. Ring AM, Garland JS, Stafeil BR, Carr MH, Peckman GS, Pircon RA (2007) The effect of a prolonged time interval between antenatal corticosteroid administration and delivery on outcomes in preterm neonates: a cohort study. Am J Obstet Gynecol 196:457
10. Garite TJ, Kurtzman J, Maurel K, Clark R (2009) Impact of a 'rescue course' of antenatal corticosteroids: a multicenter randomized placebo-controlled trial. Am J Obstet Gynecol 200:248
11. Crowther CA, Harding JE (2007) Repeat doses of prenatal corticosteroids for women at risk of preterm birth for preventing neonatal respiratory disease. Cochrane Database Syst Rev 3:CD003935. doi:10.1002/14651858.CD003935.pub2
12. Murphy KE, Hannah ME, Willan AR, Hewson SA, Ohlsson A, Kelly EN, MACS Collaborative Group et al (2008) Multiple courses of antenatal corticosteroids for preterm birth (MACS): a randomised controlled trial. Lancet 372:2143–2151
13. National Institute for Health and Care Excellence guidelines [NG25]. Preterm labour and birth. https://www.nice.org.uk/guidance/ng25?unlid=929103607201621320125 7. Accessed Nov 2015
14. Brownfoot FC, Gagliardi DI, Bain E, Middleton P, Crowther CA (2013) Different corticosteroids and regimens for accelerating fetal lung maturation for women at risk of preterm birth. Cochrane Database Syst Rev 8:CD8006764. doi:10.1002/14651858.CD006764.pub3
15. Surbek D, Drack G, Irion O, Nelle M, Huang D, Hoesli I (2012) Anatenatal corticosteroids for fetal lung maturation in threatened preterm delivery: indications and administration. Arch Gynecol Obstet 286:277–281. doi:10.1007/s00404-012-2339-x
16. Greenough A (2012) Respiratory distress syndrome. In: Rennie JM (ed) Textbook of neonatology. Churchill Livingstone, London, pp 468–485
17. Papile LA, Burstein J, Koffier H (1978) Incidence and evolution of sub- ependymal and intraventricular hemorrhage: a study of infants with birth weights less than 1500 g. J Pediatr 92:529–534
18. Kliegman RM, Hack M, Jones P, Faranoff AA (1982) Epidemiologic study of necrotizing enterocolitis among low-birth-weight infants: absence of identifiable risk factors. J Pediatr 100:440–444
19. Peaceman AM, Bajaj K, Kumar P, Grobman WA (2005) The interval between a single course of antenatal steroids and delivery and its association with neonatal outcomes. Am J Obstet Gynaecol 193:1165–1169
20. Fowden AL, Li J, Forhead AJ (1998) Glucocorticoids and the preparation for life after birth: are there long-term consequences of the life insurance? Proc Nutr Soc. 57:113–122
21. Bauer CR, Morrison JC, Poole WK, Korones SB, Boehm JJ, Rigatto H et al (1984) A decreased incidence of necrotizing enterocolitis after prenatal glucocorticoid therapy. Pediatrics 73:682–688
22. Peffer ME, Zhang JY, Umfrey L, Rudine AC, Monaghan AP, DeFranco DB (2015) Minireview: the impact of antenatal therapeutic synthetic glucocorticoids on the developing fetal brain. Mol Endocrinol 29(5):658–666. doi:10.1210/me.2015-1042
23. Gyamfi-Bannerman C, Thom EA, Blackwell SC, Tita ATN, Reddy UM, Saade GR et al (2016) Antenatal betamethasone for women at risk for late preterm delivery. N Engl J Med 374:1311–1320