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Gestational age–specific risks versus benefits of multicourse antenatal corticosteroids for preterm labor

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Abstract

Objective—To estimate a gestational age threshold at which the benefits of treatment with weekly courses of antenatal corticosteroids (ACS) during preterm labor outweigh the risks.

Study Design—Risk-benefit ratios by gestational age are determined using a Markov microsimulation decision-analysis model with a 1-week cycle length. Single course and multiple (weekly to max of 4) courses of ACS by gestational age of entry (23 to 31 6/7 weeks) are compared. Benefits are composite events (respiratory distress syndrome, chronic lung disease, severe intraventricular hemorrhage, periventricular leukomalacia, bronchopulmonary dysplasia or stillbirth) averted. Risks are small head circumference and small for gestational age.

Results—More composite events are averted (benefits) than risks acquired (6:1) when multiple courses of ACS are initiated at 26 weeks' gestation. When multiple courses of ACS are initiated at 29 weeks' gestation, the risk-benefit ratio is 1. Beyond 29 weeks, there is a suggestion of more risk than benefit.

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Conclusion—The model suggests that multiple courses of ACS initiated at less than 29 ‘weeks’ gestation may have increased benefit compared to risks. Further analyses are needed to determine the long term clinical significance of these findings.

Keywords

Antenatal Corticosteroids; Preterm Labor; Decision Analysis

INTRODUCTION

The neonatal benefits of antenatal corticosteroids (ACS) have been well established.[1, 2] In pregnant women at risk of preterm birth, ACS decreases risks of neonatal mortality and morbidity, with proven reductions in neonatal respiratory distress syndrome (RDS) intraventricular hemorrhage (IVH) and neonatal death. [1, 2,3,4] Single course ACS is the gold standard of care for pregnant women at risk for preterm birth. Following a single course of ACS treatment, optimal benefit is seen in neonates delivered between 24 hours and 7 days, with a possible diminished effect in those delivered after seven days.[5, 6] The National Institutes of Health (NIH) consensus statement established guidelines for routine use of ACS in women at risk for preterm birth [5, 6] This consensus statement suggested an optimal benefit between 24 hours and 7 days and additional investigations were recommended to determine if beneficial effects decreased after 7 days in women who remained undelivered but still at risk for preterm delivery. In an attempt to assure that corticosteroids are administered in the maximal effective window, a protocol of repeating treatments weekly in high-risk patients was initiated by many centers. A 2011 review of ten randomized controlled trials concluded that additional research on the long term risks and benefits of repeat doses of ACS on growth and development is needed. [4]

There are multiple factors that determine whether repeating ACS is necessary. Currently, there is no adequate and precise technique for predicting which at-risk pregnancies will deliver pre-term. In many cases a pregnancy at risk for preterm birth may continue for many weeks without delivering. In these cases, the maturational benefit of older gestational age makes retreatment unnecessary and exposes neonates to risks associated with steroid use without any added benefit. Alternatively failure to re-treat can have unwanted neonatal pulmonary consequences. While there is evidence from randomized controlled trials that multiple ACS courses in preterm neonates results in a significant reduction in RDS and other poor pulmonary outcomes,[7–9] reduced birth weight and small head circumference (SHC) have also been identified as adverse effects of multiple ACS treatment. [7–9,10,11] Therefore, many unanswered questions remain regarding the relative risks and benefits of retreatment with ACS.

To address these questions we developed a decision analysis model to determine the gestational age- specific threshold at which the benefits of weekly ACS in the management of preterm labor outweigh potential risks. Our objective was to estimate a gestational age threshold at which the benefits of treatment with weekly courses of antenatal corticosteroids (ACS) during preterm labor outweigh the risks.

The data for risks and benefits used in developing the model are from the randomized trial, Single versus Weekly Courses of Antenatal Corticosteroids: Evaluation of Safety and Efficacy, conducted by the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development Maternal Fetal Medicine Units Network. [8]

METHODS

Model Structure

Markov Modeling is a type of decision analysis that models clinical problems where events can occur more than once (i.e. preterm labor); rates of transitioning from one event to another can vary over time and the outcome can vary by when transition occurs. [12] A Markov microsimulation decision-analysis model was developed to compare the effects of ACS in women with preterm labor who received only a single course of ACS to those receiving repeat weekly courses until 32 weeks' gestation using TreeAge Pro, 2009 Healthcare software (TreeAge Software, Inc, Williamstown, MA). The model used a 1-week cycle length from gestational age of entry until gestational age at delivery. The maximum gestational age at delivery in the model is 42 weeks. The model consists of 5 discrete health states: 1- undelivered; 2- delivered healthy, defined as without both negative outcomes of either ACS treatment (combined probability of small for gestational age (SGA) or SHC) or negative outcomes of preterm birth (combined probability of RDS, chronic lung disease (CLD), severe IVH, periventricular leukomalacia (PVL), bronchopulmonary dysplasia (BPD), or stillbirth); 3- delivered with negative ACS treatment outcome 4- delivered with negative preterm birth outcome ; 5-delivered with negative outcomes of both ACS and preterm birth. In order to ensure the most conservative evaluation of multicourse ACS therapy and avoid overestimation of the beneficial effects of multicourse steroid therapy, outcomes in individuals born with both ACS and pre-term birth complications were counted against ACS use only in the model and not as a pre-term birth complication as well. A simplified graphic representation of the model is presented in Figure 1 and a simplified version of the decision tree is presented in Figure 2.

All input parameters including probabilities of delivery and ACS and preterm birth outcome measures for the decision-analysis model were calculated using data from the Wapner et al. MFMU network clinical trial, Single versus Weekly Courses of Antenatal Corticosteroids: Evaluation of Safety and Efficacy. [8] Maintenance of the MFMU Research Network database and use of its contents for analysis of patient outcomes was approved by the Institutional Review Board at Columbia University Medical Center. The Wapner et al. trial randomly assigned women with singleton or twin gestations at high risk for preterm delivery between 23 and 31 6/7 weeks' gestation who received a single course of betamethasone to either weekly courses of betamethasone or placebo. The subset of singleton gestations only were included in this analysis. The trial did have a subset who received more than four courses of steroids; however this subset was not included in this analysis. Transitional probabilities for delivery were calculated using logistic regression analysis with SAS software, where the likelihood of delivery at each subsequent week following enrollment was estimated. Transitional probabilities for ACS and preterm birth outcomes were calculated for gestational age of entry into the study.

Negative outcome measures representing "risk" of ACS treatment included either SHC or SGA, both defined as $<10^{th}$ percentile (growth standards method for birth weight and head circumference are based on curves by Alexander and Lubchenco respectively).[13,14] Because of the low incidence of SHC and SGA, the probability of either of these ACS outcomes was calculated by summing the frequency of all patients with either SGA or SHC. The relative increase in risk associated with multiple courses of ACS was calculated by subtracting the frequency of births with SHC/SGA born to mothers receiving a single course of ACS from the frequency of babies with SHC/SGA born to mothers receiving multiple courses of ACS. Negative outcomes of preterm birth included RDS, CLD, severe IVH, PVL, BPD, or stillbirth. Similar to SHC and SGA, the incidence of these preterm birth outcomes are rare. As a result, they were also combined into a single composite event outcome and probabilities calculated by summing the frequency of all patients with any of the perinatal

outcomes defined above. Effectiveness or relative benefit of multiple courses of ACS compared to a single course was defined as “composite events (CE) averted”. CE averted was calculated by subtracting the frequency of births with a composite event born to mothers receiving multiple courses of ACS from the frequency of births with a composite event born to mothers receiving a single course of ACS.

The risk-benefit ratio of repeat ACS therapy in preterm birth for each gestational week was calculated by dividing frequency of CE averted by frequency of SGA/SHC outcomes, with values >1 signifying a more favorable risk-benefit ratio. These risk-benefit ratios for each week of gestational age at entry were compared to determine if there is a gestational age threshold where the risks of weekly courses of ACS outweigh the benefits. This model equates risks of ACS treatment including SGA and SHC to averted complications associated with preterm delivery such as RDS, CLD, IVH, PVL, BPD and fetal death. Although the relative importance of these outcomes may not be equivalent to providers or patients, in particular fetal death, the decision to not assign weights to the outcomes was made to again ensure the most conservative model was used when evaluating the potential benefits of multicourse steroids.

Clinical strategies were evaluated from the standard of care (1 course) of ACS for preterm labor to weekly courses of a maximum of two, three or four courses. The counter was set to a maximum value of 4 (no more than four courses of steroids). This was done in the model to replicate the clinical situation where a physician may use weekly courses of ACS to manage undelivered preterm labor. One hundred microsimulations (representing 100,000 hypothetical women) were passed individually through each treatment Markov model and outcomes (no complication versus ACS complication versus pre-term birth complication) and health states recorded. Each trial run signified a new random selection of the model.

All computations were performed using a commercially available decision-analysis software package (TreeAge Pro 2009, Tree Age Inc, Williamstown, MA), STATA 9.0 (StataCorp LP, College Station, TX) and SAS statistical software (SAS Institute, Inc, Cary, NC).

RESULTS

Preterm labor outcomes

The Markov model is evaluated as a Monte Carlo simulation for single course ACS and multiple courses of ACS. Predicted preterm birth outcomes, represented as a frequency of composite events (CE) and composite events averted by gestational age of entry, are shown in Table 1. Although the proportion of simulated singleton births with a CE is greatest in both treatment arms (multiple courses of ACS and a single course ACS) at 23 weeks’ gestation (Table 1), the count of CE averted reaches a maximum value at 25 weeks. Specifically, of the 100,000 theoretical cases, 29,566 patients (14,786 in single course and 14,780 in multiple courses) entered the simulation at 25 weeks’ gestation and of these, 1,157 cases of CE were averted when using multiple course ACS treatment compared to a single course ACS (Table 1). As expected, across each gestational week of entry there were decreased proportions of CE in preterm pregnancies that were exposed to multiple courses versus a single course of ACS (Table 1).

Antenatal corticosteroids outcomes

The relative increased risk of SGA/SHC in the multiple courses group compared to the single course group is shown in Table 2. Predicted ACS outcomes, represented as a frequency of either SGA or SHC by gestational age of entry for single and multiple courses of ACS is displayed. Both frequency and proportion of SGA/SHC in both multiple and

single course ACS initially decrease until 25 weeks' gestation in single course and multiple course groups (Figure 3).

Risk-benefit ratios

The most favorable risk-benefit ratio occurs during the 26th weeks' gestation, where nearly six babies are born without a CE to every baby born with either SGA/SHC. Risk-benefit tradeoffs by gestational age of first ACS course in the multiple course group compared to the single course group are shown in Table 3. By 29 weeks' gestation, the incremental benefit gained from multiple courses of ACS disappears as represented by a risk-benefit ratio of 1 (Figure 4). Beyond 29 weeks the model shows that the risks of multiple courses of ACS outweigh the benefits as indicated by a risk-benefit ratio of less than 1 (Table 3).

COMMENT

Based on this model multiple courses of ACS may be justified for threatened preterm birth presenting under 29 weeks' gestation. Maximal benefit of multiple courses of ACS occurs at 26 weeks' gestation. At 29 weeks' gestation, the preterm birth complications equal the adverse effects of multiple courses of ACS, and subsequent courses of ACS may result in more incidents of SGA/SHC than preterm birth complications averted. While the data from this model suggests that the use of multiple courses of ACS may be justified for pregnancies presenting with threatened preterm birth very early in gestation, the translation of this into clinical practice requires further study using larger cohorts of exposed and unexposed pregnancies at this early gestational age. The probabilities for this model were based on trials with small cohorts of women at risk for preterm delivery. Larger cohorts could result in larger sample sizes to define probabilities for each of the outcomes measured. Furthermore, while a prospective randomized control trial would be the gold standard for answering this question and would circumvent this issue, the feasibility of conducting this is limited by resources and possibly even clinical equipoise. The unique model developed for this analysis exhibits the potential of using a decision analytic tool to guide provider practice and impact policy when gestational age specific outcomes are compared and when performance of a clinical trial is unlikely.

There are many clinical factors involved in the use of multiple courses of ACS that are difficult to predict. For example an undelivered patient is more likely to receive weekly or additional courses of ACS if at continued risk for preterm delivery. There is also the concern that those who are identified as at-risk for preterm delivery earlier in gestation are more likely to get more courses of ACS with varying gestational age specific thresholds of susceptibility to adverse effects. To address this, we performed a micro simulation with a 100,000 patient cohort. Given the random probability of micro simulation, each gestational age of entry undergoes multiple different scenarios to ensure a diverse range in options for final analyses. The range of scenarios includes one, two, three or four steroid courses. Transitional probabilities at each gestational week in our model were calculated using the Wapner et al [8] trial data. We recognize that the sample size used to calculate these baseline probabilities were small in each gestational age grouping. This limitation may be alleviated in future decision-analytic models, which can utilize a meta- analysis technique to calculate overall probabilities from baseline probabilities from multiple trials.

Several studies suggest that multiple courses of ACS exposure in the setting of preterm delivery may be associated with an increased risk for certain neonatal adverse outcomes, including SGA and SHC. [14–17] However, one study of rescue steroids demonstrated that the use of a course of rescue steroids at less than 34 weeks gestation in those who have previously received a course can reduce morbidity and mortality with no difference in birth weight or head circumference.[18] Our model as developed was not able to take into account

use of rescue steroids across varying gestational ages. However, future decision analytic models may be designed to further assess this.

In the absence of validated weights for the different outcomes included in this model, the risks of ACS treatment were assumed to be equivalent to complications associated with preterm delivery to ensure the most conservative estimates of the beneficial effects of multicourse steroids. Understanding that the relative importance of SGA and SHC may not be comparable to averted complications, in particular fetal death, it is possible that benefits of multicourse steroid therapy may be underestimated. Thus care may be modified based on the provider's and patient's relative concern for each.

The benefits of decreasing the severity and occurrence of acute RDS and other lung disease in the very preterm neonate are well described. [8, 9, 15, 16] This must be balanced against potential steroid induced growth and neurocognitive deficits. However, to date, 2 to 3 year follow-up studies of infants exposed to multiple courses, including those with a reduced birth weight and head circumference have revealed no significant differences in weight, head circumference, height, or neurocognitive development in those exposed to repeated courses of steroids. [9, 15, 17, 19] Alternatively, some behavioral differences have been noted and one study showed an insignificant trend toward a greater risk of cerebral palsy. [17] The longer term clinical significance of multiple courses of ACS is unknown; however there is compelling evidence in animal studies.[20] It can be a challenge to clinically identify women at most risk of preterm labor, particularly when deciding if a repeat course is needed. Consideration should be given to the lowest dose of ACS needed to minimize risks of repeat ACS and maximize the beneficial effects of ACS. [20] The implications for disease in later life are significant and further studies are needed. Multiple courses of ACS initiated at less than 29 weeks' gestation may have increased benefit compared to risks. As new information regarding short and long term risks and benefits of ACS becomes available, our model could be modified to account for these new data.

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Appendix

The following subcommittee members participated in protocol development and coordination between clinical research centers (Michelle DiVito, M.S.N. and Francee Johnson, R.N., B.S.N.) and protocol/data management and statistical analysis (Lisa Mele, Sc.M. and Elizabeth Thom, Ph.D.)

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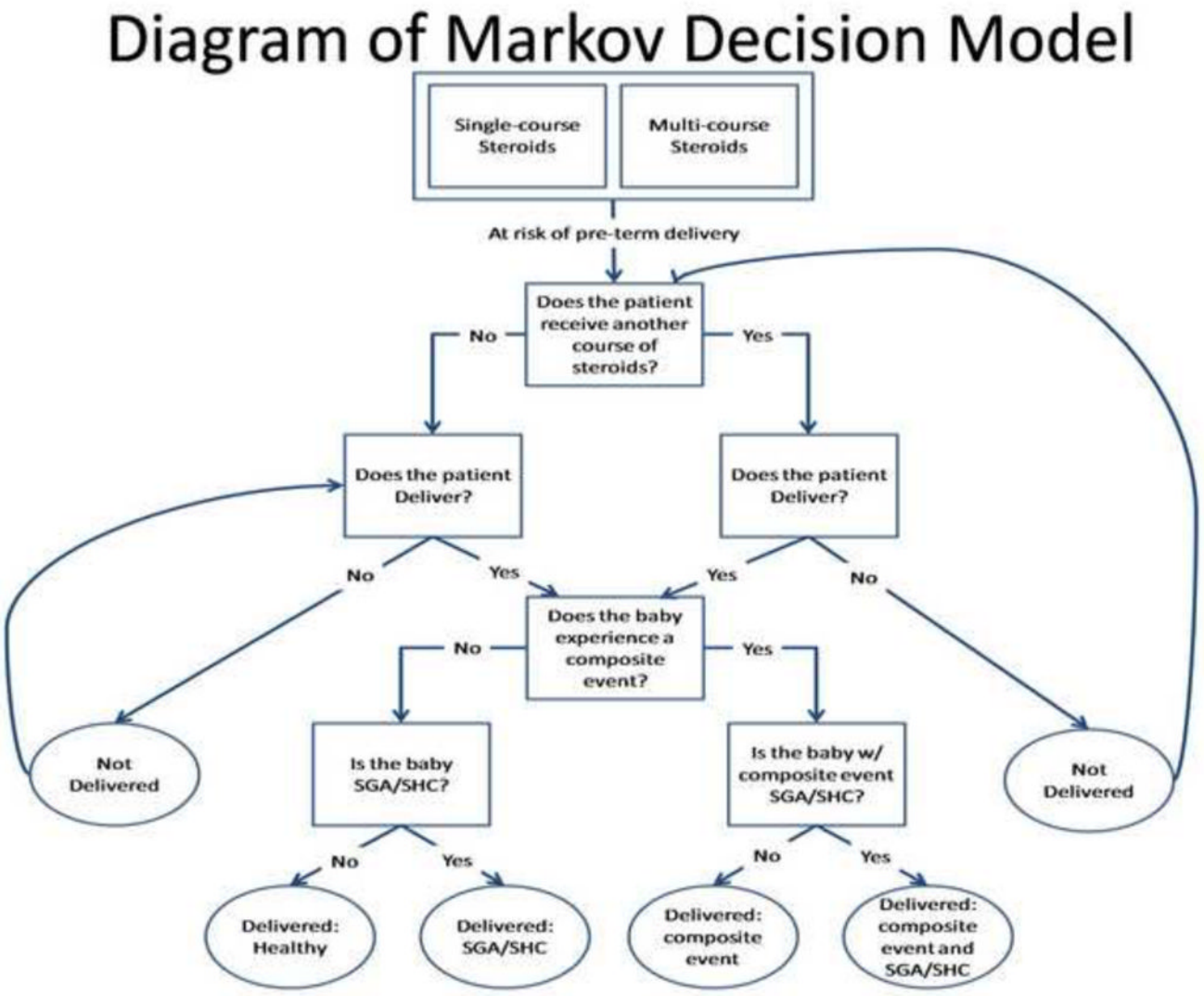

Figure 1.

The ovals at the bottom denote the four health states in the model and the arrows denote transitions between health states which the model assumes can occur on a weekly basis. When not delivered the model is re-started weekly and 100,000 microsimulations per treatment arm were performed in the model

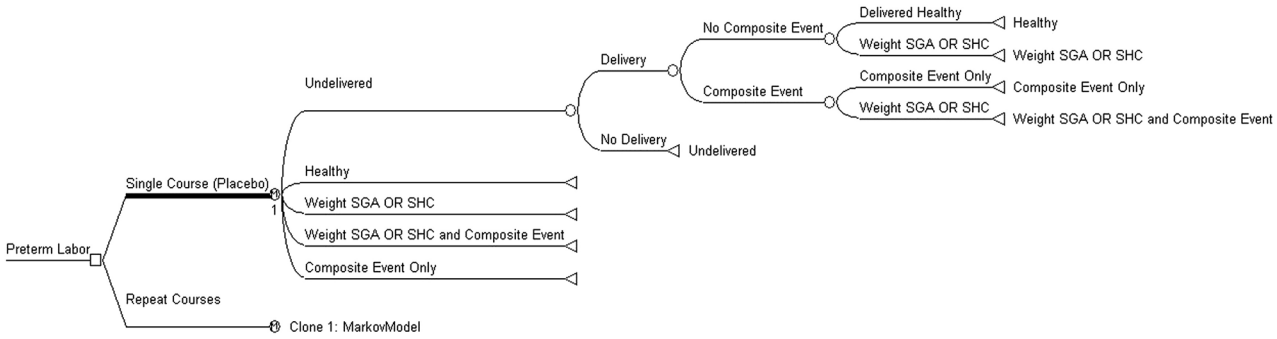

Figure 2.
Abbreviated decision tree for “risk benefit” of single course versus multiple courses of antenatal corticosteroids for the management of preterm labor

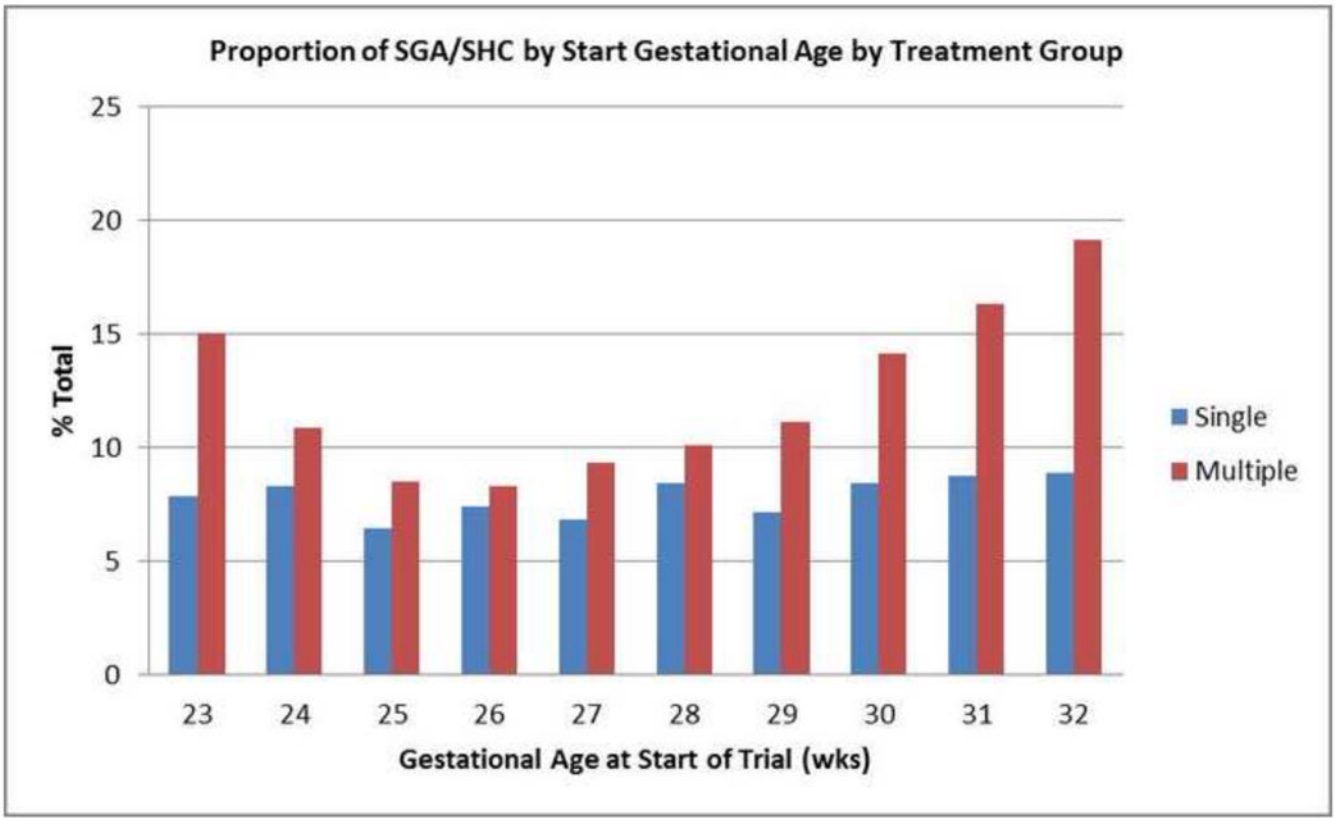

Figure 3.

Proportions of small for gestational age and small head circumference (SGA/SHC) in the entire study population. 100,000 trials were performed in the microsimulation. The x-axis has gestational age at entry. The y-axis is the proportion of SGA/SHC events that occurred within each start gestational age group n. An increased proportion of SGA/SHC are seen in multiple courses of ACS versus single course of ACS at each gestational age group of entry.

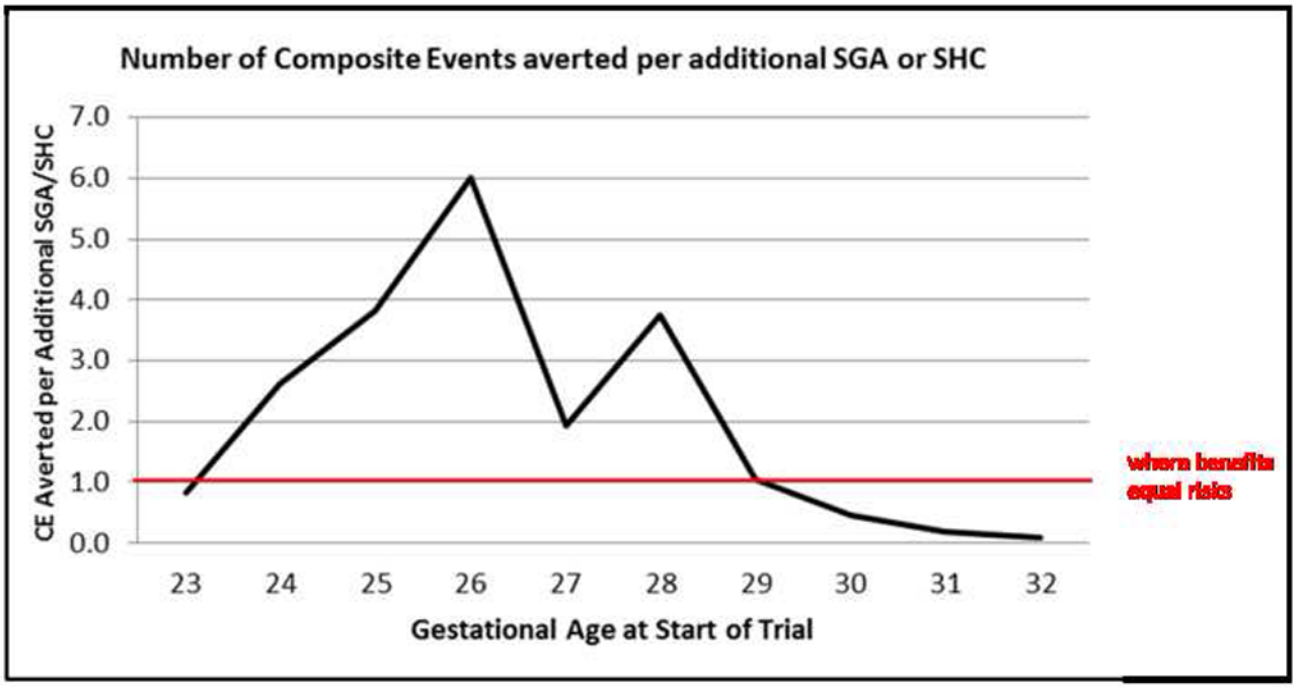

Figure 4.

Number of composite events averted per case of small for gestational age or small head circumference (SGA/SHC). The x-axis is gestational age at entry and the y – axis is number of composite events averted per case of SGA/SHC. A gestational age risk benefit threshold is seen at 29 weeks' gestation, where the risk equals the benefits.

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Table 1

Results of Composite Events Averted in single course versus multiple course groups. 100,000 micro simulation trials per treatment arm were performed in the decision-analytic model.

	Single Course			Multiple Courses			
Start Age (weeks)	**Composite Events (CE)**	**N**	**% Total**	**Composite Events (CE)**	**N**	**% Total**	**CE Averted**
23	260	944	28	192	1037	19	68
24	1955	7910	25	1406	7979	18	549
25	3099	14786	21	1942	14780	13	1157
26	2553	14242	18	1705	14328	12	848
27	1540	11151	14	986	11226	9	554
28	1016	9253	11	511	9079	6	505
29	1238	12751	10	694	12941	5	544
30	826	13094	6	490	12944	4	336
31	557	15610	4	345	15399	2	212
32	3	259	1	0	287	0	3
Total	13047	100000	13	8271	100000	8	4776

Table 2

Results of small for gestational age and small head circumference (SGA/SHC) in single course versus multiple courses ACS groups. 100,000 microsimulation trials were performed in the decision-analytic model per treatment arm.

	Single Courses			Multiple Courses			
Start Age (weeks)	SGA/SHC	N	% Total	SGA/SHC	N	% Total	Additional SGA/SHC
23	74	944	8	156	1037	15	82
24	655	7910	8	865	7979	11	210
25	956	14786	6	1259	14780	9	303
26	1053	14242	7	1194	14328	8	141
27	759	11151	7	1047	11226	9	288
28	782	9253	8	917	9079	10	135
29	914	12751	7	1437	12941	11	523
30	1101	13094	8	1830	12944	14	729
31	1366	15610	9	2511	15399	16	1145
32	23	259	9	55	287	19	32
Total	7683	100000	8	11271	100000	11	3588

Note: a rapid increase in the numbers of cases of SGA/SHC in the multiple course versus single course ACS groups is observed at weeks of entry 29, 30 and 31.

TABLE 3

Risk-Benefit Ratio (Single Course- baseline- Repeat Course (experimental). At week 26 the CE averted/SGA/SHC ratio is approximately 6:1- thus more composite events averted than SGA_SHC cases (indicating the most benefit at 26 weeks). Beyond week 29 the application of multiple courses of ACS has more risks than benefits.

Start Age (weeks)	Additional SGA/SHC	CE Averted	SGA/SHC per CE Averted	CE averted per additional SGA/SHC
23	82	68	1.2	0.8
24	210	549	0.4	2.6
25	303	1157	0.3	3.8
26	141	848	0.2	6.0
27	288	554	0.5	1.9
28	135	505	0.3	3.7
29	523	544	1.0	1.0
30	729	336	2.2	0.5
31	1145	212	5.4	0.2
32	32	3	10.7	0.1