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Antenatal corticosteroids and outcomes in gastroschisis: A multicenter retrospective cohort study

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Abstract

Objective: In gastroschisis, there is evidence to suggest that gut dysfunction develops secondary to bowel inflammation; we aimed to evaluate the effect of maternal antenatal corticosteroids administered for obstetric reasons on time to full enteral feeds in a multicenter cohort study of gastroschisis infants.

Methods: A three center, retrospective cohort study (1992-2013) with linked fetal/neonatal gastroschisis data was conducted. The primary outcome measure was time to full enteral feeds (a surrogate measure for bowel function) and secondary outcome measure was length of hospital stay. Analysis included Mann-Whitney and Cox regression.

Results: Of 500 patients included in the study, 69 (GA at birth 34 [25-38] weeks) received antenatal corticosteroids and 431 (GA at birth 37 [31-41] weeks) did not. Antenatal corticosteroids had no effect on the rate of reaching full feeds (Hazard ratio HR 1.0 [95% CI: 0.8-1.4]). However, complex gastroschisis (HR 0.3 [95% CI: 0.2-0.4]) was associated with an increased time to reach full feeds and later GA at birth (HR 1.1 per week increase in GA [95% CI: 1.1-1.2]) was associated with a decreased time to reach full feeds.

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Conclusion: Maternal antenatal corticosteroids use, under current antenatal steroid protocols, in gastroschisis is not associated with an improvement in neonatal outcomes such as time to full enteral feeds or length of hospital stay.

1 | INTRODUCTION

The most common postnatal gastroschisis-related morbidity is intestinal dysmotility with 50% of neonates taking >28 days to attain full enteral autonomy,[1,2] which carries a risk of central line sepsis and liver dysfunction from prolonged parenteral nutrition (PN). Although improved neonatal care and the advent of PN has reduced gastroschisis mortality from 60% in the 1960s to 3% to 10% in the 1990s,[1] there have been no advances in reducing gastroschisis-related intestinal dysfunction (GRID) and the time to achieve full enteral feeds.

A study mapping the natural history of fetal gastroschisis throughout gestation showed that bowel wall inflammation develops and increases during the third trimester of pregnancy.[3] In addition, amniotic fluid collected at 37 to 38 weeks gestation from fetuses with gastroschisis showed evidence of inflammation, including an elevation in neutrophil and mononuclear cell counts, and raised interleukin-8 concentration compared to age matched normal controls.[4] It has therefore been hypothesized that GRID is secondary to bowel wall inflammation during the third trimester. Animal models of gastroschisis (rabbit, rat and chick) treated with in utero dexamethasone injections have shown reduced bowel wall thickness, increased glucose uptake and increased bowel protein, DNA and enzyme content[5-7] suggesting a beneficial effect of dexamethasone on intestinal function. In humans, data are very limited but a single center prospective study of gastroschisis cases reported that maternal antenatal corticosteroids reduced duration of PN, time to full enteral feeds and length of hospital stay (Polnik et al. [unpublished] presentation at the Joint European Paediatric Surgeons' Association/British Association of Paediatric Surgeons Congress, Rome). Finally, a study of duodenal contractility, in otherwise normal premature neonates, showed that antenatal corticosteroids were associated with improved duodenal contractility[8] and antenatal corticosteroids are also known to be associated with lower rates of necrotizing enterocolitis in premature infants,[9] suggesting that corticosteroids may have a maturational effect on the intestine.

We aimed to determine whether or not maternal antenatal corticosteroids were associated with an improvement in postnatal intestinal function (measured as time to full enteral feeds) in infants with gastroschisis.

What's already known about this topic?

Infants born with gastroschisis often have a prolonged period before full enteral feeding is established. This period of gut dysfunction is thought to be secondary to the development of antenatal bowel inflammation. It is hypothesized that maternal antenatal corticosteroids may reduce bowel inflammation and therefore improve postnatal intestinal function.

What does this study add?

Maternal antenatal corticosteroid administration was not associated with an improvement in neonatal outcomes including time to full enteral feeds (surrogate marker for intestinal function) or length of hospital stay. There is no evidence to suggest that maternal antenatal corticosteroid administration improves postnatal intestinal function.

2 | METHODS

We performed an international, multicenter retrospective cohort study of infants with gastroschisis who were managed at the following linked fetal and pediatric surgical centers:

1. Fetal Medicine Unit, University College London Hospital (UCLH) and the Paediatric Surgery Department at Great Ormond Street Hospital for Children (GOSH), London, UK,
2. Fetal Medicine Unit at Mount Sinai Hospital (MSH) and the Division of General and Thoracic Surgery at The Hospital for Sick Children (HSC), University of Toronto, Canada and
3. Fetal Medicine Unit and Paediatric Surgery Department at King's College Hospital (KCH), London, UK.

Appropriate institutional approvals were obtained (MSH Research Ethics Board project number 14-0231-C was approved on October 20th 2014, HSC Research ethics Board project number 1000032644 was approved on July 31, 2014, whereas UCLH, GOSH and KCH approved the study as audits and waived the need for ethical approval) to collect antenatal and neonatal data by retrospective chart review without the need for patient consent. Linked fetal and neonatal gastroschisis data were collected for patients admitted between January 1992 and July 2014. Any fetus or neonate treated outside of the study centers was excluded from the study. Gastroschisis cases were identified through interrogation of hospital databases and patient data obtained from computerized and handwritten charts.

During the study period, all centers undertook regular (1-2 weekly) monitoring of wellbeing in fetuses with gastroschisis after 30 weeks

gestation and delivered neonates via elective vaginal delivery by induction of labor at 37 to 38 weeks gestation.[2,10] Delivery by cesarean section was performed only if deemed necessary for other obstetric concerns. Delivery before 37 weeks of gestation was performed if there were fetal or maternal indications including; nonreassuring biophysical profile or nonstress test, presence of marked intra-abdominal bowel dilatation, maternal health concerns or if labor occurred spontaneously. Maternal antenatal corticosteroids (betamethasone, two doses of 12 mg intramuscularly [IM] 24 hours apart or dexamethasone, four doses of 6 mg IM 12 hours apart) were given for fetal lung maturation if preterm labor occurred <34^{+0} weeks or caesarean section ≤38^{+6} weeks (the latter in UK centers only) occurred.

Data collected included gestational age (GA) at birth (calculated as a continuous variable with incomplete week gestation calculated as a decimal [eg, 34^{+5} = 34.7]), timing, dosage and reason for maternal antenatal corticosteroid administration and gastroschisis complexity (simple gastroschisis defined as otherwise healthy contiguous bowel; complex gastroschisis defined as concomitant bowel necrosis, atresia, stenosis or perforation[1]).

The primary outcome measure was time to establishment of full enteral feeds (ENT) and to be considered a surrogate for bowel function. Secondary outcome measures included length of hospital stay (LOS), defined as time from birth to hospital discharge, length of intensive care unit (ICU) stay, necrotizing enterocolitis, defined as Bell's stage 2 or more and sepsis (defined as isolation of a pathogenic organism from blood).

The data were described as median (range) and analyzed using Mann-Whitney for univariate analysis and Cox regression or binary logistic regression for multivariate analysis. Those infants who failed to achieve full enteral feeds (death, long term PN dependence, transfer to another hospital on PN) remained in the Cox regression analysis but were censored at the point of discharge/death. We identified complex gastroschisis, birth GA and source hospital as potential confounders and adjusted for these variables in our regression models alongside maternal antenatal corticosteroid administration. Statistical analysis was performed using GraphPad Prism v6 and SPSS v22 software. A *P*-value of <.05 was considered statistically significant.

3 | RESULTS

3.1 | Study population and demographics

Five hundred and ten infants with gastroschisis were eligible for the study. It was not possible to ascertain the status of maternal antenatal corticosteroid administration in 10 infants who were excluded from the analysis. Of the 500 infants included, 69 (GA at birth 34 [25-38] weeks) were born to mothers who received antenatal corticosteroids (none received multiple courses) whereas 431 (GA at birth 37 [31-41] were born to mothers who did not receive antenatal corticosteroids. There was an even distribution of infants who received and did not receive antenatal corticosteroids across the study centers (Table 1). Of the 69 infants who received maternal antenatal corticosteroids, 56 received a full course (total of 24 mg of betamethasone or dexamethasone in divided IM doses) and 13 a partial course (less than 24 mg of betamethasone or dexamethasone in divided IM doses). The administration of the corticosteroids varied across the group with two infants receiving corticosteroids <24 hours before birth, 42 infants between >24 hours and ≤7 days before birth, 23 infants at >7 days before birth and for two infants the time of administration was unknown. Maternal antenatal corticosteroids were administered for the following reasons; elective caesarean section delivery at 36 weeks GA (n = 3), premature labor (n = 15), threatened premature labor (n = 18), planned delivery at <37 weeks for bowel dilatation (n = 20), premature delivery for obstetric reasons (n = 10) or unknown (n = 3). As expected, infants whose mothers had received corticosteroids were born at a significantly lower GA and birth weight compared to those whose mothers had not received corticosteroids (Table 1).

3.2 | Postnatal outcomes

3.2.1 | Univariate analysis

A significantly higher proportion of "complex" patients (22%) had received maternal steroids compared with "simple" patients (12%, *P* = .03). Table 2 indicates how many simple and complex patients had

TABLE 1 Gastroschisis study population and demographics

	Maternal antenatal corticosteroids		
	No steroids	Steroids	
Study population			
Total patients included (n = 500)	431 (86%)	69 (14%)	
Centre 1 (n = 150)	128 (85%)	22 (15%)	
Centre 2 (n = 122)	103 (84%)	19 (16%)	
Centre 3 (n = 228)	200 (88%)	28 (12%)	
Birth demographics			*P*-value
Birth GA (weeks)	37.0 [30.6-41.3]	34.0 [25.1-38.3]	<.0001
Birth weight (g)	2500 [220-3884]	1960 [540-3380]	<.0001
Male	217	36	.99
Female	214	33	

TABLE 2 Gastroschisis complexity, corticosteroid administration and neonatal outcomes

	No steroids	Steroids	*P*-value
Breakdown of simple and complex gastroschisis patients (>1 pathology in 9 complex patients)			
Simple (n = 424, 85%)	372 (88%)	52 (12%)	.03
Complex (n = 76, 15%)	59 (78%)	17 (22%)	
Atresia (n = 42)	30	12	
Necrosis (n = 28)	22	6	
Perforation (n = 14)	13	1	
Stenosis (n = 8)	7	1	
Neonatal outcomes in univariate analyses			
Time to first enteral feed (days)*	12 [2-101]	13.5 [2-186]	.58
Time to full enteral feeds (days)*	26 [4-283]	30 [2-590]	.01
Length of hospital stay (days)*	35 [7-349]	46 [20-346]	.003
Deaths (n = 23, 5%)	18 (4%)	5 (7%)	.23

Note: Univariate analysis included Mann-Whitney (*median[range]) and Fisher's exact test. NB: 9 complex patients had >1 bowel pathology.

TABLE 3 The effect of antenatal maternal corticosteroids, complexity of gastroschisis and gestational age at birth on ENT and LOS

Cox regression category	Impact on ENT	HR [95% CI] *P*-value	Impact on LOS	HR [95% CI] *P*-value
Maternal antenatal corticosteroids	No effect	1.0 [0.8–1.4] 0.8	No effect	1.1 [0.7–1.5] 0.8
Complexity of gastroschisis	↑ with complex gastroschisis	0.3 [0.2–0.4] <0.001	↑ with Complex gastroschisis	0.3 [0.2–0.4] <0.001
Gestational age (GA) at birth	↓ with ↑ GA	1.1 [1.1–1.2] <0.001	↓ with ↑ GA	1.2 [1.1–1.3] <0.001

Note: Cox regression adjusted for complex gastroschisis, birth GA, source hospital and antenatal corticosteroid administration and censored for death, not achieving full feeds and not being discharged from hospital as appropriate. Data for gestational age at birth is per week later birth.
Abbreviations: CI, confidence interval; ENT, enteral feeds; HR, hazard ratio; LOS, length of hospital stay.

received maternal antenatal corticosteroids, along with the reason for classification as complex, and neonatal outcomes. Univariate analyses showed time to full feeds and length of hospital stay were significantly longer in infants whose mothers had received antenatal corticosteroids, possibly due to the higher proportion of complex patients and lower GA at birth.

3.2.2 | Multivariate analysis

Cox proportional hazard model (in which "hazard" is a specific term to denote the rate at which any event, either positive or negative, has happened) was performed in order to account for likely confounders (complex gastroschisis, birth GA and source hospital) within the univariate analysis. Analysis revealed that the administration of maternal antenatal corticosteroids had no effect on the hazard of reaching full enteral feeds (hazard ratio 1.0 [95% CI: 0.8-1.4], $P = .8$), hazard of being discharged from hospital (hazard ratio 1.1 [95% CI: 0.7-1.5], $P = .8$), or being discharged from the ICU (hazard ratio 0.9 [95% CI 0.6-1.4], $P = .7$; Table 3). Infants with complex gastroschisis had significantly lower hazard of reaching full feeds (hazard ratio 0.3 [95% CI: 0.2-0.4], $P < .001$) and being discharged from hospital (hazard ratio 0.3 [95% CI: 0.2-0.4], $P < .001$; Table 3). Conversely, those born at a later birth GA had a significantly higher hazard of reaching full feeds (hazard ratio 1.1 per week of later birth [95% CI: 1.1-1.2], $P < .001$) and hazard of being discharged from hospital (hazard ratio 1.2 per week of later birth [95% CI: 1.1-1.3], $P < .001$; Table 3). Source hospital had no effect on the hazard of reaching full enteral feeds (comparing against center 3: center 1 hazard ratio 1.2 [95% CI: 0.9-1.5], $P = .2$ and center 2 hazard ratio 1.2 [95% CI: 1.0-1.5], $P = .1$) but had a significant effect on the hazard of hospital discharge (comparing against center 3: center 1 hazard ratio 1.3 [95% CI: 1.0-1.6], $P = .07$ and center 2 hazard ratio 1.5 [95% CI: 1.2-1.9], $P = .001$) likely due to different discharge policy in center 3.

We therefore performed further hypothesis-generating analyses to investigate in detail whether maternal antenatal corticosteroid administration had any associated effect on the outcome of neonates with gastroschisis. As failure to complete the maternal antenatal corticosteroid course may have impacted on the therapeutic effect, we repeated the analysis including only those infants who received a

complete course (n = 56), which again showed no difference in time to full enteral feeds (hazard ratio 0.9 [95% CI: 0.4-1.2], P = .4) and length of hospital stay (hazard ratio 0.9 [95% CI: 0.6-1.2], P = .4). To remove the effect of outliers and extreme prematurity, we also analyzed only patients born between 31^{+0} and 36^{+6} weeks gestation (n = 65 received corticosteroids, n = 207 did not receive corticosteroids), which showed no effect on time to full enteral feeds (hazard ratio 0.9 [95% CI: 0.6-1.2], P = .4) or length of hospital stay (hazard ratio 1.2 [95% CI: 0.8-1.7], P = .4). This was also repeated including only those infants born at 34 weeks GA or above (n = 44 received steroids, n = 420 did not). There was no difference between administration of antenatal corticosteroids and time to full enteral feeds (hazard ratio 1.2 [95% CI: 0.7-1.5], P = .9) or length of hospital stay (hazard ratio 1.0 [95% CI: 0.7-1.5], P = 1.0). Those born at <34 weeks were also analyzed as a separate group (n = 25 with steroids, n = 11 no steroids), again no effect on time to full enteral feeds (hazard ratio 1.0 [95% CI: 0.4-2.2], P = .9) or length of hospital stay (hazard ratio 0.7 [95% CI: 0.3-1.6], P = .4) Additionally, we investigated whether antenatal corticosteroids reduced the time to first enteral feed, again showing no difference (hazard ratio 1.0 [95% CI: 0.7-1.5], P = .8). As the intestinal function of infants with complex gastroschisis may be adversely affected by concomitant intestinal pathologies (atresia, stenosis, necrosis and perforation) an analysis including only simple gastroschisis patients (n = 372 did not receive corticosteroids n = 52 received corticosteroids) was performed. Similarly, this analysis showed no effect on time to full enteral feeds (hazard ratio 1.0 [95% CI: 0.7-1.4], P = .8) or length of hospital stay (hazard ratio 1.0 [95% CI: 0.7-1.5], P = 1.0). To determine whether changes in neonatal practice over the 22 year study period were associated with improved gastroschisis outcomes, we added year of birth into our Cox regression model and this showed again no difference in time to full enteral feeds (hazard ratio 1.0 per year later birth [95% CI: 1.0-1.0], P = .5) or length of hospital stay (hazard ratio 1.0 per year later birth [95% CI: 1.0-1.0], P = .6). Finally, we examined whether the use of a silo affected outcomes. Infants who had a silo at any time had a significantly increased time to full feeds (hazard ratio 0.6 [95% CI: 0.5-0.7], P < .0005) and hospital stay (hazard ratio 0.6 [95% CI: 0.5-0.8], P < .0005) but steroids still did not have any effect when silo was included in the analysis (hazard ratio 1.0 [95% CI: 0.7-1.4] for both time to full feeds and hospital stay.

3.3 | Analysis of other outcomes: necrotizing enterocolitis and sepsis

Significantly more infants who had received antenatal steroids experienced an episode of NEC than those who had not (11/69 vs 21/431, P = .002). However, after adjusting for GA at birth, this difference was no longer significant (odds ratio [OR] 2.6 [95% CI: 1-6.8], P = .058). There was no difference in the incidence of sepsis between those who had received antenatal steroids and those who had not (univariate 25/69 vs 123/431, P = .2; multivariate OR 0.8 [95% CI: 0.4-1.5] P = .49).

4 | DISCUSSION

Our analysis of linked maternal and neonatal data from 500 cases of gastroschisis indicated that maternal antenatal corticosteroid administration was not associated with any effect on time to full enteral feeds, or length of hospital stay. In keeping with the published literature, we identified that both complex gastroschisis[1,11] and lower GA at birth[12-14] were associated with a significant increase in the time to full enteral feeds and length of hospital stay.

Amniotic fluid composition significantly changes after 25 weeks gestation.[15] These changes in amniotic fluid composition coincide with the increase in bowel wall inflammation in fetuses with gastroschisis in the third trimester[3] although we do not know whether changes in amniotic fluid composition are associated with GRID. We speculate that our findings of null effect could be due to late administration of steroids in our cohort during gestation. It is possible that if administered at the start of third trimester steroids might prevent the onset of bowel inflammation and in turn the gastrointestinal damage leading to intestinal dysfunction. In addition, it is also important to note that antenatal corticosteroids are fast acting with a short half-life,[16] suggesting the effect of early corticosteroid administration would be short lived. This implies that multiple courses might be required throughout the third trimester to exert a prolonged anti-inflammatory effect. However, concerns have been raised regarding multiple courses of antenatal corticosteroids even for threatened preterm births.[17-19] Given this uncertainty and the lack of apparent benefit identified in our cohort, it will be difficult to conceive a trial of multiple courses of maternal antenatal corticosteroids to improve postnatal intestinal function in fetuses with gastroschisis unless more data are available from relevant animal models. Of relevance, the recent randomized controlled trial of amnioexchange to decrease amniotic fluid-derived inflammation in gastroschisis also found no benefit.[20] Although in a multicenter French study there was an apparent benefit of corticosteroid administration on number of surgeries and time on PN,[21] these data were not controlled for major confounders such as complexity and birth GA, both of which we showed to be significantly associated with time to full enteral feeds in our study.

Our data suggested that corticosteroid administration to all mothers with gastroschisis fetuses has no effect. We undertook further hypothesis-generating analyses to explore whether there might be a subset in whom there might be a benefit. None of these analyses revealed any associated differences in gastroschisis postnatal outcomes. These data suggest that simply reducing inflammation or an intestinal maturational effect from a course of maternal antenatal corticosteroids does not prevent or reverse the intestinal changes that are responsible for postnatal GRID. It is possible that steroid administration is inadequate to prevent or reverse inflammation resulting in GRID, or that GRID is due to other causes such as mechanical factors and/or ischemic changes in the intestine.

We acknowledge the limitations of our retrospective cohort study. The antenatal care, delivery and postnatal care of cases were not standardized, and dosage and timing of antenatal corticosteroids was not controlled. In addition, centers have different policies

regarding surgical and nutritional management. To account for potential effects associated with differing antenatal and neonatal management policies, we adjusted for source hospital within our Cox regression model, although this may not account for all confounders. Also, maternal antenatal corticosteroids were administered for lung maturation to patients with threatened preterm labor or who were delivered early for other maternal or fetal concerns and not for the purpose of anti-inflammatory actions. As such, the antenatal corticosteroid group were born earlier and thus potentially had worse infant outcomes. We have accounted for these factors, as far as possible, by adjusting for GA at birth within our Cox regression model, performing a post hoc analysis of patients born between 31^{+0} and 36^{+6} weeks gestation, thus removing extreme outliers, and analyzing separately those born at 34 weeks or above and less than 34 weeks gestation. Antenatal corticosteroids were given for different reasons, and it is difficult to completely account for this in the analyses. Although gastroschisis complexity was a significant predictor of longer time to full feeds and length of hospital stay, it should also be borne in mind that complex gastroschisis cannot reliably be identified antenatally, so although complexity is an important confounder in the analyses, it could not have been used for stratifying any prospective trial of steroids. No fetuses received maternal corticosteroids at or beyond 37 weeks of gestation, and it is possible that late administration of steroids could improve outcomes. As it is unlikely that post-37 week gastroschisis fetuses would receive maternal corticosteroids under current protocols, a prospective pilot study or randomized controlled trial would be necessary to determine whether steroids could have a beneficial effect closer to normal term.

However, the strength of this study comes from the large number of patients from three centers in two countries, yielding data that very consistently shows no association between antenatal corticosteroid administration and improved postnatal outcomes. Although overall our data collection included 500 gastroschisis infants, only 69 pregnancies received steroids, which limits the power of our study to detect differences in time to full feeds. With this number of patients, and ratio of pregnancies in which steroids was administered to those in which they were not administered, we would have had 80% power to detect a hazard ratio of 1.5 (alpha = .05), which is close to the upper limit of the 95% confidence interval of our estimate if the allocation had been random. This was clearly not the case in our study, nevertheless, our data do not provide support for conducting a randomized controlled trial of steroid administration.

Although there was no evidence for benefit of steroids in our study, there was also none for adverse effects in the outcomes measured: time to full feed, hospital stay, ICU stay, NEC or sepsis, so our data do not suggest that current maternal steroids should protocols for prematurity should be changed when gastroschisis has been diagnosed.

5 | CONCLUSIONS

Maternal antenatal corticosteroids use, under current antenatal steroid protocols, in gastroschisis might not be associated with an improvement in neonatal outcomes such as time to full enteral feeds or length of hospital stay.

There is a need for further research into the pathophysiology underpinning gastroschisis-related intestinal dysfunction in order to develop either prenatal or postnatal therapies to improve intestinal function.

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CONFLICT OF INTEREST

The authors report no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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