Mini-CAT: Summer 2019
Rotation 6, Week 4

Clinical Question:
While in the NICU, we came across the topic of spina bifida and wanted to know whether delivery method affects the size of the spinal defect, especially due to the increased pressure needed to deliver the baby during vaginal delivery.

Search Question:
Are Caesarian sections a superior mode of delivery for fetuses with open neural tube defects, in particular myelomeningocele (spina bifida) as compared to vaginal delivery?

PICO Question:

P	I	C	O
Pediatrics/infants	Caesarian section	Vaginal delivery	Improved neurological outcomes
Myelomeningocele	C-section	Normal spontaneous vaginal delivery	Increased motor functional level
Spina bifida			Less neurodevelopmental consequences
Open neural tube defects			Less complications

Search Strategy:

Search tools and strategy used:

Database	Terms Used	Filters Applied	# of Articles
PubMed	Optimal mode of delivery neural tube defect	Humans	4
Cochrane Library	Neural tube defect best delivery	-	2
ScienceDirect	Optimal mode of delivery neural tube defect	5 years, review articles	124

Due to the nature of the topic, it is understandable that there may not be RCTs comparing vaginal delivery and Caesarean delivery because ultimately, it is up to the patient whether she wants to deliver vaginally or via C-section. It also does not make sense to randomly assign patients a delivery method because they should have a choice.

In PubMed, there were only 4 articles left after applying the “humans” filter. The first article is one of the first meta-analyses to cover the neurological outcomes by mode of delivery for infants with open neural defects such as spina bifida that was very recently published in February 2019. The authors acknowledge that there is current controversy on which delivery method is safer and more beneficial for such patients. They conducted a search from multiple databases such as MEDLINE, Embase, Scopus, and

ClinicalTrials and paid particular attention to possible study biases. Ultimately, they identified 9 studies with 672 total women, 327 who underwent vaginal delivery and 345 who underwent C-section.

As for the second article, although it is not the highest level of evidence being a retrospective cohort, it still provides valuable information due to the in unavailability of RCTs and because it tracked patients backwards since birth, enabling us to determine whether the delivery method contributed to worsening of the open neural tube defects or other consequences or complications later on in time. Again, this study mentions that previous studies suffered from nonstandardized outcome measures, selection bias, relatively small sample sizes, and that larger studies date back over 15 years, thus requiring more recent research. This study was conducted in the University of Pittsburgh Medical Center and identified 72 maternal-neonatal pairs. The primary outcome measured was the different between functional/anatomic motor levels in children at the age of 2 based on their mode of delivery.

The third article is also a retrospective cohort conducted in the Netherlands. However, the methods and outcomes of this study aligned with the previous studies. Again, this retrospective cohort sought to determine whether vaginal delivery or C-section affected early neurological outcomes in infants with spina bifida, which is consistent throughout the previous articles as well. As a result, we may have stronger evidence to support our clinical bottom line if both the United States and other countries come to the same conclusion. There were 95 neonates evaluated and in addition to assessing the difference between the functional and neurological level of the defect, they also evaluated this using X-ray. Additionally, they specified where the neural tube defects were in the infants, with 21.1% in the thoracic region, 76.8% in the lumbar region, and 2.1% in the sacral region of the spine.

The fourth article is a retrospective cohort from 2017 that compared the differences in mode of delivery used for infants with myelomeningocele. It gathered data from the Healthcare Cost and Utilization's National Inpatient Sample to find a total of 10,147 hospitalizations for deliveries among women with infants with myelomeningocele and 42,197,763 (!!!) for those without. Additionally, this study compared the rates of C-section now for myelomeningocele now versus that in the past to see if trends are currently changing.

Citation	1. Neurological outcomes by **mode** of **delivery** for fetuses with open **neural tube defects**: a systematic review and meta-analysis. Tolcher MC, Shazly SA, Shamshirsaz AA, Whitehead WE, Espinoza J, Vidaeff AC, Belfort MA, Nassr AA. BJOG. 2019 Feb;126(3):322-327. doi: 10.1111/1471-0528.15342. Epub 2018 Jul 18. PMID: 29924919
Abstract	**Abstract** **BACKGROUND:** Controversy exists regarding the optimal mode of delivery for fetuses with open neural tube defects. **OBJECTIVE:** To compare neurological outcomes among infants with open neural tube defects who underwent vaginal compared with caesarean delivery. **SEARCH STRATEGY:** Electronic databases MEDLINE, EMBASE, Scopus, and Clinicaltrials.gov were searched from inception to November 2017.

	SELECTION CRITERIA: Eligible studies included observational or randomised studies comparing vaginal and caesarean delivery in pregnancies with fetal open neural tube defects who did not undergo prenatal repair. **DATA COLLECTION AND ANALYSIS:** Two reviewers independently reviewed abstracts and full-text articles. Outcomes were compared between vaginal and caesarean delivery and prelabour caesarean versus exposure to labour. The primary outcome was motor-anatomic level difference. Secondary outcomes included shunt requirement, sac disruption, meningitis, and ambulation at 2 years. Meta-analysis was performed and mean difference or odds ratios with 95% CI were calculated. **MAIN RESULTS:** Of 201 abstracts identified in the primary search, nine studies (672 women) met the eligibility criteria. Comparing vaginal and caesarean delivery, there was no significant difference in motor-anatomic level difference (mean difference -0.10, 95% CI -0.58 to 0.38; I^2 = 57%). The vaginal delivery group was less likely to require a shunt or have sac disruption [odds ratio (OR) 0.37, 95% CI 0.14-0.95 and OR 0.46, 95% CI 0.23-0.90, respectively]. Comparisons by prelabour caesarean versus exposure to labour showed no significant difference in motor-anatomic level difference (OR 1.29, 95% CI 0.63-3.21) or ambulation at 2 years (OR 2.13, 95% CI 0.35-13.12). **CONCLUSION:** Caesarean delivery was not associated with improved neurological outcomes among fetuses with open neural tube defects.
PDF Link	Article 1 - Tolcher

Citation	2. The impact of **mode** of **delivery** on infant neurologic outcomes in myelomeningocele. Greene S, Lee PS, Deibert CP, Tempel ZJ, Zwagerman NT, Florio K, Bonfield CM, Emery SP. Am J Obstet Gynecol. 2016 Oct;215(4):495.e1-495.e11. doi: 10.1016/j.ajog.2016.05.028. Epub 2016 May 27. PMID:27242203
Abstract	**Abstract** **BACKGROUND:** Controversy exists regarding the optimal route of delivery for fetuses who are diagnosed prenatally with myelomeningocele. Current recommendations are based partly on antiquated studies with questionable methods. All studies that have been published to date suffer from nonstandardized outcome measures, selection bias, and small sample size. The larger studies are >15 years old. **OBJECTIVE:** The purpose of this study was to provide information for evidence-based decision-making regarding the impact of route of delivery on motor outcomes for pediatric patients with prenatally were diagnosed myelomeningocele in a well-defined retrospective cohort. **STUDY DESIGN:** Medical records were reviewed retrospectively for all neonates who had been diagnosed with a myelomeningocele at birth from 1995-2015 within the University of Pittsburgh Medical Center system, as identified through the Children's Hospital of Pittsburgh

	Neurosurgery Department operative database. Records were matched with maternal records with the use of the Center for Assistance in Research that used eRecord. Data from 72 maternal-neonatal pairs were analyzed for multiple variables. The primary outcome measure was the difference between the functional and anatomic motor levels in the child at the age of 2 years, stratified by mode of delivery and presence or absence of labor. The sample size necessary to detect a difference between the groups with power of 0.8 and significance of .05 was calculated to be 52 subjects total (26 per group). **RESULTS:** Functional levels were slightly better than predicted by anatomic levels for all pediatric patient groups, regardless of mode of delivery or presence of labor. Anatomic levels were slightly lower (better), and defects were smaller for those infants who underwent vaginal delivery or a trial of labor, likely attributable to selection bias. Attempts to correct for this selection bias did not change the results. No other outcomes that were analyzed were associated significantly with mode of delivery or presence of labor. **CONCLUSION:** No benefit to motor function from delivery by cesarean section or avoidance of labor was demonstrated statistically in this mother-infant cohort.
PDF Link	Article 2 - Greene

Citation	3. Influence of birth **mode** on early neurological outcome in infants with **myelomeningocele**. Cuppen I, Eggink AJ, Lotgering FK, Rotteveel JJ, Mullaart RA, Roeleveld N. Eur J Obstet Gynecol Reprod Biol. 2011 May;156(1):18-22. doi: 10.1016/j.ejogrb.2011.01.012. Epub 2011 Feb 17. PMID: 21333435
Abstract	**Abstract** **OBJECTIVE:** The aim of the study was to determine whether route of birth affects early neurological outcome in infants with myelomeningocele. **STUDY DESIGN:** In a retrospective cohort study, 95 neonates with myelomeningocele evaluated at the Radboud University Nijmegen Medical Centre between 1990 and 2006 were reviewed. The effect of delivery mode on early neurological outcome was assessed as the difference between the functional neurological level of the defect and the X-ray level (ΔFAX). **RESULTS:** Early neurological outcome was better in the vaginally delivered infants (ΔFAX 0.96 ± 2.1) than in those delivered by cesarean section (ΔFAX 0.20 ± 2.5). After correction for confounders, multiple regression analysis demonstrated that vaginal deliverywas associated with significantly better early neurological outcome as compared to cesarean section (β=1.21; 95% CI 0.16; 2.27; p=0.03) for infants in vertex and breech position combined. Subgroup analysis revealed a non-significant trend towards better outcome after vaginal delivery that was more pronounced in infants in breech position than in vertex position. **CONCLUSION:** In infants with myelomeningocele, born in either vertex or breech position, there is no

	clinical evidence that early neurological outcome is improved by cesarean section.
PDF Link	Article 3 - Cuppen

Citation	4. **Pregnancy** among **mothers** with **spina bifida**. Shepard CL, Yan PL, Hollingsworth JM, Kraft KH. J Pediatr Urol. 2018 Feb;14(1):11.e1-11.e6. doi: 10.1016/j.jpurol.2017.08.001. Epub 2017 Sep 6. PMID: 28943353
Abstract	**Abstract** **INTRODUCTION:** Recognizing the importance of sexual and reproductive health to patients with spina bifida (SB), pediatric urologists have taken responsibility for initiating conversations regarding this topic with adolescent and young adult SB patients. However, the sexual and reproductive health of women with SB remains under-investigated. It is unknown how many women are having babies, what mode of delivery is used, and if this has changed over time with the increasing life expectancy of these patients. A better understanding of pregnancy and delivery among young women with SB will enable urologists to provide more informed, comprehensive counseling to patients. **OBJECTIVE:** We sought to compare hospitalizations for delivery in women with and without SB to determine differences in the mode of delivery used and changes in the rate of deliveries over time. **STUDY DESIGN:** Using the Healthcare Cost and Utilization's National Inpatient Sample, we identified all hospitalizations for delivery in 2003-2013. After distinguishing between hospitalizations among women with and without SB, temporal trends analysis and bivariate comparison were performed to determine differences in patient and hospital characteristics and mode of deliveries. **RESULTS:** We identified 10,147 hospitalizations for deliveries among women with SB and 42,197,763 among women without. Of all hospitalizations for deliveries, the percentage of deliveries by women with SB increased by 56% between 2003 and 2013 (629-925 deliveries per year, $p < 0.001$). Women with SB hospitalized for a delivery differed from those without SB. They had a higher number of comorbidities and were more likely to be white, have Medicare or private insurance, live outside a city, and deliver at an urban teaching hospital (all $p < 0.001$). Women with SB were significantly more likely to undergo a caesarean section (see Figure, 52.4% of women with SB vs. 31.9% of those without, $p < 0.001$), although nearly half were able to undergo vaginal delivery. For women with SB, 25.9% of all deliveries occurred by age 22, which did not differ significantly from women without SB (24.7% of all deliveries). **DISCUSSION:** There are significant differences in the characteristics and mode of delivery between women with and without SB who are hospitalized for a delivery. The number of deliveries among these women are significantly increasing and over a quarter of the deliveries occur by age 22.

	CONCLUSION: With increasing rates of deliveries and young age at delivery for women with SB, it is imperative that pediatric and transitional urologists initiate discussions on sexual and reproductive health beginning in adolescence.
PDF Link	Article 4 - Shepard

Summary of the Evidence:

Author (Date)	Level of Evidence	Sample/Setting (# of subjects/ studies, cohort definition etc.)	Outcome(s) studied	Key Findings	Limitations and Biases
Tolcher, et. al., 2019	-Meta-analysis/systematic review	-Conducted in accordance to MOOSE guidelines -Databases used include MEDLINE, Embase, Scopus, Clinicaltrials.gov using the following terms: neural tube defect, myelomenigocele, mode of delivery, caesarean, delivery -Ultimately included 9 studies (1 prospective cohort, 8 retrospective cohorts) with 672 women, 327 vaginal delivery and 345 caesarean delivery	-Primary outcome was difference in motor and anatomic level of paralysis, determined by subtracting anatomic level of lesion from motor level -Secondary outcomes were shunt requirement, sac disruption, meningitis, ambulation at 2 years follow up	-There are no improved neurological outcomes in fetuses with open neural tube defects delivered via C-section -Worsening motor function, the requirement of a shunt, sac disruption, and meningitis are not supported by evidence -Rather, the "association" between vaginal delivery and decreased rates of shunt placement or sac disruption were explained because fetuses with more severe hydrocephalus or other open	-Possible selection bias due to inclusion of prospective cohort studies and 1 retrospective cohort study -Moderate heterogeneity across studies -Unable to account for differences in management of L&D or with care provided postnatally for infants with neural tube defects

				neural tube defects were already selected for C-section -Sac disruption does not correlate with traumatic delivery or higher infection rates -The assumption that trauma on the neural placode is enhanced during contractions is not proven and delivery via C-section does not guarantee this absence of trauma	
Greene, et. al., 2017	-Retrospective cohort	-Retrospective chart and related radiology reviews were assessed in all infants who had primary closure of myelomeningocele defect at the Children's Hospital of Pittsburg between 1995-2015 -Initial 80 maternal-neonatal pairs were identified, but inclusion of 72 final pairs due to losses to follow up or death within 2 years of birth (those were	-Primary outcome measured included motor function relative to anatomic level of myelomeningocele defect at age of 2	-The only maternal variable that was statistically significant was longer hospitalization stay for the mother after C-section than after vaginal delivery, which is to be expected due to the nature of the surgery -It was found that infants who were delivered vaginally had a smaller spina	-Not highest level of evidence but given nature of the topic, this cohort still provides valuable information -Sample size smaller than optimal, which may affect trends to reach statistical significance -Infants with larger/higher lesions were automatically delivered by C-section, possibly

		excluded)		bifida defect and longer length of stay but this is attributed to selection bias -Infants delivered vaginally also had increased risk of seizure disorder -There is no relationship between the rate of shunt placement and the mode of delivery -There is no benefit to motor function from C-section delivery or the avoidance of natural labor	underestimating the intrinsic risk/morbidity of delivery vaginally
Cuppen, et. al, 2011	-Retrospective cohort	-All records of neonates evaluated for spina bifida between the years of 1990-2006 at the Radboud University Nijmegen Medical Centre were included for this retrospective review -150 neonates were initially evaluated, 55 were excluded due to having multiple diagnoses or incomplete data -Remaining 95 cases were analyzed for	-Primary outcome included differences in anatomical and functional levels of myelomeningocele on the 1st, 2nd, 3rd days after birth -Anatomical level of defect was measured by "anatomical X- ray (AX) level, measured as the lowest intact vertebral arch of the spinal column on a standard anteroposterior X-ray" -Functional level was measured by	-There is no significant difference between where the open neural tube defect was in vaginal delivery group versus C-section group -The mean size for the neural tube defect was slightly larger in the C-section group than in the vaginal delivery group -Regression analysis	-Study was conducted in a hospital in the Netherlands but still yields conclusions consistent with those performed in the United States -Selection of delivery route was based on judgment from clinicians rather than randomly assigning delivery methods to patients and mothers

		neurological impairment as groups and by route of delivery	"composite of motor and sensory function; the lowest intact spinal segment on the most affected side of the body was taken as measure of severity"	demonstrated the neurological impairment favored vaginal delivery over C-section, meaning vaginal delivery is not harmful and that C-section is not protective for fetuses with spina bifida -There is no clinical evidence supporting that early neurological outcome is improved via C-section	-Sample size is small and not optimal -Not highest level of evidence but given nature of the topic, this cohort still provides valuable information
Farmer, et. al, 2018	-Retrospective cohort	-Reviewed hospitalizations from the Healthcare Cost and Utilization's National Inpatient Sample to identify all deliveries from 2003-2013 -Final count of 10,147 deliveries of infants with spina bifida and 42,197,763 of infants without spina bifida	-Outcomes studied included comparison of hospitalizations for delivery in women with infants with and without spina bidifa to determine differences in mode of delivery and changes in delivery method choice over time	-Women who gave birth to infants with spina bifida had higher mean number of comorbidities and more likely to be Caucasian, have private insurance or Medicare, live outside cities, and delivery at urban teaching hospitals -There is a 56% increase in the number of women delivering an infant with	-Not highest level of evidence but given nature of the topic, this cohort still provides valuable information -Using a national sample is prone to analysis and accuracy of coding in these patients -There was no randomization of what delivery method was given to what patient

				spina bifida, with a mean age of 27.3 -Women with infants with spina bifida were more likely to undergo C-section -However, there is no significant difference in the change in the mode of delivery over time	

Conclusion(s):

Tolcher et. al, demonstrated that there are no improved neurological outcomes in fetuses with open neural tube defects delivered via C-section as compared to being delivered vaginally. There is no evidence of worsening motor function, the requirement of a shunt, sac disruption, and meningitis when delivered vaginally. Rather, the association between vaginal delivery and decreased rates of shunt placement or sac disruption were explained because fetuses with more severe hydrocephalus or other open neural tube defects were already selected for C-section.

Green et. al, demonstrated that the only statistically significant maternal variable was longer hospitalization stay for C-section deliveries than vaginal deliveries, which is expected due to nature of surgery and subsequent recovery. Vaginally delivered infants were found to have smaller extents of spina bifida defect and longer length of stay. There is no relationship between the rate of shunt placement and the mode of delivery and no benefit to motor function from C-section delivery or the avoidance of natural labor.

Cuppen et. al, demonstrated that there is no significant difference between vaginal delivery and C-section. However, the mean size for the neural tube defect was slightly larger in the C-section group than in the vaginal delivery group. Further analysis determined that neurological impairment favored vaginal delivery and there is no clinical evidence supporting improvements of early neurological outcome with C-section delivery.

Farmer et. al, demonstrated that the women who gave birth to infants with myelomeningocele had higher mean number of comorbidities and were more likely to be Caucasian, have private insurance or Medicare, live outside cities, and delivery at urban teaching hospitals. Overall, more women have giving birth to infants with myelomeningocele but they are more likely to undergo C-section. There seems to be no significance difference in changes in the mode of delivery over time for infants with myelomeningocele.

In conclusion, there are no significant differences in neurological outcomes in fetuses with open neural tube defects that are delivered vaginally versus those delivered via C-section. However, the mean size for the neural tube defect was slightly larger in the C-section, which could be due to natural selection of C-section for infants with more complicated myelomeningoceles. Mothers who underwent C-sections stay in the hospital for longer periods of time. Ultimately, there is no relationship or benefits to avoidance of natural labor

Clinical Bottom Line:

The first article is one of the first meta-analyses to cover the neurological outcomes by mode of delivery for infants with open neural defects such as spina bifida that was very recently published in February 2019. Moreover, the authors acknowledge that there is current controversy on which delivery method is safer and more beneficial for such patients. It included a total of 9 studies with 672 total participants, the most of all the studies included in this mini-CAT. There are no improved neurological outcomes in fetuses with open neural tube defects delivered via C-section as compared to being delivered vaginally.

Even though the second article (a retrospective cohort analysis) was not of highest evidence, it still provided us with valuable information due to the in unavailability of RCTs and because it tracked patients backwards since birth. Again, this study mentions that previous studies suffered from nonstandardized outcome measures, selection bias, relatively small sample sizes, and that larger studies date back over 15 years. The primary outcomes measured were consistent with those of the first article, which was a plus and there is no benefit to motor function from C-section delivery or the avoidance of natural labor.

The third article (another retrospective study) sought to determine whether vaginal delivery or C-section affected early neurological outcomes in infants with spina bifida. Additionally, they specified where the neural tube defects were in the infants, with 21.1% in the thoracic region, 76.8% in the lumbar region, and 2.1% in the sacral region of the spine. The authors concluded that again, there is no significant difference between vaginal delivery and C-section. Although this study was performed in the Netherlands, it yielded conclusions consistent with those performed in the United States.

The fourth article is another retrospective study that aimed to compare hospitalizations for delivery in women with infants with and without spina bidifa to ultimately determine differences in mode of delivery and changes in delivery method choice over time. As this is the most recent cohort study, I weighed this study more as compared to the other cohort studies. However, there seems to be no significance difference in changes in the mode of delivery over time for infants with myelomeningocele for now as compared to the past.

Open neural tube defects such as spina bifida are fairly common and occur in about 1 in 1000 pregnancies in the United States (population of 327 million). Theoretically, traction placed on the neural placode (ectoderm that gives rise to subsequent structures of the nervous system) during vaginal delivery and other complications such as sac disruption and exposure to possible sources of infection were thought to negatively impact future neurological function. However, evidence has shown the C-section does not improve the overall outcome of fetuses with spina bifida. In the most recent meta-analysis, there is no evidence to support that C-section prevents the requirement of a shunt or has decreased rates of sac disruption or meningitis. The assumption that trauma on the neural placode is enhanced during uterine contractions is not clinically proven and delivery through C-section does not guarantee the absence of such trauma.

Ultimately, vaginal delivery is not proven to be more harmful for fetuses with spina bifida or other open neural tube defects and C-section is not proven to be more protective. In the absence of such data establishing the advantages of C-section, vaginal delivery should still be acceptable as a possible route for delivery for fetuses with open neural tube defects. However, the decision should be individualized and discussed with the mother to take her preferences in consideration.