Three-Dimensional Sonographic Evaluation of the Position of the Fetal Conus Medullaris at First Trimester

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3D sonographic evaluation of the position of the fetal conus medullaris at 1st trimester

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Short Title: Position of the conus medullaris at 1st trimester

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Abstract

Objectives:

To assess the position of the conus medullaris (CM) at first trimester 3D ultrasound in a cohort of structurally normal fetuses.

Methods:

This was a multicenter prospective study involving a consecutive series of structurally normal fetuses between 11 – 13 weeks of gestation (CRL between 45 – 84 mm). All fetuses were submitted to 3D transvaginal ultrasound using a sagittal view of the spine as the starting plane of acquisition. At offline analysis, the position of the conus medullaris was evaluated by two independent operators with a quantitative and a qualitative method: 1) the distance between the most caudal part of the conus medullaris to the distal end of the coccyx (CMCd) was measured; 2) a line perpendicular to the fetal spine joining the tip of the conus medullaris to the anterior abdominal wall was traced to determine the level of this line in relation to the umbilical cord insertion (Conus to-abdomen-line or CAL). Interobserver agreement for the CCMd was evaluated. Linear regression analysis was used to determine the association between CMCd and CRL and a normal range was computed based on the best-fit model. The absence of congenital anomalies was confirmed in all cases after birth.

Results:

In the study period between December 2019 and March 2020, 143 fetuses were recruited. In 130 fetuses (90.9%), the visualization of the CM was feasible. The mean value of the CMCd was 1.09 ± 0.16 cm. The 95% limits of agreement for the interobserver variability in measurement of the CMCd were -0.24 and 0.26 cm. The interobserver variability based on the ICC for the CCMd was good (ICC= 0.81). We found a positive linear relationship between the CCMd and the CRL. In all these fetuses, the CAL encountered the abdominal wall at or above the level of the cord insertion.

Conclusion:

In normal fetuses the assessment of the conus medullaris position is feasible at first trimester 3D ultrasound with a good interobserver agreement. The CM level was never found below the fetal umbilical cord insertion, while the CMCd was noted to increase according to the gestational age, confirming the “ascension” of the CM during fetal life.

Introduction

Closed spinal dysraphism (CSD) is an abnormality of the posterior arch formation in which the defect is covered by the skin (1). The prevalence of CSD is estimated to be 2 – 4 in 1000 live births (2,3). The clinical manifestations of the CSD may vary between the absence of symptoms and severe neurologic, genitourinary, gastrointestinal and musculoskeletal anomalies. The most common pathological condition associated with CSD is represented by the tethered cord syndrome, which is associated with the pathological elongation of the distal part of the conus medullaris (CM) due to its anchorage to the surrounding tissues (1,4,5).

The prenatal diagnosis of CSD is challenging even in expert hands, with only few cases reported so far mainly during the 2nd trimester and associated with a subcutaneous mass or a cyst (6,7). CSD without a subcutaneous mass is mostly reported in the postnatal imaging literature (8,9,10). This is mainly because of the absence of a visible defect at the level of the lumbar spinal cord and indirect cranial signs of spinal dysraphism (6). Based on the “ascension” of the CM during the fetal period, which is described by the elevation of the conus medullaris from the sacral position up to the level of the second lumbar vertebra at birth (11-13), some authors have hypothesized that the caudal displacement of the conus medullaris may represent an indirect sign of CSD. An unusually low position of the CM could therefore raise the suspicion of a tethered cord syndrome indicating a lack of ascent of the CM in the spinal canal (4,12,14). However, the standard prenatal ultrasound assessment of the position of the CM is not performed on a routine basis.

Several studies have attempted to describe the position of the CM prenatally in a quantitative or a qualitative manner in order to establish the normal level of the CM at different gestational ages. Among the different approaches proposed, the measurement of the distance of the CM from the coccyx and the evaluation of the position of the CM in relation to a lumbar level have been attempted mainly in the second and third trimesters (11,12,14,17-22). To the best of our knowledge no study has so far evaluated the normal position of the CM between 11+0 and 13+6 weeks of gestation. We therefore conducted a multicenter prospective study to assess the position of the conus medullaris at first trimester 3D ultrasound in a cohort of normal fetuses.

Materials and Methods

This was a multicenter prospective study conducted between November 2019 and February 2020 and involving 2 Centers of Prenatal Diagnosis in Italy, the University Hospital of Parma, and the University Hospital of Insubria. The recruitment was stopped earlier after 4 months due to the Covid-19 pandemic. All pregnant women gave written consent to participate before the scan. The study was approved by the local ethics committee (561/2018).

The inclusion criteria were as follows: singleton pregnancy, gestational age between 11+0 – 13+6 weeks (CRL between 45 – 84 mm), normal nuchal translucency (NT) and no obvious fetal abnormalities at ultrasound examination. Cases where it was not possible to obtain a high-quality 3D volume of the fetal spine, or it was not possible to identify the CM and the last vertebral body were excluded from further analysis.

All ultrasonography examinations were performed by sonographers with competence on first trimester ultrasound as certified by the Fetal Medicine Foundation, London. Ultrasonography was performed using a Samsung W10 Hera System ultrasound machine, equipped with a 4-8 Mhz 3D endocavitary Samsung Medison Co. Ltd., Seoul, South Korea). First a midsagittal longitudinal plane of the fetal spine facing anteriorly, focusing on the most caudal part of the spine, was obtained transvaginally. High quality three-dimensional ultrasound volumes were acquired and stored for offline processing. The volumes were not acquired if the fetus was in a hyperflexed or hyperextended state.

Offline analysis of the volumes was carried out by two operators (N.V. and G.B.L.S.). N.V. analyzed all the 143 3D-images, while G.B.L.S. evaluated only the first 40 3D-images. On the midsgittal plane the CM was visualized as a hypoechoic triangular structure at the caudal end of the spinal cord. The position of the CM was evaluated using two approaches: 1) On the midsagittal plane we measured quantitatively the distance between the most caudal part of the conus medullaris and the distal end of the coccyx (CMCd); 2) while navigating on the 3D multiplanar volume acquired, we compared qualitatively the level of the CM in relation to the umbilical cord insertion by tracing a line perpendicular to the fetal spine joining the tip of the conus medullaris to the anterior abdominal wall (Conus-to-abdomen line or CAL) (Figure 1).

Statistical analysis

Statistical analysis was performed using Statistical Package for Social Sciences (SPSS) v. 22 (IBM Inc., Armonk, NY, USA). Data were shown as mean + standard deviation. The 95% CI for each continuous variable was also calculated. The Kolmogorov–Smirnov test was used to assess the normality of the distribution of the data.

Interobserver variability of the CMCd was assessed by Bland-Altman plots with 95% limits of agreement (LOA) and by the intraclass correlation coefficient (ICC). For interobserver variability, the first 40 measurements were repeated by both operators and compared using both methods. The ICC was interpreted as an indicator of excellent (> 0.90), good (0.75–0.90), moderate (0.50–0.75), or poor (< 0.50) agreement.

Linear regression analysis and Spearman's and Pearson's correlations were used to evaluate the correlation of the CCMd as a function of CRL. $p < 0.05$ was considered as statistically significant.

Results

We screened 172 patients for eligibility, from which 29 were excluded due to maternal or fetal reasons (Figure 2). Overall, 3D US volumes of 143 consecutive fetuses were obtained, among whom the CM position could be successfully evaluated in 130 consecutive, structurally normal fetuses, all of which were included in this study. The remaining 13 cases did not meet the inclusion criteria, for different reasons such as persistently unfavorable fetal position (spine down) or inadequate volume acquisition and were excluded from further analysis (Figure 2). The absence of fetal structural defects and particularly of spine abnormalities was confirmed at postnatal assessment for all the included cases.

The mean gestational age (GA) at enrolment was 12+3±0+4 weeks with a mean CRL of 62.91 ± 7.65 mm. Table 1 summarizes the maternal characteristics.

At quantitative assessment, the CCMd followed a normal distribution (Figure 3) and its mean value was 1.09 ± 0.16 (95% CI 1.062 – 1.118) cm. Linear regression analysis showed a correlation between the CCMd and the CRL (Pearson's correlation coefficient $r = 0.24$, $p = 0.006$; and Spearman's correlations coefficient $r = 0.27$, $p = 0.002$). The best-fit formula between CMCd and CRL was as follows: CCMd = 0.0051 x CRL + 0.7715. Figure 4 shows the normal range together with the 5th and 95th percentiles.

The mean difference in the CMCd among the 40 repeated measurements of both operators was 0.01 mm (95% LOA, -0.24 to 0.26 cm). The Bland-Altman plot is shown in Figure 5. The ICC value for the CMCd measurement was 0.81, indicating that the interobserver agreement could be considered as good (Figure 6).

At qualitative evaluation, the CAL encountered the abdominal wall at or above the level of the cord insertion in all the included fetuses.

Discussion/Conclusion

Main findings

In our study, we have shown that the evaluation of the position of the CM in the spinal canal is feasible in roughly the 90% of the cases at expert first trimester 3D-ultrasound.

We found a linear direct relationship between the CMCd and CRL, with good interobserver agreement. Normal values of CMCd according to the CRL have been also defined. Based on our data it is possible to predict the normal CMCd according to a given CRL and to calculate the 5th and 95th percentiles of the measurement.

Furthermore, the tip of the CM was never found to be below the level of the umbilical cord insertion.

Interpretation of study findings and comparison with previous studies

The position of the CM in adults is well documented between L1 and L2, terminating at or above L2-L3 in more than 98% of cases (23). However, the position of the CM during fetal life is considered to be more caudal and the time of ascent of the CM to its final position is still a matter of debate. According to the early hypothesis, the CM was thought to ascend to its normal adult level in infancy (24,25). Since then, this theory has been disputed by some studies involving autopsies and neonatal imaging, which have shown that the final ascent was already completed at or before birth (26,27). Prenatal studies support the theory that the ascent of the CM begins during the fetal life (11), as the CM was sonographically imaged at or above the level of L2-L3 in the vast majority of mid-trimester fetuses in several studies. Robbin et al. (12) evaluated 33 fetuses at 19 weeks of gestations and found that the position of the CM was at about L2-L3 or higher. Zalel et al. (11) examined 110 fetuses between 13 and 40 weeks of gestation. They found that in 100% of their fetuses between 13 and 18 weeks of gestation, the CM was at L4 or lower. In 97% of the cases, they reported a shift of the CM towards L2-L3 between 18 – 24 weeks. The cranial ascension of the CM was continuous throughout the pregnancy and at term the CM was reported to lie at or above L1-L2. Perlitz et al. (18) demonstrated the CM level in 110 fetuses between 20 and 24 weeks and found that the CM was between L2 and L3 in 93% of cases. More recently, Zhai et al. (22) came to the same conclusions observing the CM position in 521 fetuses between 20 and 38 weeks of gestation. In our study, we did not evaluate the level of the CM in relation to the vertebral level, rather to the level of the cord insertion on the anterior abdominal wall. The former measurement has been shown to be inaccurate, because of the mild ossification of the lower spine in the first trimester of gestation (28) and the small size of the lumbosacral vertebras, which reduces the accuracy of the determination of the vertebral level. Moreover, a low interobserver concordance of this measurement has been also reported in prenatal life (20).

Different quantitative evaluations of the CM position have been also proposed by some authors in the second and third trimester. Hoopmann et al. (19) suggested the measurement of the distance between the CM and the sacrum in 300 pregnant women between 15 weeks of gestation and term; this case series included 5 cases of skin-covered spina bifida, among whom the distance between the CM and the sacrum was below the 5th percentile. Hoopman et al. also reported a positive linear relationship between the measurement and the GA and biometric parameters such as femur length, head circumference and abdominal circumference. Another study by Mottet et al. (14) evaluated the distance between S1 and the CM in 194 pregnant women after 17 weeks of gestations showing also a linear relationship between such measurement and the GA. Consistent results were reported by Zhai et al. in a cohort of 521 fetuses, among whom the Authors also demonstrated a high interobserver concordance of the measurement (22). To our knowledge ours is the first study evaluating the distance between the CM and the coccyx at first trimester ultrasound. In accordance with previous studies, we found a positive linear relationship between the GA and the CMCd and a high interobserver concordance. Our study strengthens the theory of the prenatal ascension of the CM, as it shows a progression of its distance from the coccyx from 11 to 13 weeks of gestation.

Additionally, some studies have reported that 3D ultrasound could improve the accuracy of the measurements used to describe the position of the CM. He et al. (29) found that measuring the fetal conus distance in a cohort of 468 normal fetuses and 14 fetuses with tethered cord syndrome between 14 – 40 weeks of gestation by 3D ultrasonography was more accurate and reliable than 2D ultrasound. Similarly, Lei et al. (17) examined 150 fetuses between 20 to 38 weeks of gestation using 3D ultrasonography concluding that 3D ultrasound may accurately determine the CM vertebral level.

Clinical implications

There is increasing awareness regarding the antenatal diagnosis of skin-covered spinal dysraphism, due to its possible association with tethered cord syndrome. Indeed, the prenatal suspicion of a tethered cord syndrome would allow the most appropriate birth plan for the couple opting for a conservative management of the pregnancy as early surgical management of the tethered cord is important to preserve function and avoid irreversible neurological damage (4,5,15,16).

CSD can be classified as with or without a subcutaneous mass. CSD with a subcutaneous mass represents only 18.8% of the CSD, lipomas with a dural defect accounting for 87.4% of the cases (1).

Based on this data, the majority of cases of CSD do not show any visible defect on the ultrasound scan, and a low-lying CM could be the only sign of a CSD with tethered cord syndrome. Therefore, the use of a quantitative measurement as the CMCd could help us to diagnose reliably a low-lying CM. At second and third trimester, the measurement of the CMCd has already been shown to have a higher interobserver concordance than the CM location based on anatomical landmarks (20-22). However, the measurement of the CMCd in the first trimester requires a high level of expertise, as the correct identification of the coccyx and of the CM itself is of crucial importance to achieve an appropriate measurement, also considering the small size of these structures. In this respect, the addition of 3D ultrasonography can improve the accuracy of the CMCd measurement (17,29). The 3D multiplanar mode supported by a high-resolution algorithm allows a better visualization the fetal spine, thus improving the identification of the CM in relation to the bony components of the spine at 1st trimester.

In addition to the quantitative measurement, the qualitative evaluation of the CM position in relation to the vertebral level described in the second or third trimester could be difficult at 11-13 weeks of gestation as due to the lower ossification of the vertebral bodies the vertebral count may be challenging in particular in the lumbosacral region (28). Therefore, we have proposed the umbilical cord insertion as a new landmark to assess the position of the CM, as we believe it allows an easier and more accurate characterization of the position of the CM compared to the vertebral count. This new marker could be easily measured when navigating the 3D volume obtained for the CMCd. As described above, the CM was always found to be above the insertion of the umbilical cord.

Therefore, we have established on a qualitative and quantitative basis the expected level of the CM at first trimester among structurally normal fetuses. Based on the study performed by Hoopmann et al., which found that all cases of CSD has a CM distance well below the 5th percentile, we recommend that a CMCd below the 5th percentile should prompt referral to a specialized fetal medicine center in order to exclude a CSD diagnosis in expert hands. However, a CMCd below the 5th percentile is not necessarily associated with a tethered cord syndrome since by definition this can be observed in 5% of normal fetuses.

The same recommendation should be made, if the CM is found to be below the umbilical cord insertion. Further studies at 11 – 13 weeks of gestation including fetuses affected by tethered cord syndrome are needed to determine the real clinical utility of these two markers and their predictive value when diagnosing CSD.

Strengths and limitations

The main strengths of our study are its original and prospective design and the large number of fetuses examined. Our study is also the first study to describe these markers between 11+0 and 13+6 week of gestations and to incorporate the use of 3D ultrasonography to improve its precision. Another strength of the study is the high interobserver concordance observed.

There are also some limitations that must be acknowledged. In first instance, although our results are in line with previous studies, the exclusion of cases with an unfavorable fetal position or a suboptimal echogenicity (i.e., high BMI patients) may have introduced selection bias as the values obtained might not be representative of the whole population. However, among obese women the rate of technically inadequate ultrasound scans at 1st trimester is higher, and this could negatively influence our study, by adding fetuses with overlooked malformations to our cohort. Secondly, we acknowledge that the sonographic assessment of the CM position at first trimester might be technically challenging and therefore we cannot recommend yet their inclusion on daily routine examinations. Nevertheless, our study has shown that the measurements are feasible in the hands of fetal medicine experts, with a success rate of 90,9 %.

Conclusions

We have shown that the evaluation of the position of the CM is feasible in the first trimester using 3D ultrasound. In normal cases, the level of the CM was never found to be below the fetal umbilical cord insertion, whereas the CMCd was noted to increase with advancing gestational age, confirming the "ascension" of the CM during fetal life. We envisage that our data may contribute to elucidate the natural history of skin-covered spinal dysraphism and to improve its sonographic detection during fetal life.

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Statement of Ethics: this study complies with the guidelines for human studies and has been conducted ethically in accordance with the World Medical Association Declaration of Helsinki. Subjects have given their written informed consent and the study protocol has been approved by the local ethics committee (561/2018)

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Author Contributions

Ramirez Zegarra R, di Pasquo E, Dall'Asta A, Volpe N, Ghi T: substantial contributions to the conception or design of the work, the acquisition, analysis, or interpretation of data for the work

Volpe N, Bertelli E, Amoreli GM, Ferraro L, Schera GBL, Cromi A, Dall'Asta A, Ghezzi F: Collection of the 3D volumes from the 2 centers.

Ramirez Zegarra R, Volpe N, Ghi T, Dall'Asta A: Drafting the work or revising it critically for important intellectual content

Dall'Asta A, Ghi T, Frusca T: Final approval of the version to be published

Frusca T, Ghi T: Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Figure Legends

Fig. 1. 3D representation on the multiplanar mode of the conus medullaris in a midsagittal plane, showing the measurement of the distance between the conus medullaris and the distal end of the coccyx (CMCd), and of the Conus-to-Abdomen line (CAL). On the lower right corner, a magnified image of the CM (*), showing a hypoechoic triangular structure at the caudal end of the spinal cord.

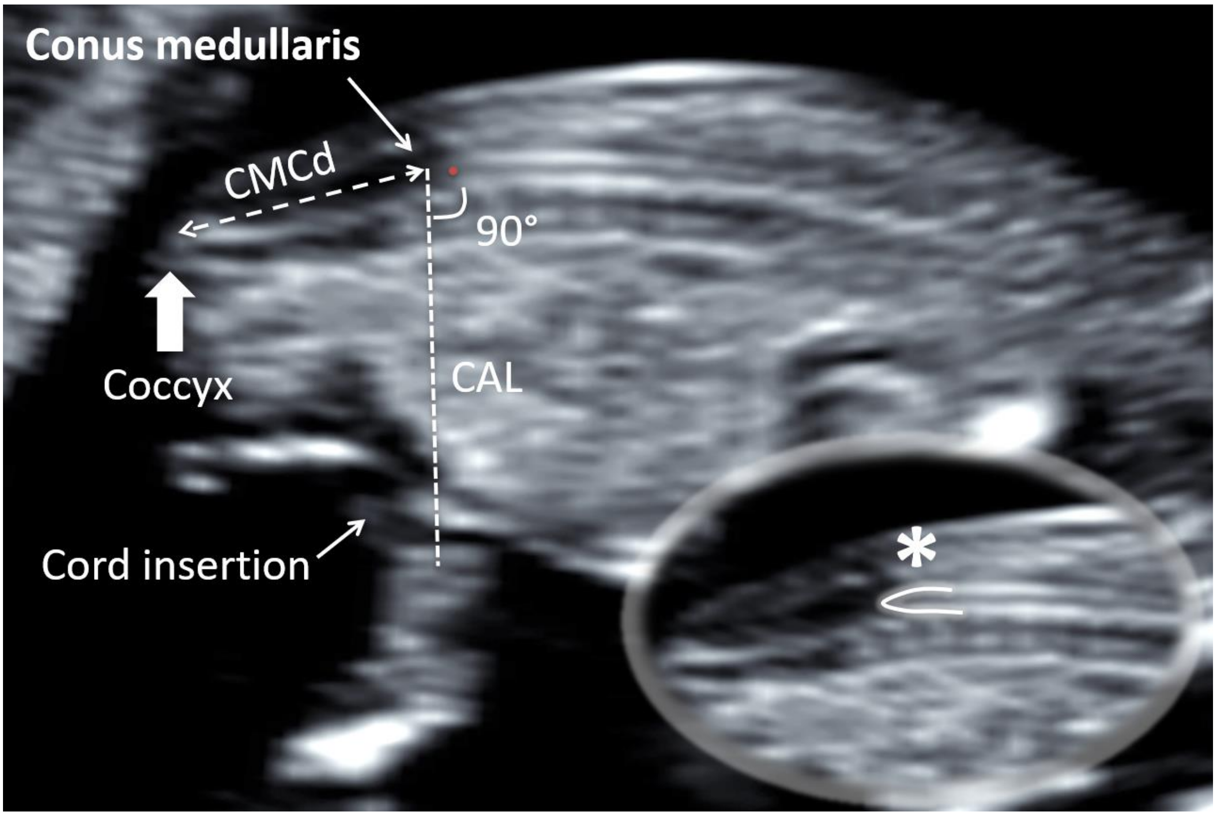
Fig. 2. Flow diagram of patient enrollment of a consecutive series of structurally normal fetuses between 11 – 13 weeks of gestation (CRL between 45 – 84 mm), who got submitted to 3D transvaginal ultrasound, and the conus medullaris was visualized.

Fig. 3. Distribution of the distance (cm) between the tip of the conus medullaris and the distal part of the coccyx (CMCd) of fetuses between 11 – 13 weeks of gestation.

Fig. 4. Linear correlation between the distance between the tip of the conus medullaris with the distal part of the coccyx (CMCd), and the CRL with their respective 5th and 95th percentile.

Fig. 5. Bland-Altman plot showing the interobserver variability in the measurement of the distance between the tip of the conus medullaris and the distal part of the coccyx (CMCd), between two operators.

Fig. 6. Interobserver variability of the measurement of the distance between the tip of the conus medullaris and the distal part of the coccyx (CMCd), between two operators using intraclass correlation coefficient.



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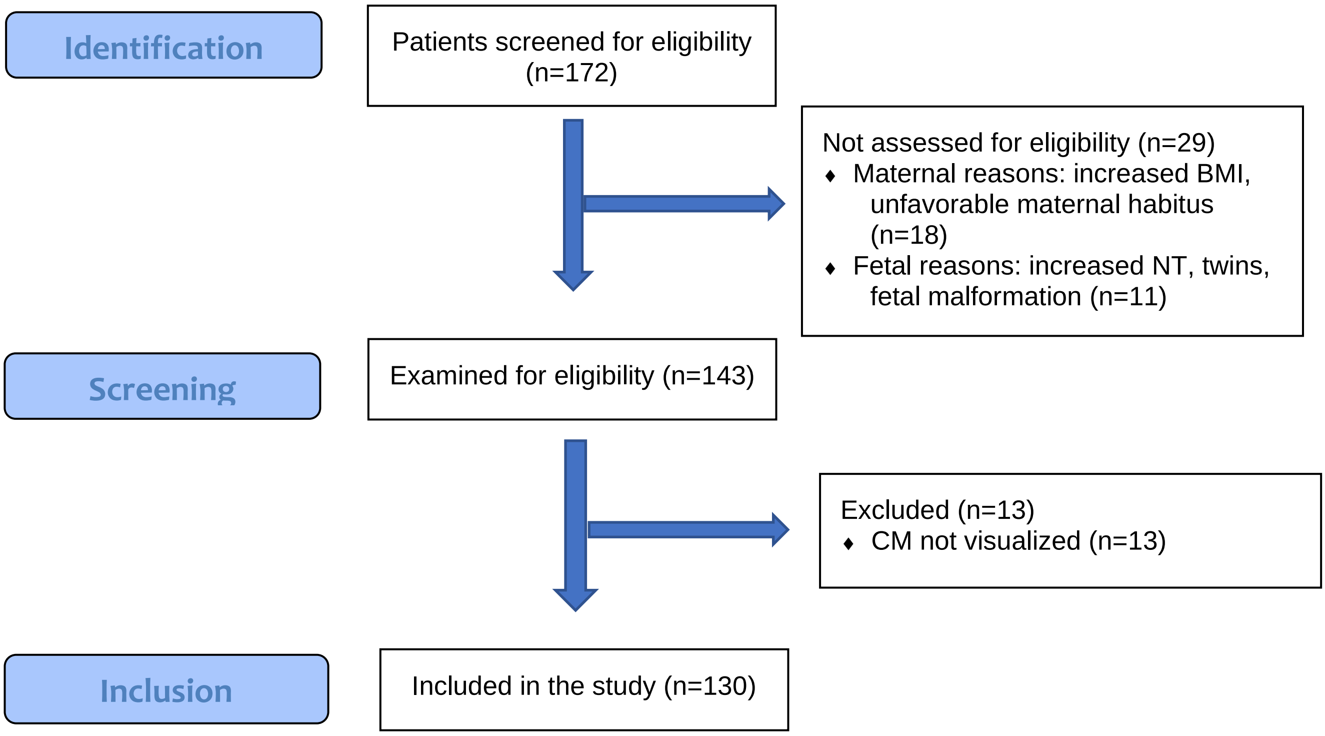

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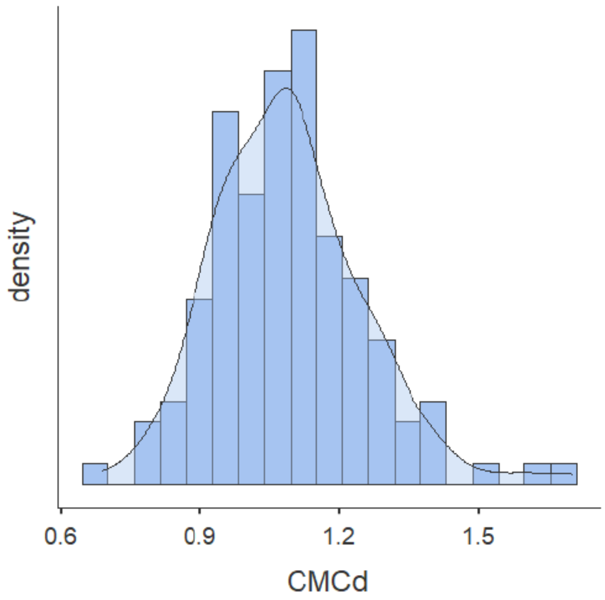

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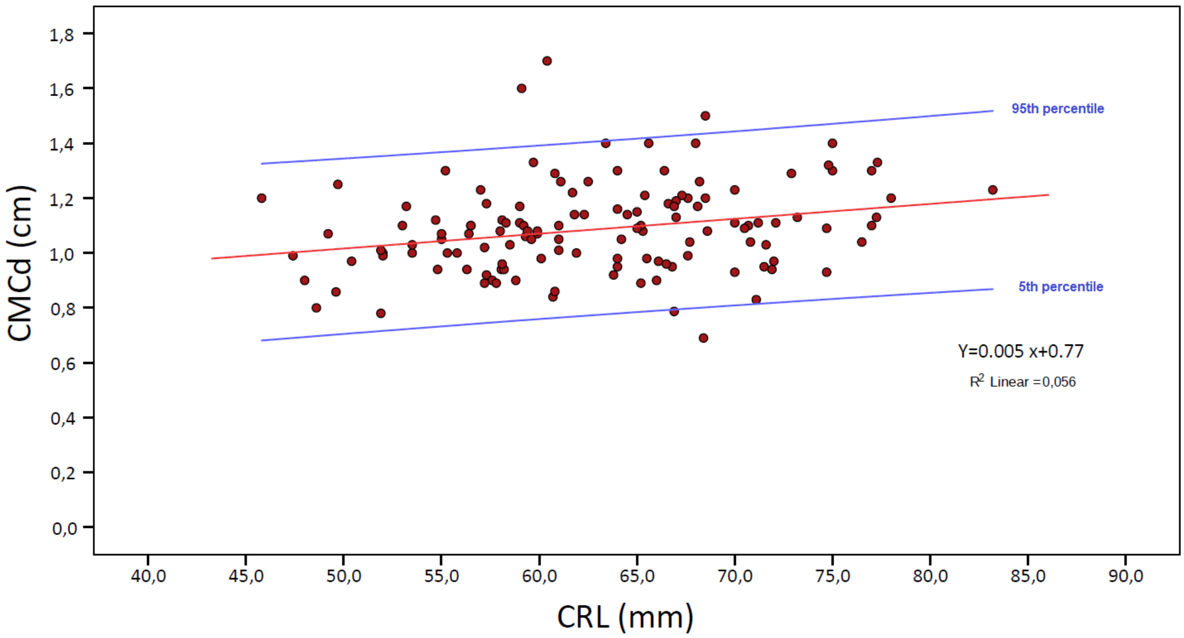

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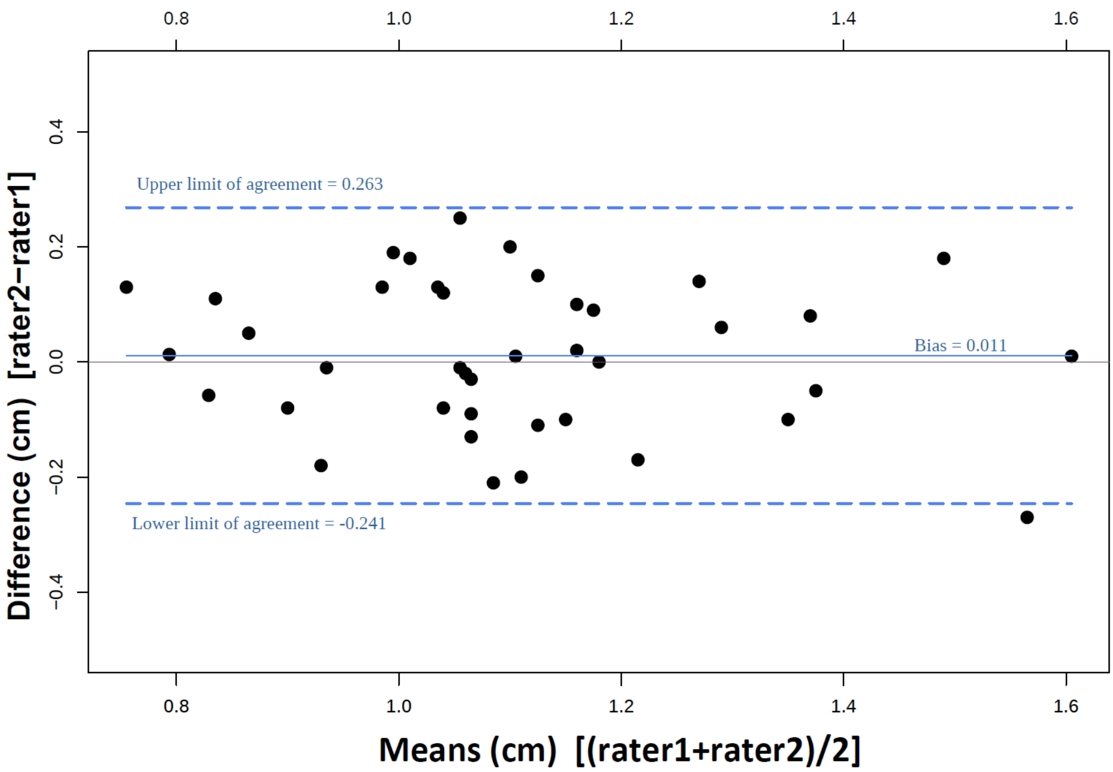

Figure 5. Bland-Altman plot showing the interobserver variability in the measurement of the distance between the tip of the conus medullaris and the distal part of the coccyx (CMCd), between two operators.

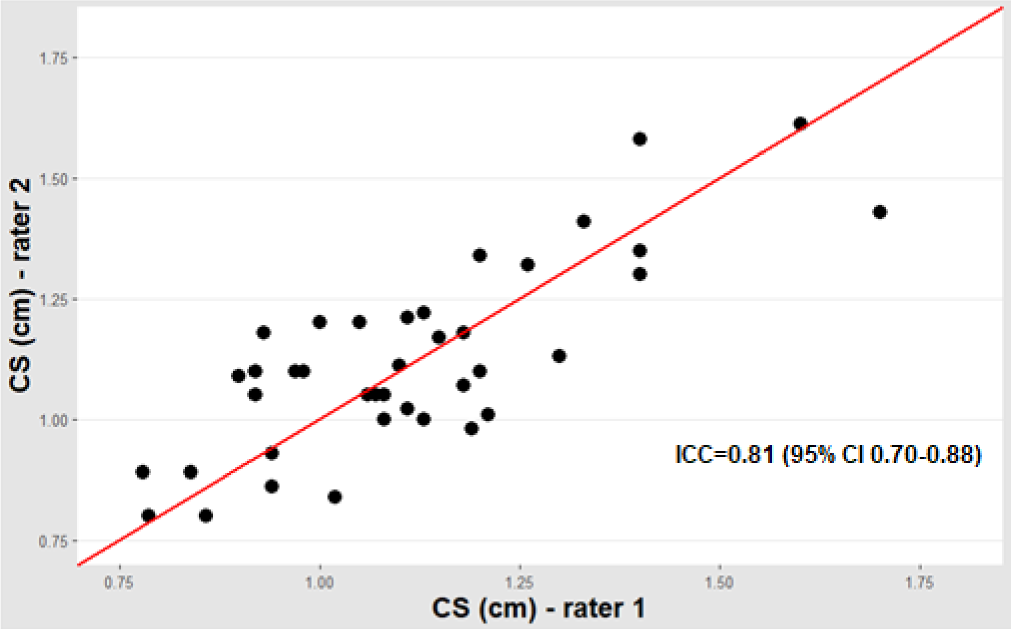

Figure 6. Interobserver variability of the measurement of the distance between the tip of the conus medullaris and the distal part of the coccyx (CMCd), between two operators using intraclass correlation coefficient.

Demographic and Obstetrical Variables	Mean ± SD
Gestational age at examination (weeks)	12.52 ± 0.59
Maternal age (years)	32.87 ± 5.26
Maternal BMI (kg/m2)	24.45 ±5.96
CRL (mm)	62.91 ± 7.65

Table 1. Demographic and Obstetrical Variables of the study

Reviewer Comments:

Reviewer 1

1. In the present study, the authors aimed to assess the position of the conus medullaris (CM) at first trimester 3D ultrasound in a cohort of normal fetuses. They found that the assessment of the conus medullaris position was feasible with a good interobserver agreement. In their population, the conus medullaris level was never found below the fetal umbilical cord insertion, while the distance from CM to coccyx (CMCd) was noted to increase according to the gestational age. The idea of the study is interesting. The study however has many limitations. Examining the conus medullaris may have the potential to assess the cord tethering in case of closed spina bifida. Diagnosis of closed spina bifida remain a challenge even in the second and third trimester. In absence of cranial signs, the vast majority of cases pass undiagnosed. Fortunately, almost all cases of closed spina bifida are asymptomatic or have excellent prognosis. Adding a 3D examination of the conus medullaris in the first trimester to improve early diagnosis of this benign malformation to which there is no prenatal intervention is of questionable usefulness, at best.

Reply:

We thank the reviewer for the comment, but we respectfully disagree with him. The reviewer questions the usefulness of our study based on the absence of prenatal intervention for a CSD and on the lack of severity of the disease. Although it is true that most of the cases are asymptomatic and have a good prognosis, there is a certain number of cases, especially those related with tethered cord syndrome, which could be associated with severe neurological, gastrointestinal, genitourinary and musculoskeletal disorders. Moreover, early detection of these cases and prompt surgical management are associated with a better prognosis and preservation of function.

This study is also important for the understanding of the ascension of the CM during the embryonal period, in order to be able to fully understand this complex group of malformations. It has been speculated that the CM starts its cranial ascension prenatally. However, it is unknown when this process starts. Most of the studies have evidenced an ascension of the CM during the 2nd and 3rd trimester of pregnancy. But no study to date has shown if this ascension is already visible during the first trimester. Our study shows that the CM has already started its ascension during the 11th and 14th week of pregnancy.

The addition of 3D, as previously shown in studies performed in the 2nd and 3rd trimester, increases the diagnostic accuracy of the position of the CM.

- Lei T, Xie HN, Zheng J, Feng JL, Du L, Wang N. Prenatal evaluation of the conus medullaris position in normal fetuses and fetuses with spina bifida occulta using three-dimensional ultrasonography. *Prenat Diagn*. 2014; **34(6)**: 564-569. doi:10.1002/pd.4349
- He S, Ruan J, Wang X, Lyu G, Wei Y, Huang T, Zeng P. Measurement of fetal conus distance with 3D ultrasonography as a reliable prenatal diagnosis method for tethered cord syndrome. *J Obstet Gynaecol*. 2020; **46**: 587-594. doi:10.1111/jog.14202

No change has been made to the manuscript.

2. The authors suggest using the 5-95th centile to describe normality. I would be very cautious in suggesting such a recommendation. By definition, 5% of fetuses will lie in the this group. The incidence of a tethered cord is extremely rare, therefore almost all fetuses with CMCd under 5th centile will be normal fetuses.

Reply:

We thank the reviewer for comment. We have just established the percentiles for the CMCd in a normal population of fetuses with no structural malformations, which could be used during the first trimester to screen for a low-lying CM. However, a CMCd below the 5th percentile would be normal, by definition, in 5% of normal fetuses, which means that not all cases below the 5th percentile are associated with a tethered cord syndrome. Moreover, based on the study by Hoopmann et al. (ref. below), which found that all the cases of CSD had a conus distance well below the 5th percentile, we recommend that a value of the CMCd below the 5th percentile should prompt referral to a specialized feto-maternal center in order to exclude a CSD diagnosis in expert hands. CMCd should be used as a screening tool but not as a diagnostic tool of CSD.

- Hoopmann M, Abele H, Yazdi B, Schuhmann MU, Kagan KO. Prenatal evaluation of the position of the fetal conus medullaris. *Ultrasound Obstet Gynecol*. 2011; **38(5)**: 548-552. doi:10.1002/uog.8955

The explanation has been added on the clinical implications of the discussion.

3. It is important to add in the results the 18 women excluded due to maternal BMI, although this is an uncommon reason for unsatisfactory endovaginal ultrasound.

Reply:

We thank the reviewer for this comment. It is true that high BMI patients are rarely excluded based on an unsatisfactory endovaginal ultrasound. However, it is also well-know that high BMI patients are difficult to scan, including transvaginal scan, and have more chances of an unsatisfactory scan. Based on this, we excluded the patients because we could not be 100% sure that the baby was structurally normal, which could have introduced bias into our study.

4. Statistics:

A) the authors state that they used or planned to use Chi-square test, Fischer exact test to compare categorical variables. Compare what categorical variables between which groups?

Reply:

We thank the reviewer for the comment. This was a typing mistake. There are no categorical variables on the study.

The manuscript has been corrected.

B) They also state that they applied T-test for independent samples. Which independent samples do the authors have? They have a single population of healthy fetuses.

Reply:

We thank the reviewer for the comment. This was a typing mistake. The continuous variables of the population were shown as mean ± standard deviation or as numbers (percentages).

The manuscript has been corrected.

C) There are some relevant assessments for the interobserver evaluations which they did not perform, such as systematic difference.

Reply:

We thank the reviewer for this comment, but we respectfully disagree with the reviewer. We used Bland-Altman plots and intraclass correlation coefficient, which are among reliable tests to measure interobserver variability between 2 subjects, and their use is also extremely common in research on obstetric ultrasound.

No change has been made to the manuscript.

5. The authors claim that the cord insertion corresponds to L3-L4. In supporting their claim, they refer to neonatal studies, while they examined fetuses at 11-13 weeks.

Reply:

We agree with the reviewer with this comment. No claim has been now made on the vertebral level of the umbilical cord insertion between the 11^{th} and 13^{th} week of gestation.

We have amended the manuscript accordingly.

6. In the figure that the authors chose to demonstrate the technique, I cannot see the cord insertion, only the arrow.

Reply:

We thank the reviewer for the comment. We have added a new picture with a visible CM and cord insertion (Figure 1).

7. In the multiplanar figure, the conus medullaris is not seen.

Reply:

We thank the reviewer for this comment. Figure 1 showed only the plane of acquisition of the 3D volume in the multiplanar mode. We have removed the Figure 1 as it did not add anything important to the manuscript.

8. I would recommend attaching a clip to illustrate the technique for the interested reader.

Reply:

We thank the reviewer for this comment. A video showing the acquisition of both measurements (CMCd and CAL) on 2D could be added as a supplement to the manuscript, if required by the reviewers. However, a video documenting the 3D volume acquisition and the post-processing analysis and measurements would be difficult to provide.

9. In the abstract they describe the distance CMCd as 1 mm. This is probably an error.

Reply:

We thank for the comment. The manuscript has been corrected.

Reviewer 2

1. I congratulate the authors for their interest in this topic and for proposing an easy and reproducible method for the evaluation of the medullary cone.

Reply:

We thank the reviewer for this positive comment. No change has been made to the manuscript.

2. FEASIBILITY:

A) Line 126: you mention that evaluation of the position of the medullary cone was feasible in roughly 90% of cases. I suggest not to underline this but to mention the fact that this study is not a feasibility study because the cases were initially selected in a non-consecutive manner and 13/143 cases were not used. Please explain why these 13 cases are excluded from the analysis.

Reply:

We thank the reviewer for this comment. It was in fact a consecutive cohort of structurally normal fetuses. There was a typing mistake on the abstract, where it was cited as a non-consecutive cohort of fetuses. The 13 cases got excluded from the study for different reasons such as persistently unfavorable fetal position (spine down) or inadequate volume acquisition. We have added the explanation to the results section.

The manuscript has been amended accordingly.

B) In addition, it should be noted that the agreement of the offline analysis measures of the selected images does not match the agreement of the case measures when you have to select the images and then perform these measures. There may be additional bias if images are pre-selected. You must also evaluate the repeatability of the image.

Reply:

We thank the reviewer for this comment. We would like to point out that the first operator reviewed all the 143 pictures, of whom 130 were included in the analysis. For the interobserver variability, the second operator reviewed the first 40 pictures. Both operators excluded the same pictures based on the inclusion criteria. We did not evaluate the intraobserver variability.

The manuscript has been corrected.

C) Most spinal cord syndromes are diagnosed in the third trimester of pregnancy due to the visualization of a fatty mass (lipoma) at the end of the spinal cord, or by the visualization of an increase in cerebrospinal fluid surrounding the conus medullaris as an obstruction. I suggest to develop a little more for the readers all the signs (direct and indirect) that can be encountered in the spinal cord syndrome.

Reply:

We thank the reviewer for this comment. We have added more information in the introduction section regarding the different classification of CSD for the interested reader. However, our study focuses more on the position of the conus medullaris as a possible clue for the antenatal diagnosis of the CSD without a subcutaneous mass, where the identification of the anomaly is more challenging because of the absence of a visible defect.

An explanation has been added in the clinical implications section of the discussion.

D) Given the natural variability of the conus medullaris posture, I find it difficult to believe in the usefulness of quantitative measures of the distance between the tip of the conus medullaris and the sacrum in the first trimester of pregnancy. Your quantitative analysis makes it possible to argue about the probable ascent of the tip of the medullary cone during the fetal period, but the diagnostic usefulness of these measurements seems to me to be much debatable.

Reply:

We respectfully disagree with the reviewer. The usefulness of the distance between the tip of the CM and the sacrum has been already demonstrated in the 2nd and 3rd trimester in the identification of a low-lying CM, which could herald a tethered cord syndrome. Hoopmann et al. showed in their study, that in all cases of CSD, the distance of the CM to the sacrum was well below the 5th percentile. The early detection of a tethered cord syndrome would allow the most appropriate birth plan and surgical approach for couple opting for a conservative management of the pregnancy as early surgical management of the tethered cord is important to preserve function and avoid irreversible neurological damage.

- Hoopmann M, Abele H, Yazdi B, Schuhmann MU, Kagan KO. Prenatal evaluation of the position of the fetal conus medullaris. *Ultrasound Obstet Gynecol*. 2011; **38(5)**: 548-552. doi:10.1002/uog.8955

No change has been done to the manuscript.