Prenatal Assessment and pregnancy outcomes of foetal low-lying conus medullaris using 3D Ultrasound

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Abstract

Objectives This study aimed to follow up cases with low conus medullaris (CM) using three dimensional (3D) ultrasonography and analyze and explore the correlation between the CM location and the final prognosis.

Methods 39 cases of low CM diagnosed prenatally in the Peking University First Hospital was collected retrospectively from January, 2019 to December, 2020. The location of CM was confirmed by 3D ultrasonography and clinical data including postnatal outcomes were collected.

Results The average gestational weeks when low CM was diagnosed was between 23 and 24 weeks. Among 39 cases, there are 9 cases (23.1%) which were complicated with spine abnormality (3 cases of open spina bifida, 6 cases of tethered cord syndrome). Apart from 9 cases of pregnancy termination, the remaining 30 cases of live births had good prognosis, though 5 of 6 cases of tethered cord syndrome underwent the surgical release. The mean location of cases of open spinal dysraphism and cases of closed dysraphism/tethered cord syndrome was at L5 and between Lumber vertebra (L)5 and Sacral vertebra (S) 1 respectively, which showed statistically significance compared with the postnatally normal group. When we set Lumber 4.25 as the cut-off value to predict the diagnosis of spine abnormality (mainly open spina dysraphism and closed spinal dysraphism/tethered cord syndrome, the sensitivity was 66.7 and the specificity was 96% with the area under curve (AUC) at 0.877.

Conclusion Low CM was related with spinal defects (mainly open spinal dysraphism and closed spinal dysraphism/tethered cord syndrome). Clinicians should be cautious especially when the location of CM was lower than L4. In cases of tethered cord syndrome, release surgery was needed according to the postnatal condition. Otherwise, the prognosis of low CM was good.

Introduction

With advances in ultrasound technology, improvements in probe resolution, and the growing understanding of foetal disorders, the implementation of prenatal ultrasound for foetal central nervous system examination has become more and more important. The International Society of Ultrasound in Obstetrics and Gynaecology (ISUOG) has recently updated its guidelines on foetal central nervous system ultrasound, in which it suggested that the conus medullaris is helpful in determining the normality of the lumbosacral spine^[1] and can help to detect neural tube defects. The most common neural tube defects are spina bifida and meningocele^[2,3], along with the closed spinal dysraphisms. These are associated with lipoma, diastematomyelia, epidermoid cyst, and dermoid cyst^[4].

A low-lying conus medullaris (CM) could lead to some clinical symptoms, such as motor and sensory dysfunction of lower extremities, urination and defecation function disturbance. As a result, the diagnosis of "low-lying CM by prenatal ultrasound has become increasingly frequent in recent years. There are relatively few studies on the correlation between ultrasonic manifestations during pregnancy and

postnatal pregnancy outcomes. The purpose of this study was to provide our experience and clinical outcomes of fetuses prenatally diagnosed with low conus medullaris.

1. Data And Methods

1.1 Study Subjects

A total of 39 patients with a diagnosis of low conus medullaris on ultrasound were retrospectively collected from January 2019 to December 2020 at the Department of Obstetrics and Gynaecology, Peking University First Hospital, China.

1.2 Instruments and Study Methods

1.2.1 Apparatus:

General Electric E6, E8, and E10 ultrasound diagnostic instruments with transducer frequencies of 1.5-6.0 MHz were used. The appropriate ultrasound examination conditions were selected according to the gestational week and maternal abdominal tissue conditions. The study was conducted according to the guidelines of the Declaration of Helsinki, and approved by the Institutional Review Board of Peking University First Hospital (protocol code 2013[572]). Informed consent was obtained from all patients.

1.2.2 Foetal Systemic Ultrasound:

All foetal structures were further examined according to the ISUOG guidelines^[5]. The spine was assessed in the transverse, sagittal, and coronal planes in accordance with the guidelines on foetal central nervous system ultrasound published by ISUOG^[1].

1.2.3 Foetal Conus Medullaris Position Examination:

While displaying the median sagittal section of the spine, we instructed the pregnant woman to hold her breath and then initiated a three-dimensional (3D) volumetric scan (Figure 1). We manually adjusted the parameters so that the D plane showed the spine and rib structure clearly. we determined the position of the 12th thoracic vertebra based on the position of the 12th rib. Then we counted the lumbar vertebrae 1, 2, 3, ... downwards until they were at the level of the reference point (Figure1, green dot). If the conus medullaris was between the 3rd and 4th lumbar vertebrae (L3-L4), this was recorded as 3.5.

1.2.4 Definition of Low Conus Medullaris:

When the conus medullaris was below L3 (excluding L3)^[1], it was diagnosed as low conus medullaris^[1], regardless of gestational age.

1.2.5 Clinical Data Collection:

The clinical data of all patients were collected: age, gestation week when the foetal conus medullaris was first detected, changes in ultrasound presentation during pregnancy, presence of other foetal structural abnormalities, pregnancy outcome, gestational age at birth, birth weight, and postnatal follow-up. The postnatal follow-up was conducted by telephone and included the general condition of the baby after birth and further management after birth. The follow-up ran until August 1, 2021

Statistical Methods:

The clinical data of patients with foetal conus medullaris found during pregnancy were analysed descriptively. The mean ($\pm$ standard deviation) was calculated for measurement data, and the number of cases (percentage) is reported for count data. The conus medullaris positions of the normal and abnormal groups were compared by t-test, and the differences were considered statistically significant with $P < 0.05$. Spine disraphisms were diagnosed according to clinical criterias. Receiver operating characteristic (ROC) curve analysis was done to explore the diagnostic value of conus medullaris position using 3D. The cut-off values were estimated according to sensitivity and specificity. Statistical analysis was done with IBM SPSS 25.0 software.

2. Results

2.1 General Information

As shown in Table 1, the average age of 39 pregnant women was 31.8 years, and the gestational age when low-lying conus medullaris was first detected was 23-24 weeks. There were seven cases of other foetal structural anomalies, including one case of absent nasal bone and enhanced echogenicity of the intestinal wall, one case of left renal agenesis and ventricular septal defect, one case of anal atresia, one case of multiple punctate echogenicity of the liver and non-visualisation of gallbladder, one case of bilateral ventriculomegaly and bilateral hydronephrosis, one case of cleft lip and palate, and one case of short long bones.

A total of nine pregnancies (23.1%) were terminated, three of which were due to a combination of other structural abnormalities, three due to open spina bifida, two due to suspected tethered spinal cord, and one due to genetic abnormality (single-copy duplication variant in the long arm of chromosome 16, region 2, band 4, sub band 1).

A total of twelve pregnant women underwent non-invasive prenatal testing (NIPT). Seven women agreed to do amniocentesis, three of whose indication for amniocentesis were multiple anomalies and these three pregnancies were terminated ultimately; another three of whose indication were advanced age (one chose to terminate the pregnancy due to foetal genetic anomalies, and the other two had normal genetic results; and the last one's indication was due to low-lying conus medullaris with normal genetic results.

Table 1

Demographic Data and Pregnancy Characteristics of Study Population

Clinical Data	Number
Age	31.82 (±4.35)
Singleton	35 (89.7%)
Twin	4 (10.3%)
Gestation week at which "low-lying conus medullaris " was first detected	23.77 (±3.75)
With other foetal structural abnormalities	7 (17.9%)
Pregnancy Outcome	
Live birth	30 (76.9%)
Termination of Pregnancy (TOP)	9 (23.1%)
Spinal anomalies	
Open spinal dysraphism	3 (7.7%)
Closed spinal dysraphism/Tethered spinal cord	6 (15.4%)
Dermatomal sinus	1 (2.6%)
Lipoma	1 (2.6%)

2.2 Spinal anomalies with the conus medullaris at different location

Table 2 demonstrated spinal anomalies at different conus medullaris locations. For the foetus confirmed with spinal dysraphism, the position of conus medullaris was below L4.

Table 2

Position of conus modularis and final postnatal diagnosis

	Number of cases (%)	Open spinal dysraphism	Closed spinal dysraphism/Tethered spinal cord
L3-L4	10 (25.6%)	0	0
L4	20 (51.3%)	1	2
L4-L5	3 (7.7%)	1	1+1*
L5	2 (5.1%)	0	1
S1-S2	1 (2.6%)	1	0
S2	1 (2.6%)	0	1
S3	1 (2.6%)	0	1
S5	1 (2.6%)	0	1*
*These two cases were suspected to have tethered spinal cord, so termination could not be definitively diagnosed			

2.3 Comparison of CM Location Between foetus with spinal defects and those with normal spine

In this part, the lumbar vertebra was marked as 1 at position L1, 2 at L2, and so forth. The vertebral positions of the conus medullaris in the spinal defects group were compared with those in the normal group respectively (Table 3). The average CM position was found to be at the L5 level in the open spinal bifida group, between L5 and S1 in the closed spinal dysraphism and tethered cord syndrome group, and above L4 in the normal group. The differences between groups were statistically significant.

Table 3

Comparison of CM Position between the spinal defects group and normal group

	Conus medullaris position, mean (standard deviation)	P
Open spinal dysraphism (N = 3)	5 (1.32)	< 0.001
Closed dysraphisms/Tethered cord syndrome (N = 6)*	5.42 (1.69)	< 0.001
Normal (N = 28)	3.8 (0.33)	
* Another two suspected tethered spinal cord patients were not included in the analysis due to TOP and failed follow-up		

2.4 ROC Curve Analysis

ROC curves were drawn for conus medullaris position and spinal defects. Figure 1 shows that the ROC curve had an area under the curve (AUC) of 0.877. When the vertebral body position was at 4.25, it had its highest predictive value, with a sensitivity of 66.7% and specificity of 96% (Figure 2).

2.5 Postnatal Outcome After Confirmed Tethered Spinal Cord Syndrome

In our study, six foetus with prenatally diagnosed closed spinal dysraphism were live births. Among them,. five underwent surgical release. One infant had a dermal sinus, one had a lipoma, one still required intermittent catheterisation postoperatively, and the rest developed and grew well (Table 4).

Table 4

Summary of six infants with prenatally diagnosed of closed spinal dysraphism/tethered cord syndrome

Cases	Postnatal imaging	Postnatal management	Postnatal development
Case1	Postal MRI detected CM at L4 and dermal cyst 1 month after birth	Surgical release + excision of the dermal cyst sinus at 2 months after birth	7 months old, with normal development
Case2	Postnatal MRI detected CM at L3-L4 level Unknown MRI examine date	Surgical release at 11 months after birth	16 months old, with slightly delayed gross motor function and paediatric recommendation for observation
Case3	Postnatal MRI detected CM at L4 1 month after birth	Surgical release at 1 month after birth	10 months old, with normal development
Case4	Postnatal MRI suggested a borderline low CM unknown details	Expectant no surgery	20 months old with normal development
Case5	Postnatal MRI detected lipoma and unknown CM position, 2 months after birth suggested tethered spinal cord, location unknown	Surgical release + lipoma removal at 2 months after birth	18 months old, requires intermittent catheterization
Case6	Postnatal MRI detected low CM, unknown details	Surgical release at 5 months after birth	28 months old, with normal development

3. Discussion

The conus medullaris refers to a structure at the lower end of spinal cord, which tapers to a cone-like shape. Between the 3rd and 4th week of embryogenesis, the central nervous system, begins to develop from the neural plate, followed by progressive folding, closure of the neural tube and separation from the ectoderm. At the 27th day after fertilisation, the caudal end of the neural tube closes. By the day 38, the caudal segment eventually becomes the end of the conus medullaris, the terminal filament, and the terminal ventricle (a local expansion of the central canal of the conus medullaris)^[6]. During the first 3 months of embryonic development, the spine is almost equal in length to the spinal cord. Then the spine extends caudally and grows faster than the spinal cord. Since the upper end of spinal cord is attached to the medulla oblongata, so visually it seems that the spinal cord is moving upward compared to the spine^[7]. Therefore, the positions of the conus medullaris and its corresponding vertebral bodies are changing throughout pregnancy.

Lu et al. found that the foetal conus medullaris rose rapidly to the L3 level by 21 weeks and then rose slowly to reach a more stable level (L2-L3) by 28 weeks according to data from 828 normal fetuses at 17-39 weeks' gestation. Despite of the large sample, this study may not reflect the true level of the foetal spinal conus due to inaccurate findings from prenatal ultrasound^[8]. Arthurs et al. performed MRI on 84 fetuses that died between 14 and 41 weeks of gestation; 84.2% of foetal conus medullaris were located at L4/5 or above by 20 weeks' gestation, 22.8% at L3 or above, 50.7% of conus medullaris at L3 by 26 weeks, and 94.8% at L3 by the time of birth^[9]. This suggests that the position of the foetal conus medullaris increases with gestation week.

Since The normal range of conus medullaris position has not reached a consensus, we defined a low-lying conus medullaris as being below L3, according to the ISUOG guidelines, which do not take into account the upward shift of the conus medullaris with gestational age^[1]. Zalel et al. conducted a prospective study that recorded the conus medullaris position in 110 normal fetuses throughout pregnancy (13-40 weeks). The team found that all fetuses' conus medullaris were at L3-L4 between 13 and 18 weeks' gestation, 97% were at L2-L3 between 19 and 24 weeks, and 100% were above L3 between 25 and 42 weeks^[10]. In China, Li et al. also analysed 282 normal fetuses from 20 weeks to 26 weeks of gestation and came to a similar conclusion that 95.5% of fetuses' conus medullaris were at L3 and above^[11]. Additionally, Perlitz et al. summarized the location of the conus medullaris in 110 normal fetuses from 20 to 24 weeks of gestation. He found that 93% of fetuses' conus medullaris were above L3 and that the location of the conus medullaris did not differ with gestational age, maternal age, or foetal sex^[12]. In our study, the mean gestational week when low-lying conus medullaris was first noticed was 23 weeks, ranging 21 gestational weeks at minimum and the 36 gestational weeks at most. All of the above has proved that the definition of low-lying conus medullaris as below L3 (excluding L3) in our study were evidence based.

Perlitz et al. mentioned the need for vigilance when the conus medullaris is below L3^[12]. In Li et al's study, there are 10 fetuses with spinal dysraphisms, whose conus medullaris were located below the L3 level^[11]. In our study, we only collected data of 39 fetuses with a conus medullaris below L3. Among them, 10 (25.6%) fetuses' conus medullaris were between L3 and L4, whom had no spinal anomalies eventually. Of the 29 fetuses with conus medullaris at L4 and below, three had open spinal dysraphisms, six had closed spinal dysraphisms and another two had suspicion of tethered cord syndrome without further verification postnatally. According to the ROC analysis, if the conus medullaris was at L3.75, the sensitivity was 100% and specificity was 63%, whereas if the conus medullaris was at L4.25, the sensitivity was 66.7% and specificity was 96.4%. Hence, we assume that conus medullaris at L4 and below is more suggestive of a spine defect.

In general, many researchers used 2D ultrasound to locate the conus medullaris because of its simple and convenient operation. For example, Lu et al used angled lumbosacral joint (a 15–20° angle between L5 and S1) as a reference to assess the relative relationship between the CM and the vertebra^[8]. Hopmann et al and Zhao et al. measured the distance between the CM and the end of the sacral vertebrae (conus

distance, CD) and found a linear correlation between CD and gestational week, biparietal diameter, abdominal circumference and femoral length^[13,14]. However, the 2D ultrasound display is limited by the fact that the time of sacral vertebra ossification is correlated with gestational week. Consequently, this method has advantages of easy measurement, but the results are affected by the curvature of the foetal spine and visualisation of sacral vertebrae. With the advancement of 3D technology, the direct application of 3D reconstruction, together with using the T12 corresponding to the lowermost rib as reference, is becoming more authentic. Zhao et al. compared 2D CD measurements with 3D imaging and found that 3D imaging is easier and more accurate when determining the location of foetal conus medullaris^[14]. Moreover, the application of high-frequency ultrasound showed the vertebral anatomy more clearly, giving it a significant advantage in the diagnosis of spinal dysraphisms.

In this study, there were six cases of confirmed tethered cord syndrome (4 isolated and 2 complicated with dermal sinus and lipoma respectively) and two cases of unconfirmed tethered cord syndrome. Tethered cord syndrome is a neurological injury caused by fixation of the caudal end of the spinal cord by a hypertonic and/or fatty infiltrated terminal filament, which in turn produces neurological symptoms corresponding to the lower segment of the spinal cord^[15]. Tethered spinal cord syndrome may occur as an isolated lesion or be associated with other lesions such as lipomas, dermal sinuses, fatty infiltration of the terminal filaments, and caudal degeneration. Postnatal neurosurgical consultation and early neonatal surgery will reduce the risk of neurological injury^[16].

We found no evidence of a clear correlation between an isolated foetal low-lying conus medullaris and chromosomal anomalies. There are several cases of low-lying conus medullaris with some genetic syndromes, such as Pallister–Killian syndrome^[17] and Russell–Silver syndrome^[18]. However, these are sporadic case reports, and the genetic syndromes always involve multiple structural anomalies. There is one case of genetic abnormality identified in our paper according to the result of an amniocentesis performed for advanced maternal age. The clinical significance of the single-copy-number variants was not clear. The foetal conus medullaris position rose to the L3 level during this woman's pregnancy follow-up, but the patient and family chose to terminate the pregnancy because of the genetic abnormality.

This study was a retrospective analysis with a relatively small number of cases. Some fetuses that were terminated did not have a definitive pathological diagnosis. The follow-up age of the infants in this study ranges from 4 to 28 months. Our main outcome focused only on a definitive diagnosis and did not include the results of the long-term follow-up, thereby needing further follow-up for long-term neurological development and function.

4. Conclusion

Low-lying conus medullaris is associated with spinal defects. There is a need for increased vigilance for spinal related disorders in fetuses with conus medullaris at L4 or below. Most infants with congenital tethered cord syndrome require surgical release after birth and have a good prognosis after surgery.

Declarations

Ethical approval and consent to participate

The study was conducted according to the guidelines of the Declaration of Helsinki, and approved by the Institutional Review Board of Peking University First Hospital (protocol code 2013[572]).

Consent to publication

Written informed consent was obtained from the patient for publication.

Availability of data and materials

The datasets obtained and/or analyzed during the current study are available. From the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

Author contributions

JBH and HJZ designed the research and drafted the manuscript. YS provided substantial edits and additions to the manuscript. All authors have accepted responsibility for the entire content of this manuscript and approved its submission.

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Figures

Figure 1

The A plane was adjusted to the sagittal plane of the foetal spine to clearly show the end of the conus medullaris, and the reference point was placed here (Figure1, white dot); the B plane is the view of transverse spine; the C plane was the coronal spine view; and D was the 3D reconstruction of the spine. The green dot in D plane correspond to the white dot in A plane.

Figure 2

The area under the curve (AUC) was 0.877. When the vertebral body position was at 4.25, it had its highest predictive value, with a sensitivity of 66.7% and specificity of 96%.