Prenatal visualisation of the torcular herophili by means of a Doppler technology highly sensitive for low-velocity flow in the expert assessment of the posterior fossa: a prospective study

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Keywords:	DOPPLER ULTRASOUND, FETAL DIAGNOSIS AND THERAPY
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Abstract:	Objective To evaluate the usefulness of a Doppler technology highly sensitive for low velocity flow in the antenatal imaging of the torcular herophili (TH) in the second trimester of pregnancy. Design Prospective study. Setting Referral Fetal Medicine Unit. Population Non-consecutive series of singleton pregnancies submitted to antenatal neurosonogram between 20 and 28 weeks of gestation. Methods A midsagittal section of the fetal brain was obtained by insonating through the anterior fontanelle, then the MV-FlowTM and LumiFlowTM presets were selected in order to visualize the TH as the posterior confluence of the superior sagittal sinus and the straight sinus. Main outcome measures Evaluation of the anatomic relationship of the TH with the "transpalatal line" joining the upper bony palate to the fetal skull. Results 99 cases were recruited, including 1 case of open spina bifida, 1 Dandy-Walker malformation (DWM) and 2 Blake's pouch cysts. In normal cases the TH appeared to lie on or just below the "transpalatal line". In the

	cases of Blake's pouch cyst the position of the TH appeared normal if compared to controls, while in DWM a supraelevated position of the TH in respect of the transpalatal line was demonstrated. Finally, in the case of Chiari II malformation the TH was identified below the "transpalatal plane". Conclusions The prenatal US visualization of the TH by means of newly developed Doppler technologies characterized by high sensitivity for low velocity flow is feasible and allows the indirect evaluation of the insertion cerebellar tentorium in the second trimester.

TITLE PAGE

Prenatal visualization of the torcular herophili by means of a Doppler technology highly sensitive for low velocity flow in the expert assessment of the posterior fossa: a prospective study.

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22 **Running title**

23 Prenatal imaging of the torcular herophili.

Abstract

Objective

To evaluate the usefulness of a Doppler technology highly sensitive for low velocity flow in the antenatal imaging of the torcular herophili (TH) in the second trimester of pregnancy.

Design

Prospective study.

Setting

Referral Fetal Medicine Unit.

Population

Non-consecutive series of singleton pregnancies submitted to antenatal neurosonogram between 20 and 28 weeks of gestation.

Methods

A midsagittal section of the fetal brain was obtained by insonating through the anterior fontanelle, then the MV-Flow™ and LumiFlow™ presets were selected in order to visualize the TH as the posterior confluence of the superior sagittal sinus and the straight sinus.

Main outcome measures

Evaluation of the anatomic relationship of the TH with the "transpalatal line" joining the upper bony palate to the fetal skull.

Results

99 cases were recruited, including 1 case of open spina bifida, 1 Dandy-Walker malformation (DWM) and 2 Blake's pouch cysts. In normal cases the TH appeared to lie on or just below the "transpalatal line". In the cases of Blake's pouch cyst the position of the TH appeared normal if compared to controls, while in DWM a supraelevated position of the TH in respect of the transpalatal line was

demonstrated. Finally, in the case of Chiari II malformation the TH was identified below the "transpalatal plane".

Conclusions

The prenatal US visualization of the TH by means of newly developed Doppler technologies characterized by high sensitivity for low velocity flow is feasible and allows the indirect evaluation of the insertion cerebellar tentorium in the second trimester.

Funding: none.

Keywords: Doppler ultrasound, fetal cerebellum, Dandy-Walker malformation, Blake's pouch cyst, tentorium cerebelli.

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Introduction

The torcular herophili (TH), also known as "confluence of sinuses", is a venous structure draining the major vessels of the intracerebral venous system, among whom the superior sagittal sinus and the straight, transverse, sigmoid, cavernous and occipital sinuses (1,2).

Under normal circumstances the TH is located in the middle aspect of the occipital bone and posterior to the cerebellum, just inside the cranial vault (2,3), and lies in the erosion of the occipital bone where the major venous sinus tributaries congregate (4), which is located at the junction of the falx cerebri with the tentorium cerebelli. The antenatal assessment of this latter anatomic structure is of great interest for the Fetal Medicine Specialists in the accurate classification and differential diagnosis of posterior fossa abnormalities. Indeed, the upwards displacement of the tentorium cerebelli in respect of its normal insertion on the occipital clivus is among the diagnostic criteria of Dandy-Walker Malformation (DWM) in fetuses with hypoplastic and supraelevated cerebellar vermis and abnormal communication between the fourth ventricle and the cisterna magna (1,5,6). However, the antenatal visualization of the position of the tentorium cerebelli at grey-scale ultrasound on the midsagittal plane of the fetal brain is technically challenging, and this may lead to a limited agreement in the diagnosis of DWM in fetuses with abnormal findings of the posterior fossa.

Due to their close anatomic relationship, the position of the TH may be assumed as a clue of the insertion of cerebellar tentorium on the fetal skull. On this basis the antenatal sonographic demonstration of the TH at Doppler imaging has been proposed as a proxy of the direct visualization of the tentorium (1). On the midsagittal view of the fetal brain at 1st trimester ultrasound (US) Volpe et al. have accurately determined the insertion of the tentorium in fetuses with normal or abnormal posterior fossa, by measuring the angle between the brainstem and the TH (7). However, the antenatal imaging of the TH at conventional Doppler imaging is also technically challenging. MV-

Flow™ and LumiFlow™ (Samsung Medison Co Ltd, Seoul, South Korea) are newly developed Doppler technologies that represent an alternative to Power Doppler for the visualization of slow flow microvascularized structures and vascular connections. In this study we evaluate the usefulness of MV-Flow™ technology combined with LumiFlow™ algorithm in the antenatal imaging of the TH in the second trimester of pregnancy.

Methods

The study was conducted at two Italian Fetal Medicine referral Units (University Hospital of Parma and Carlo Poma Hospital of Mantua). The study population included a non-consecutive series of singleton pregnancies either referred from local US Departments or submitted to detailed antenatal neurosonogram due to clinical indication between 20 and 28 weeks of gestation. According to the Guidelines of the International Society on Ultrasound in Obstetrics and Gynecology, the fetal neurosonogram "usually includes the visualization of four coronal and three sagittal planes", as well as of "the convolutions of the fetal brain that change throughout gestation" in addition to the axial views required for the basic examination (8).

In all the included cases, a dedicated assessment of the fetal anatomy was performed using a Samsung HERA W10 system equipped with multifrequency volumetric (4-8 MHz) transducer and MV-Flow™ and LumiFlow™ technology. For the purposes of the study, a midsagittal section of the fetal brain was obtained by insonating through the anterior fontanelle in order to visualize the corpus callosum and the cerebellar vermis on two-dimensional (2D) ultrasound. The MV-Flow™ and LumiFlow™ presets were selected and the insonation angle was adjusted in order to visualize the pericallosal arteries and the torcular herophili as the posterior confluence of the superior sagittal sinus and the straight sinus (Figure 1). The anatomic relationship of the TH with the "transpalatal line" joining the upper bony palate to the fetal skull was assessed in all cases. The mean time required to visualize the TH using the MV-Flow™ and LumiFlow™ presets was calculated in all cases. The US examinations were performed for clinical or research purpose by four Authors (AD, GG, NV and TG). Exclusion criteria for the study were represented by the antenatal finding of abnormalities of the fetal central nervous system not involving the posterior fossa and by the failure to obtain a satisfactory view of the TH on the midsagittal view of the brain. Clinical data of the pregnancy and postnatal outcomes were obtained in all cases through medical records, while the ascertainment of

the antenatal diagnosis was performed either by neonatal ultrasound or, in the case of abnormal findings, by magnetic resonance imaging with or without pathology examination.

The study was conducted in the context of an unrestricted research collaboration with Samsung Medison Healthcare, Italy and approved by the local Ethics Committee of the University Hospital of Parma. Core outcome sets and patient involvement were not deemed as relevant for the research.

This case series was reported according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines (9).

Results

Over the study period, 122 pregnant women between 20 and 28 gestational weeks were submitted to prenatal ultrasound in the two Fetal Medicine Centres involved. The study group consisted in 99 (81.1%) patients, among whom 95 showed normal appearance of the forebrain and of the posterior fossa and 4 cases with abnormal findings of the posterior fossa including 1 open spina bifida, 1 DWM and 2 Blake's pouch cysts (BPC) (Figure S1). A summary of the demographic and clinical details of the study group is shown on Table S1. The median gestational age at ultrasound was 21^{+3} weeks ($20^{+0} – 27^{+6}$).

In all the included cases optimal views of the TH together with the superior sagittal sinus and the straight sinus could be obtained by means of the MV-Flow™ and the LumiFlow™ presets. Among the fetuses with normal intracranial findings, at qualitative evaluation the TH appeared to lie on or just below a line drawn through the "transpalatal line" as shown in Figure 1. With regards to the three fetuses with cystic anomaly of the posterior fossa, in the cases of BPC the position of the TH appeared normal if compared to normal controls (Figure 2), while in DWM a supraelevated position of the TH in respect of the transpalatal line was demonstrated consistently with the upward displacement of the tentorium (Figure 3). Finally, in the case of Chiari II malformation the TH was identified well below the "transpalatal plane" (Figure 4). In all cases the prenatal US diagnosis was confirmed following delivery.

The time required to visualize the TH when the midsagittal view of the fetal brain was obtained was less than one minute in all cases.

Discussion

Main findings

This study demonstrates that the prenatal US visualization of the TH by means of newly developed MV-Flow™ and LumiFlow™ Doppler techniques is feasible, and expert US seems to represent a reliable approach for the indirect evaluation of the cerebellar tentorium insertion in the second trimester.

Strengths and limitations

The original design of the study and the small number of Fetal Medicine Specialists undertaking the data collection represent the major strengths of our work. On the other hand, the mixed referral population, the non-consecutive recruitment of the cases and the small number of fetuses with abnormal findings may be acknowledged as limitations as they do not allow to comment on the performance of this novel method in the antenatal diagnosis of upward or downward displacement of the tentorium cerebelli. A larger prospective study assessing the accuracy of MV-Flow™ and LumiFlow™ in the antenatal classification of cystic abnormalities of the posterior fossa is warranted before any clinical implementation of the technique may be proposed.

The cystic malformations of the posterior fossa represent only a proportion of the large group of midbrain and hindbrain malformations which commonly present with some degree of vermian hypoplasia or dysplasia (10), and other conditions such as arachnoid cysts may be associated with the upward displacement of the TH with a normal insertion of the tentorium. Another limitation is that we were unable to visualize the TH in 17 cases showing normal appearance of the posterior fossa, however the midsagittal view of the fetal brain is not required outside the context of the expert assessment of the fetal brain. In this present study only the persistently unfavourable position of the fetal head precluded to obtain the midsagittal view required to visualize the TH, however other conditions impairing the spread of the US beam, among whom high BMI and uterine

fibroids, may limit the visualization of the TH. Finally, we have not attempted any formal comparison with Doppler techniques from other manufacturers characterized by high sensitivity for slow flow (1,7,11,12), which we believe is beyond the scope of this current paper. Based on the findings of our work it is not possible to speculate that MV-Flow™ and LumiFlow™ are superior to similar Doppler techniques, therefore no specific Doppler technique is to be deemed as required as long as the prenatal visualization of the TH on a midsagittal plane including also the bony palate can be accomplished.

Interpretation

The evaluation of the posterior fossa on the midsagittal plane is of paramount importance for the differential diagnosis between DWM and other conditions such as BPC and vermian hypoplasia (13-15). More specifically, the height, the rotation and the morphology of the cerebellar vermis have been reported to be feasible with either 2D or three-dimensional (3D) US as the cerebellar vermis is a hyperechoic structure which can be clearly distinguished from the brainstem and fourth ventricle, which lie anteriorly, and the fluid-filled cisterna magna (16-19).

While the vermian anatomy and biometry is crucial for the differential diagnosis between DWM and the other cystic malformations of the posterior fossa, another important additional finding to be considered in the diagnostic workout is represented by the tentorium cerebelli insertion (6,16). It has been postulated that its supraelevation is a mandatory diagnostic requisite of DWM, while a normally inserted tentorium in fetuses with upwards rotated vermis and wide communication between the 4th ventricle and cisterna magna is compatible with BPC. On this ground, the brainstem-tentorium angle (BTA) has been proposed for the quantitative evaluation of the insertion of the tentorium cerebelli by means of 3D US (16-19). To our knowledge, there is no study evaluating the feasibility of the quantitative assessment of the BTA on 2D imaging, which can be due to the fact that the visualization of the BTA on 2D US is challenging even among experienced investigators. Very

recently, another technique relying on the subjective assessment of the position of the choroid plexus in relation to the roof/cyst inlet of the fourth ventricle using 3D US has been proposed for the differential diagnosis of the posterior fossa cystic malformations, however such novel approach was evaluated retrospectively, on a limited number of cases and at a single Tertiary referral centre with expertise on 3D US and prenatal neurosonology (20). In such context, fetal MRI has been shown to add in the prenatal diagnosis of abnormalities of the fetal brain compared to expert ultrasound (21), and represents a valuable tool for the differential diagnosis of the cystic malformations of the posterior fossa by enabling the accurate assessment of the lobulation and fissuration of the fetal cerebellar vermis as well as the evaluation of the position of the cerebellar tentorium and of the TH (22,23,24). However, fetal MRI is an expensive second-level test which may not be readily available in all Units; furthermore, high expertise is required in order to interpret the anatomic characteristics of the posterior fossa across gestation (25).

A research by Volpe et al. has demonstrated the role of the visualization of the straight and of the superior sagittal sinus by means of color or power Doppler in the identification of the tentorial insertion when measured on 2D US at a gestational age between 11 and 14 weeks in the midsagittal view used to measure the nuchal translucency (7). In our cohort of fetuses in the second trimester of pregnancy with normal intracranial findings and in the cases with BPC we found that the TH and consequently the tentorium insertion lay on or just below a line drawn tangentially above the bony palate ("transpalatal plane"). On the other hand, in the case diagnosed with DWM, the TH was demonstrated to lie above the transpalatal plane, thus confirming the upward displacement of the tentorium, while in open spina bifida the TH was clearly imaged below the "transpalatal plane", which is consistent with the caudal displacement of the posterior fossa structures which characterize the Chiari 2 malformation. Therefore, the insertion of the tentorium cerebelli may be derived from the evaluation of the TH in relation to the "transpalatal plane". Such information,

which can be obtained in less than one minute when the midsagittal view of the fetal brain through the anterior fontanelle is obtained, is of crucial importance for the differential diagnosis, the prognostic assessment as well as the parental counseling of cases diagnosed with cystic malformations of the posterior fossa (14). We do not envisage that MV-Flow™ and LumiFlow™ Doppler techniques will allow an easy and straightforward differential diagnosis of the cystic abnormalities of the posterior fossa, however we believe that these technologies are worth to be prospectively tested in referral Fetal Medicine Units with expertise in the diagnosis and classification of such conditions.

Conclusion

In conclusion, the use of a Doppler technology highly sensitive for low velocity flow represents an easy tool enabling a comprehensive assessment of the intracranial venous system of the fetus, which has the potential to improve our capability to assess the normal anatomy and to differentiate the abnormalities of the posterior fossa. Further prospective studies are required in order to confirm the usefulness of the visualization of the TH as an indirect evaluation of the tentorium cerebelli in a clinical setting.

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None.

Disclosure of interest.

The Authors state no financial interest related to the content of this work.

Conflict of interest statement

This work was conducted in the context of an unrestricted and unremunerated research collaboration with Samsung Medison Healthcare, Italy.

Dr Dall'Asta states other unrestricted and unremunerated research collaborations with Samsung Medison Korea.

Dr Ghi acknowledges the receipt of speaking honoraria from Samsung Medison & Co., outside the submitted work.

Dr Fabiana Sorrentino is a biomedical engineer employed by Samsung Electronics Italy, Milan, Italy. She has been in charge for the optimization of the newly developed Doppler technique evaluated in this study and has actively contributed in the conceptualization and in the finalization of this work.

Contribution to Authorship

Andrea Dall'Asta – Conceptualization, data collection, manuscript writing and editing.

Gianpaolo Grisolia – Conceptualization, data collection.

Nicola Volpe – Data and outcome collection, manuscript writing and editing.

Giovanni Battista Luca Schera – Data and outcome collection, manuscript writing and editing.

Fabiana Sorrentino – Conceptualization, ultrasound assistance and setting, manuscript review.

Tiziana Frusca – Conceptualization, manuscript review.

Tullio Ghi – Conceptualization, data collection, manuscript review.

Details of ethics approval

The study was approved by the local Ethics Committee of the University Hospital of Parma on 19/06/2019 (Number of approval 660)

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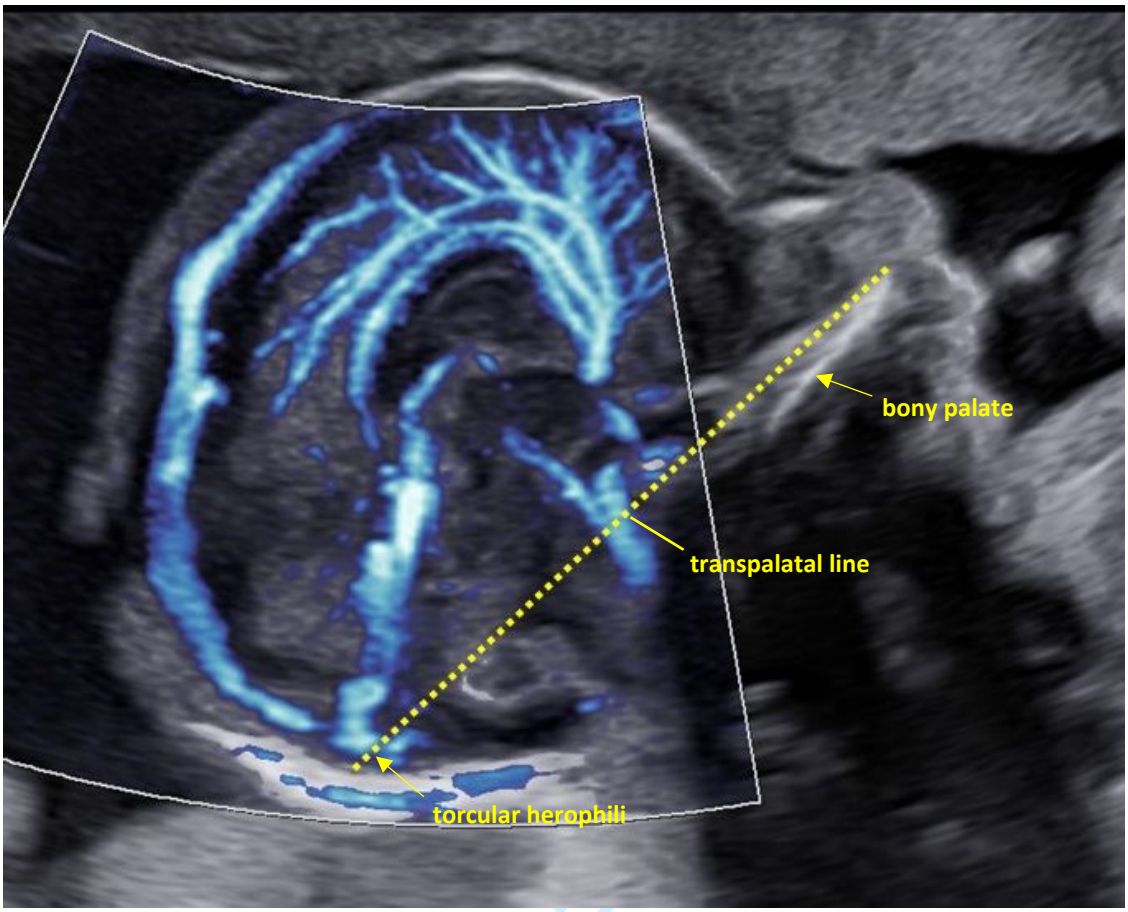
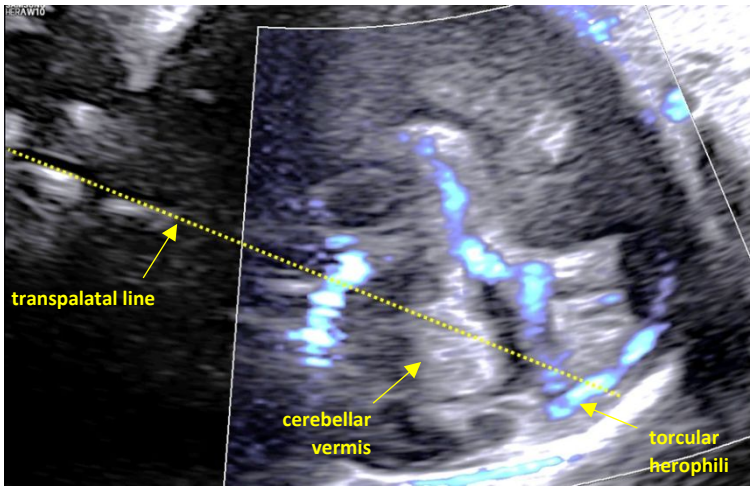


Figure 1 – Midsagittal section of the fetal brain with MV-Flow™ and the LumiFlow™ presets and visualization of the relationship between the torcular herophili and the "transpalatal line" in a 21 weeks' normal fetus.



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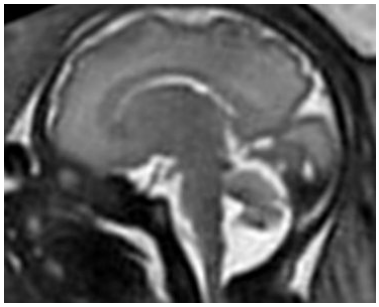
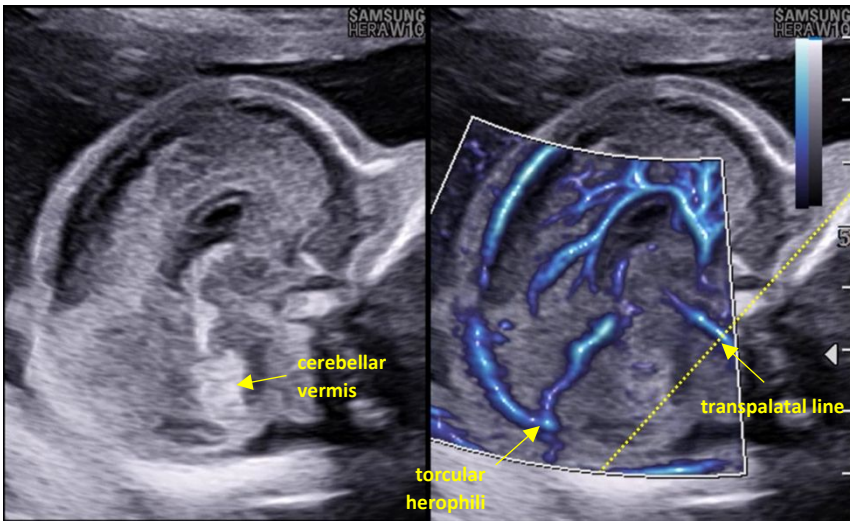
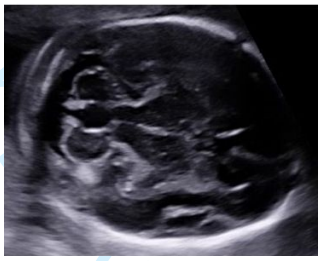


d.

Figure 2 – a-c) Neurosonogram in a case of Case of Blake's pouch cyst imaged at 25 weeks. a) Midsagittal section of the fetal brain with MV-Flow™ and the LumiFlow™ presets and visualization of the relationship between the torcular herophili and the "transpalatal line"; b) transcerebellar axial section on 2D gray scale and c) midsagittal view of the posterior fossa on multiplanar mode. d) Magnetic resonance imaging showing the midsagittal section of the fetal brain of the same fetus at 22 weeks of gestation.



a.



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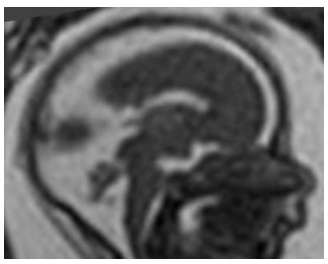
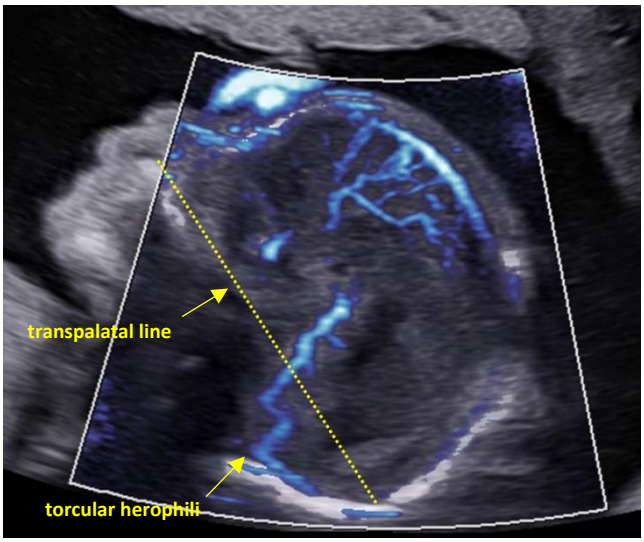


d.

Figure 3 – a-c) Neurosonogram in a case of Dandy Walker malformation imaged at 21 weeks. a) Midsagittal section of the fetal brain with MV-Flow™ and the LumiFlow™ presets and visualization of the relationship between the torcular herophili and the "transpalatal line"; b) transcerebellar axial section on 2D gray scale and c) midsagittal view of the fetal brain demonstrating the upward rotation of the cerebellar vermis, which appears dysmorphic. d) Magnetic resonance imaging showing the midsagittal section of the fetal brain of the same fetus at 21 weeks of gestation.



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d.

Figure 4 – a) Midsagittal section of the fetal brain with MV-Flow™ and the LumiFlow™ presets and visualization of the relationship between the torcular herophili and the "transpalatal line" in a 21 weeks' fetus diagnosed with open spina bifida with kyphoscoliosis and Chiari II malformation; b) transthalamic axial view showing lemon shaped skull and enlarged lateral ventricles; c) transcerebellar axial view showing banana shaped cerebellum and obliteration of the cisterna magna; d) sagittal view of the spine demonstrating the vertebral defect and the myelomeningocele.

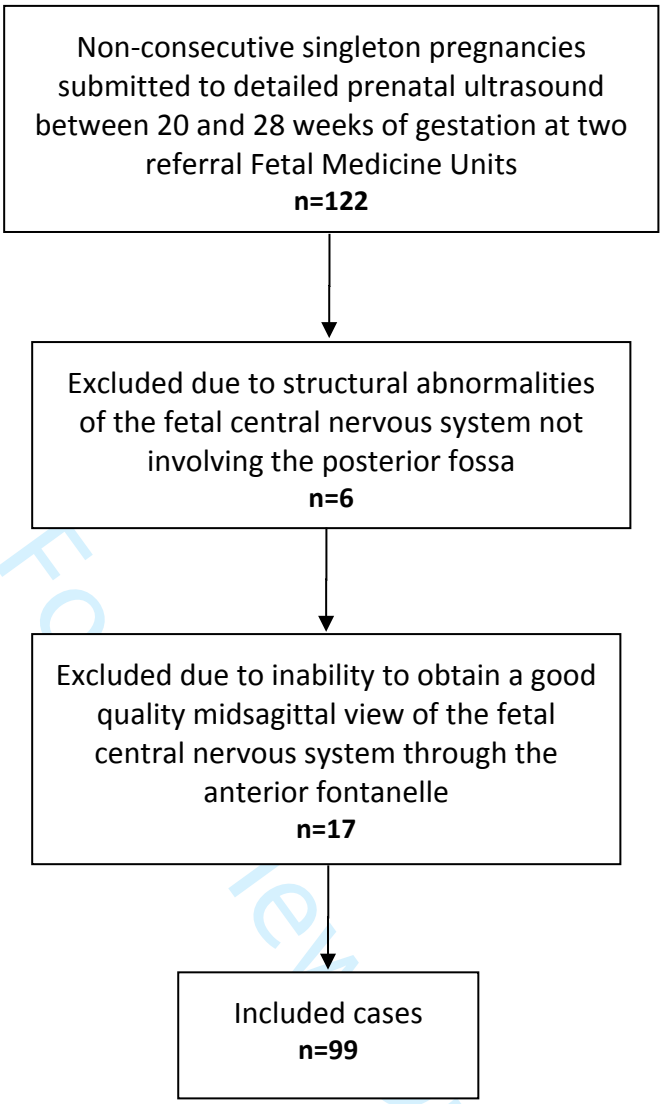

Figure S1 – Flow chart (according to STROBE guidelines) (9) for inclusion of cases.

Table S1 – Features of the included cases.

Age (years), mean ± SD	27.0 ± 6.1
BMI (kg/m^2), mean ± SD	25.1 ± 4.7
Parity, N (%)	Nulliparae N 52 (52.5%)
Gestation at US weeks^{+days}, median (range)	21^{+3} (20^{+0} – 27^{+6})
Indication for US	- High risk CST N 7 (7.1%) - Abnormality suspected at screening anomaly scan N 20 (20.2%) - Maternal or familiar past medical history N 33 (33.3%) - Medical complications of the pregnancy N 28 (28.3%) - Other (twins or higher order pregnancies, TORCH, low lying placenta) N 11 (11.1%)

BMI: body mass index

US: ultrasound

CST: combined screening test

TITLE PAGE

Prenatal visualization of the torcular herophili by means of a Doppler technology highly sensitive for low velocity flow in the expert assessment of the posterior fossa: a prospective study.

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22 **Running title**

23 Prenatal imaging of the torcular herophili.

Abstract

Objective

To evaluate the usefulness of a Doppler technology highly sensitive for low velocity flow in the antenatal imaging of the torcular herophili (TH) in the second trimester of pregnancy.

Design

Prospective study.

Setting

Referral Fetal Medicine Unit.

Population

Non-consecutive series of singleton pregnancies submitted to antenatal neurosonogram between 20 and 28 weeks of gestation.

Methods

A midsagittal section of the fetal brain was obtained by insonating through the anterior fontanelle, then the MV-Flow™ and LumiFlow™ presets were selected in order to visualize the TH as the posterior confluence of the superior sagittal sinus and the straight sinus.

Main outcome measures

Evaluation of the anatomic relationship of the TH with the "transpalatal line" joining the upper bony palate to the fetal skull.

Results

9983 cases were recruited, including 1 case of open spina bifida, 1 Dandy-Walker malformation (DWM) and 21 Blake's pouch cysts. In normal cases the TH appeared to lie on or just below the "transpalatal line". In the cases of Blake's pouch cyst the position of the TH appeared normal if compared to controls, while in DWM a supraelevated position of the TH in respect of the

transpalatal line was demonstrated. Finally, in the case of Chiari II malformation the TH was identified below the “transpalatal plane”.

Conclusions

The prenatal US visualization of the TH by means of newly developed Doppler technologies characterized by high sensitivity for low velocity flow is feasible and allows the indirect evaluation of the insertion cerebellar tentorium in the second trimester.

Funding: none.

Keywords: Doppler ultrasound, fetal cerebellum, Dandy-Walker malformation, Blake’s pouch cyst, tentorium cerebelli.

Tweetable abstract: Prenatal imaging of the torcular herophili using a Doppler technology highly sensitive for low velocity flow.

Introduction

The torcular herophili (TH), also known as "confluence of sinuses", is a venous structure draining the major vessels of the intracerebral venous system, among whom the superior sagittal sinus and the straight, transverse, sigmoid, cavernous and occipital sinuses (1,2).

Under normal circumstances the TH is located in the middle aspect of the ~~ferior to the~~ occipital bone~~s~~ and posterior to the cerebellum, just inside the cranial vault (2,3), and lies in the erosion of the occipital bone where the major venous sinus tributaries congregate (4), which is located at the junction of the falx cerebri with the tentorium cerebelli. The antenatal assessment of this latter anatomic structure is of great interest for the Fetal Medicine Specialists in the accurate classification and differential diagnosis of posterior fossa abnormalities. Indeed, the upwards displacement of the tentorium cerebelli in respect of its normal insertion on the occipital clivus is among the diagnostic criteria of Dandy-Walker Malformation (DWM) in fetuses with hypoplastic and supraelevated cerebellar vermis and abnormal communication between the fourth ventricle and the cisterna magna (1,~~4,~~5,6). However, the antenatal visualization of the position of the tentorium cerebelli at grey-scale ultrasound on the midsagittal plane of the fetal brain is technically challenging, and this may lead to a limited agreement in the diagnosis of DWM in fetuses with abnormal findings of the posterior fossa.

Due to their close anatomic relationship, the position of the TH may be assumed as a clue of the insertion of cerebellar tentorium on the fetal skull. On this basis the antenatal sonographic demonstration of the TH at Doppler imaging has been proposed as a proxy of the direct visualization of the tentorium (1). On the midsagittal view of the fetal brain at 1st trimester ultrasound (US) Volpe et al. have accurately determined the insertion of the tentorium in fetuses with normal or abnormal posterior fossa, by measuring the angle between the brainstem and the TH (~~6~~7). However, the antenatal imaging of the TH at conventional Doppler imaging is also technically challenging. ~~Among~~

~~the limitations is the paucity of ultrasound techniques available for the imaging of the intracerebral veins, which are characterized by low blood flow velocities and therefore require sensitive color Doppler ultrasound in order to be reliably displayed (1). Within this context,~~ MV-Flow™ and LumiFlow™ (Samsung Medison Co Ltd, Seoul, South Korea) are newly developed Doppler technologies that ~~capable to provide a detailed view of the blood flow in relation to surrounding tissue and~~ represent~~s~~ an alternative to Power Doppler for the visualization of slow flow microvascularized structures and vascular connections. In this study we evaluate the usefulness of MV-Flow™ technology combined with LumiFlow™ algorithm in the antenatal imaging of the TH in the second trimester of pregnancy.

Methods

The study was conducted at two Italian Fetal Medicine referral Units (University Hospital of Parma and Carlo Poma Hospital of Mantua) ~~over a five-month period, between 1st July and 30th November 2019~~.

The study population included a non-consecutive series of singleton pregnancies either referred from local US Departments or submitted to detailed antenatal neurosonogram due to clinical indication between 20 and 28 weeks of gestation. According to the Guidelines of the International Society on Ultrasound in Obstetrics and Gynecology, the fetal neurosonogram "usually includes the visualization of four coronal and three sagittal planes", as well as of "the convolutions of the fetal brain that change throughout gestation" in addition to the axial views required for the basic examination (8~~7~~).

In all the included cases, a dedicated assessment of the fetal anatomy was performed using a Samsung HERA W10 system equipped with multifrequency volumetric (4-8 MHz) transducer and MV-Flow™ and LumiFlow™ technology ~~(Samsung Medison Co Ltd, Seoul, South Korea)~~. For the purposes of the study, a midsagittal section of the fetal brain was obtained by insonating through the anterior fontanelle in order to visualize the corpus callosum and the cerebellar vermis on two-dimensional (2D) ultrasound. The MV-Flow™ and LumiFlow™ presets were selected and the insonation angle was adjusted in order to visualize the pericallosal arteries and the torcular herophili as the posterior confluence of the superior sagittal sinus and the straight sinus (Figure 1). The anatomic relationship of the TH with the "transpalatal line" joining the upper bony palate to the fetal skull was assessed in all cases. The mean time required to visualize the TH using the MV-Flow™ and LumiFlow™ presets was calculated in all cases.

The US examinations were performed for clinical or research purpose by four Authors (AD, GG, NV and TG). Exclusion criteria for the study were represented by the antenatal finding of abnormalities

of the fetal central nervous system not involving the posterior fossa and by the failure to obtain a satisfactory view of the TH on the midsagittal view of the brain. Clinical data of the pregnancy and postnatal outcomes were obtained in all cases through medical records, while the ascertainment of the antenatal diagnosis was performed either by neonatal ultrasound or, in the case of abnormal findings, by magnetic resonance imaging with or without pathology examination.

The study was conducted in the context of an unrestricted research collaboration with Samsung Medison Healthcare, Italy and approved by the local Ethics Committee of the University Hospital of Parma. Core outcome sets and patient involvement were not deemed as relevant for the research.

This case series was reported according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines (98).

Results

Over the study period, 12205 pregnant women between 20 and 28 gestational weeks ~~pregnant women at a gestation between 20 and 28 weeks~~ were submitted to prenatal ultrasound in the two Fetal Medicine Centres involved. The study group consisted in 9983 (8179.10%) patients, among whom 9580 showed normal appearance of the forebrain and of the posterior fossa and 43 cases with abnormal findings of the posterior fossa including 1 open spina bifida, 1 DWM and 21 Blake's pouch cysts (BPC) (Figure S12). A summary of the demographic and clinical details of the study group is shown on Table S1. The median gestational age at ultrasound was 21^{+32} weeks (20^{+0} – 27^{+6}).

In all the included cases optimal views of the TH together with the superior sagittal sinus and the straight sinus could be obtained by means of the MV-Flow™ and the LumiFlow™ presets. Among the fetuses with normal intracranial findings, at qualitative evaluation the TH appeared to lie on or just below a line drawn through the "transpalatal line" as shown in Figure 1. With regards to the threewo fetuses with cystic anomaly of the posterior fossa, in the cases of BPC~~Blake's pouch cyst~~ the position of the TH appeared normal if compared to normal controls (Figure 23a), while in DWM~~Dandy-Walker malformation~~ a supraelevated position of the TH in respect of the transpalatal line was demonstrated consistently with the upward displacement of the tentorium (Figure 33b). Finally, in the case of Chiari II malformation the TH was identified well below the "transpalatal plane" (Figure 44). In all cases the prenatal US diagnosis was confirmed following delivery.

The time required to visualize the TH when the midsagittal view of the fetal brain was obtained was less than one minute in all cases.

Discussion

Main findings

This study demonstrates that the prenatal US visualization of the TH by means of newly developed MV-Flow™ and LumiFlow™ Doppler techniques ~~characterized by high sensitivity for low velocity flow~~ is feasible, and expert US ~~in expert hands and~~ seems to ~~allows the visualization of the dural sinuses lying on the midsagittal plane of the fetal brain and of the TH in all cases~~represent ~~. The findings of the study suggest that expert 2D US with the adjunct of MV-Flow™ and LumiFlow™ techniques represents a simple and~~ a reliable approach for the indirect evaluation of the ~~insertion~~ cerebellar tentorium insertion in the second trimester. ~~Thanks to these newly developed Doppler technologies, which are sensitive to slow venous flow and are capable to depict microvascularized structures, the TH can be documented at antenatal ultrasound and, due to their close anatomic relationship, the position of tentorium can be indirectly worked out.~~

Strengths and limitations

The original design of the study and the small number of Fetal Medicine Specialists undertaking the data collection represent the major strengths of our work. On the other hand, the mixed referral population, the non-consecutive recruitment of the cases and the small number of fetuses with abnormal findings may be acknowledged as limitations as they do not allow to comment on the performance of this novel method in the antenatal diagnosis of upward or downward displacement of the tentorium cerebelli. A larger prospective study assessing the accuracy of MV-Flow™ and LumiFlow™ in the antenatal classification of cystic abnormalities of the posterior fossa is warranted before any clinical implementation of the technique may be proposed.

The cystic malformations of the posterior fossa represent only a proportion of the large group of midbrain and hindbrain malformations which commonly present with some degree of vermian hypoplasia or dysplasia (10), and other conditions such as arachnoid cysts may be associated with

the upward displacement of the TH with a normal insertion of the tentorium. Another limitation is that we were unable to visualize the TH in 17 cases showing normal appearance of the posterior fossa, however the midsagittal view of the fetal brain is not required outside the context of the expert assessment of the fetal brain. In this present study only the persistently unfavourable position of the fetal head precluded to obtain the midsagittal view required to visualize the TH, however other conditions impairing the spread of the US beam, among whom high BMI and uterine fibroids, may limit the visualization of the TH. Finally, we have not attempted any formal comparison with Doppler techniques from other manufacturers characterized by high sensitivity for slow flow (1,7,11,12), which we believe is beyond the scope of this current paper. Based on the findings of our work it is not possible to speculate that MV-Flow™ and LumiFlow™ are superior to similar Doppler techniques, therefore no specific Doppler technique is to be deemed as required as long as the prenatal visualization of the TH on a midsagittal plane including also the bony palate can be accomplished.

Interpretation

The evaluation of the posterior fossa on the midsagittal plane is of paramount importance for the differential diagnosis between DWM~~andy-Walker malformation~~ and other conditions ~~associated with better prognosis~~ such as BPC~~Blake's pouch cyst~~ and~~d~~ vermian hypoplasia ~~vermian hypoplasia~~ (13~~9~~-15~~1~~). More specifically, the height, the rotation and the morphology of the cerebellar vermis have~~s~~ been reported to be feasible with either 2D or three-dimensional (3D) US as the cerebellar vermis is a hyperechoic structure which can be clearly distinguished from the brainstem and fourth ventricle, which lie anteriorly, and the fluid-filled cisterna magna (16~~2~~-19~~5~~).

While the vermian anatomy and biometry is crucial for the differential diagnosis between DWM and the other cystic malformations of the posterior fossa, another important additional finding to be considered in the diagnostic workout ~~such~~ is represented by the tentorium cerebelli insertion (6,16). ~~The assessment of the insertion of the tentorium cerebelli is crucial for the antenatal classification and differential diagnosis of posterior fossa malformation (5,12).~~ It has been postulated that its ~~the~~ supraelevation ~~of the tentorium in respect to its normal insertion on the occipital clivus~~ is a mandatory diagnostic requisite of DWM, while a normally inserted tentorium in fetuses with upwards rotated vermis and wide communication between the 4th ventricle and cisterna magna is compatible with BPC~~Blake's pouch cyst~~. On this ground, the brainstem-tentorium angle (BTA) has been proposed for the quantitative evaluation of the insertion of the tentorium cerebelli by means of 3D US (16~~2~~-19~~5~~). ~~Such measurement has been reported to be feasible and reproducible only by means of 3D US (13).~~ To our knowledge, there is no study evaluating the feasibility of the quantitative assessment of the BTA on 2D imaging, which can be due to the fact that the visualization of the BTA on 2D US is challenging even among experienced investigators. ~~This represents a potential limitation given that the post-processing of 3D US volumes may be time consuming and warrants proper training.~~ Very recently, another technique relying on the subjective assessment of the position of the choroid plexus in relation to the roof/cyst inlet of the fourth ventricle using 3D US has been proposed for the differential diagnosis of the posterior fossa cystic malformations, however such novel approach was evaluated retrospectively, on a limited number of cases and~~, importantly,~~ at a single ~~in the context of a~~ Tertiary referral centre with expertise on 3D US and prenatal neurosonology (20~~16~~). ~~In such context, fetal MRI has been shown to add acknowledged to add~~ in the prenatal diagnosis of abnormalities of the fetal brain compared to expert ultrasound (21), and represents a valuable tool for the differential diagnosis of the cystic malformations of the posterior fossa by enabling the accurate assessment of the lobulation and

fissuration of the fetal cerebellar vermis as well as the evaluation of the position of the cerebellar tentorium and of the TH (22,~~18~~,23,24~~19~~). However, fetal MRI is an expensive second-level test which may not be readily available in all Units; furthermore, ~~adds costs to the~~ high expertise is required in order to interpret the anatomic characteristics of the posterior fossa across gestation (25).

A~~nother recently published~~ research by Volpe et al. has demonstrated the role of the visualization of the straight and of the superior sagittal sinus by means of color or power Doppler in the identification of the tentorial insertion when measured on 2D US at a gestational age between 11 and 14 weeks in the midsagittal view used to measure the nuchal translucency (7). ~~the role of the BTA in the differential diagnosis between Dandy-Walker malformation and Blake's pouch cyst when measured on 2D US at a gestational age between 11 and 14 weeks in the midsagittal view used to measure the nuchal translucency (6). In the same work, the Authors acknowledged the role of the visualization of the straight and of the superior sagittal sinus by means of color or power Doppler in the identification of the tentorial insertion.~~

In our cohort of fetuses in the second trimester of pregnancy with normal intracranial findings and in the ~~single~~ cases with BPC~~Blake's pouch cyst~~ we ~~originally~~ found that the TH and consequently the tentorium insertion lay on or just below a line drawn tangentially above the bony palate ("transpalatal plane"). On the other hand, in the case diagnosed with DWM, the TH was demonstrated to lie above ~~the maxillary line~~the transpalatal plane, thus confirming the upward displacement of the tentorium, while ~~. Finally,~~ in open spina bifida the TH was clearly imaged below the "transpalatal plane", which is consistent with the caudal displacement of the posterior fossa structures which characterize the Chiari 2 malformation. Therefore, the insertion of the tentorium cerebelli may be derived ~~the antenatal tracking of the TH by means of Doppler technologies enabling the visualization of slow flow may have a major impact for the fetal medicine specialist dealing with~~

~~the abnormalities of the posterior fossa, as~~ from the evaluation of the TH in relation to the "transpalatal plane" ~~the insertion of the tentorium cerebelli may be derived~~. Such information, which can be obtained in less than one minute when the midsagittal view of the fetal brain through the anterior fontanelle is obtained, is of crucial importance for the differential diagnosis, the prognostic assessment as well as the parental counseling of cases diagnosed with cystic malformations of the posterior fossa (148). We do not envisage that MV-Flow™ and LumiFlow™ Doppler techniques will allow an easy and straightforward differential diagnosis of the cystic abnormalities of the posterior fossa, however we believe that these ~~these techniques which rely on the most recent Doppler~~ technologies~~y~~ are worth to be prospectively tested in referral Fetal Medicine Units with expertise in the diagnosis and classification of such conditions.

~~Strengths and limitations~~

~~The original design of the study and the small number of Fetal Medicine Specialists undertaking the data collection represent the major strengths of our work. On the other hand, the mixed referral population, the non-consecutive recruitment of the cases and the small number of fetuses with abnormal findings may be acknowledged as limitations as they do not allow to comment on the performance of this novel method in the antenatal diagnosis of upward or downward displacement of the tentorium cerebelli. A larger prospective study assessing the accuracy of MV-Flow™ and LumiFlow™ in the antenatal classification of cystic abnormalities of the posterior fossa is warranted before any clinical implementation of the technique may be proposed. Finally, we have not attempted any formal comparison with other Doppler techniques characterized by high sensitivity for slow flow microvascularized structures and vascular connections from other manufacturers (1,6,720,218), which we believe is beyond the scope of this current paper. The properties of MV-Flow™ and LumiFlow™ make them suitable for the antenatal evaluation of vascular structures characterized by slow flow, however it is important to point out that based on the findings of our~~

~~work it is not possible to speculate that MV-Flow™ and LumiFlow™ are superior to similar Doppler techniques by other manufacturers.~~

Conclusion

In conclusion, ~~our study has shown that~~ the use of a Doppler technology highly sensitive for low velocity flow ~~adds substantial information over conventional Doppler imaging and~~ represents an easy tool enabling a comprehensive assessment of the intracranial venous system of the fetus, which has the potential to improve our capability to assess the normal anatomy and to differentiate the abnormalities of the posterior fossa. Further prospective studies are required in order to confirm the usefulness of ~~MV-Flow™ and LumiFlow™ technology for~~ the visualization of the TH as an indirect evaluation of the tentorium cerebelli in a clinical setting.

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Disclosure of interest.

The Authors state no financial interest related to the content of this work.

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Conflict of interest statement

This work was conducted in the context of an unrestricted and unremunerated research collaboration with Samsung Medison Healthcare, Italy.

Dr Dall'Asta states other unrestricted and unremunerated research collaborations with Samsung Medison Korea.

Dr Ghi acknowledges the receipt of speaking honoraria from Samsung Medison & Co., outside the submitted work.

Dr Fabiana Sorrentino is a biomedical engineer employed by Samsung Electronics Italy, Milan, Italy. She has been in charge for the optimization of the newly developed Doppler technique evaluated in this study and has actively contributed in the conceptualization and in the finalization of this work.

Contribution to Authorship

Andrea Dall'Asta – Conceptualization, data collection, manuscript writing and editing.

Gianpaolo Grisolia – Conceptualization, data collection.

Nicola Volpe – Data and outcome collection, manuscript writing and editing.

Giovanni Battista Luca Schera – Data and outcome collection, manuscript writing and editing.

Fabiana Sorrentino – Conceptualization, ultrasound assistance and setting, manuscript review.

Tiziana Frusca – Conceptualization, manuscript review.

Tullio Ghi – Conceptualization, data collection, manuscript review.

Details of ethics approval

The study was approved by the local Ethics Committee of the University Hospital of Parma on 19/06/2019 (Number of approval 660)

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