**Biometric assessments of the posterior fossa by fetal MRI: a systematic review**

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2D biometric assessments of the posterior fossa by fetal MRI

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***Conflicts of interest***

No conflicts of interest to declare

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***What is already known about this topic?***

* Posterior fossa abnormalities are one of the most common reasons for fetal MRI.
* Biometric measurements of the posterior fossa are well characterised in antenatal ultrasound studies.
* Many different measurements have been used to assess the posterior fossa on fetal MRI in health and disease, but not consistently.

***What does this study add?***

* This review identified 11 validated 2D biometric measurements were used in 10 or more studies for assessment of the posterior fossa on fetal MRI.
* Consistent application of these measurements will be useful in delineation of different types of posterior fossa abnormalities.

***Data availability***

Data available on request from the authors

***Abstract***

Posterior fossa abnormalities (PFAs) are commonly identified within routine screening and are a frequent indication for fetal magnetic resonance imaging (MRI). Although biometric measurements of the posterior fossa (PF) are established on fetal ultrasound and MRI, qualitative visual assessments are predominantly used to differentiate PFAs. This systematic review aimed to assess 2-dimensional (2D) biometric measurements currently in use for assessing the PF on fetal MRI to delineate different PFAs. The protocol was registered (PROSPERO ID CRD42019142162). Eligible studies included T2-weighted MRI PF measurements in fetuses with and without PFAs, including measurements of the PF, or other brain areas relevant to PFAs. 59 studies were included – 6859 fetuses had 62 2D PF and related measurements. These included linear, area and angular measurements, representing measures of PF size, cerebellum/vermis, brainstem, and some supratentorial measurements. 11 measurements were used in 10 or more studies and at least 1200 fetuses. These dimensions were used to characterise normal for gestational age, diagnose a range of pathologies, and predict outcome. A selection of validated 2D biometric measurements of the PF on fetal MRI may be useful for identification of PFA in different clinical settings. Consistent use of these measures, both clinically and for research, is recommended.

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N/A

***Introduction***

The cerebellum starts developing early in brain formation, but has ongoing development into the postnatal period.(1) This makes it vulnerable to developmental events, making posterior fossa abnormalities (PFAs) one of the most common fetal intracranial abnormalities, and one of the most common reasons for referral for fetal magnetic resonance imaging (MRI).(2) There are a range of PFA diagnoses, and differentiating these at an early stage of development is challenging,(3) making accurate antenatal counselling of parents difficult.

 Many biometric measurements of the posterior fossa (PF) and the brain overall are well established in fetal ultrasound (US), but these are not always immediately comparable to fetal MRI measurement – for example biparietal diameter (BPD) is well correlated between MRI and US, whereas lateral ventricle measurements are poorly correlated in late gestation fetuses.(4)(5) Qualitative fetal MRI assessments show correlations with postnatal diagnosis, with up to 93% diagnostic accuracy in brain anomalies.(6) However, in assessment of fetopathology for individuals with PFAs this is not consistent across diagnoses – vermian hypoplasia and cerebellar hemisphere hypoplasia showed poor agreement between MRI and final diagnosis.(7)

 MRI is increasingly used as an antenatal imaging modality, and improves diagnostic accuracy in fetal brain abnormalities in addition to US by 16-22%.(8)(9) Quantitative assessment may be better than qualitative visual description(10) in predicting outcome, and communicating findings with colleagues and families.

 Although magnetic resonance spectroscopy, functional MRI, diffusion-weighted and diffusion tensor imaging and tractography have been used in the research assessment of the fetal brain, (11) this systematic review will focus on morphological assessments, as these are not yet widely used clinically.

This study aims to identify validated 2D biometric measurements of the PF on fetal MRI and explore whether they can be used to differentiate types of PFA.

***Materials and Methods***

*Data sources*

 This systematic review was performed according to an *a-priori* designed protocol. It was reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) (12) and Meta-analysis of Observational Studies in Epidemiology (MOOSE) (13) guidelines, and registered with the International Prospective Register of Systematic Reviews (PROSPERO ID CRD42019142162). No ethical approval or patient consent was required. The search was performed in June 2019 via PubMed, Web of Science, UCL MetaLib, Scopus, Mendeley, ProQuest Dissertations/Theses, Cochrane Library, and through citation searching. The search terms were: (newborn OR neonat\* OR fetus OR fetal) AND (posterior fossa OR dandy walker OR cerebell\* OR brain stem) AND (mri OR magnetic resonance imaging).

*Eligibility criteria*

 Eligible studies included fetuses where T2-weighted MRI PF measurements were performed, in fetuses with and without PFAs. This included measurements used to differentiate normal and abnormal PFs, to determine normal fetal controls, and/or to predict outcome. Measurements included were all measurements of the PF, or other areas of the brain relevant to PFAs.

Studies assessing post-mortem specimens or animals alone were excluded. We did not include other morphological assessments that were not measurements, such as counting lobulation. Also excluded were studies exclusively assessing other forms of MRI assessment, such as diffusion or spectroscopy measurement, or using MRI with additional reconstruction or segmentation processing prior to measurements, or other imaging types such as US. However, papers using multiple imaging modalities but including measurements by fetal MRI were included for these measurements only. This was to focus on measurements with most widespread clinical use – for example segmentation is not available in all centres with MRI.

 Individual case reports, studies or case series with a sample size of ≤3 cases, and reviews were not included; all other study types were included, including theses and conference abstracts. There was no language restriction. Duplicates were removed. When the same data was used for multiple publications/conference abstracts, the version including the most detail was used.

*Study selection*

 Titles and abstracts were assessed to select potentially relevant papers, then the full text of these was assessed for eligibility. One reviewer (KM) assessed articles for selection.

In five articles where full details were not included, authors of selected articles were contacted for additional information.

*Quality assessment*

 Two reviewers (KM and LS) then separately assessed articles for bias and quality, using the QUADAS-2 (Quality Assessment of Diagnostic Accuracy Studies) tool (14). This recorded whether the study described appropriate patient selection criteria, appropriate and independent reference test and index test, appropriate time period between tests, and blinding of the index test and reference tests. These factors were then used to assess the risk of bias and whether concerns were raised regarding applicability to the review. Disagreements were resolved by consensus.

*Data extraction, summary measures and synthesis of results*

 Two reviewers (KM and LS) extracted data for analysis with Microsoft Excel (Office 365). Extraction included assessment of details of each study type, patient information including demographics, numbers and diagnoses, MRI methodology, measurements taken, and follow up duration and method if included.

***Results***

A total of 804 studies were initially screened and 59 publications were included in the final systematic review(15)(16)(17)(18)(19)(20)(21)(22)(23)(24)(25)(7)(26)(5,27)(28)(29)(30)(31)(32)(33)(34)(35)(36)(37)(38)(39)(40)(41)(42)(43)(44)(4)(45)(46)(47)(48)(49)(50)(51)(52)(53)(54)(55)(56)(57)(58)(59)(60)(61)(62)(63)(64)(65)(66)(67)(68)(69) (Fig. 1)(Supplementary Table 1). Separate publications with duplicated data from those included were assessed.(70)(71)(72)(73)(74)(75)(76)(77)(78)(79)(80)(81)

*Studies included*

<FIGURE 1>

 Studies included CNS (central nervous system) and PF abnormalities such as “Dandy-Walker continuum”, Joubert syndrome, megacisterna magna, spina bifida with associated Chiari II malformation, plus small for gestational age (GA) fetuses, twin-twin transfusion syndrome, Down syndrome, congenital heart disease, congenital diaphragmatic hernia, and viral infections (parvovirus and zika). Publications came from 14 countries globally, although USA was the most common country of origin (20/59), and European countries most represented (28/59).

 Quality assessment with QUADAS scoring(14) showed that the majority of studies included had either a high or unclear risk of bias, and high or unclear applicability concerns (Supplementary Table 2). Only six papers had an entirely low risk of bias and low concerns regarding applicability.

*MRI methodology and parameters*

 The studies assessed measurements on fetal MRI between 13 and 42 weeks of gestation, with median 28 weeks (IQR 23-33 weeks). There was variation in the magnetic field strength used for imaging in the different studies; where described, this varied from 0.5-T (Tesla) to 3-T. There was also variation in slice thickness, from 2.5-10mm.

 All three slice planes were used for measurements – sagittal views in 43 studies, axial views in 28 studies, and coronal views in 17 studies. These included the same measurements in different views. For eight studies, it was not clear which slices were used.

*Measurements of the posterior fossa*

 Over the 59 studies, 6859 fetuses had 62 different 2D measurements of the PF and related areas (Supplementary Table 3) (Figure 2). These included linear, area and angular measurements, which represent measures of PF size, cerebellum/vermis, brainstem, and some supratentorial measurements. Following the measurements, various further ratios and calculations were performed.

<FIGURE 2>

 Nine measurements were evaluated in different planes by different studies – TCD (transverse cerebellar diameter), lateral ventricle transverse diameter, BPD (cerebral, cranial), fronto-occipital distance (cerebral, cranial), CM (cisterna magna) depth (craniocaudal), transverse diameter of the PF, and 4th ventricle anteroposterior diameter.

TCD was measured as total, or the right and left hemispheres separately. Cerebellar surface area was total, right and left. Vermis surface area was total, anterior and posterior. Vermis craniocaudal diameter was measured as the total, plus measuring the height above and below the declive line. Cerebral BPD was total, or right and left hemispheres separately. Lateral ventricle measurements were most variable, including right and left ventricle measurements, either including both or the largest measurement only, plus anterior and posterior ventricle measurements.

We assessed the most commonly used measurements by looking at how many studies employed the measurement, and by a total number of fetuses on which the measurement has been performed (Table 1). 11 measurements were used in 10 or more studies and at least 1200 fetuses.

<TABLE 1>

The most frequently used measurement by both assessments was the TCD. Other commonly used linear measures of the PF were of the vermis (craniocaudal diameter, anteroposterior diameter, surface area) and CM depth. The most frequent angle measured was the TVA (tegmento-vermian angle), also known as the brainstem-vermis angle. This was drawn between the dorsal surface of the brainstem and the ventral surface of the vermis, so giving an evaluation of upward rotation of the vermis. The next most common angle was the CSOA (clivus-supraoccipital angle). This was the angle between lines drawn on the postero-superior surface of the clivus and the antero-superior surface of the supraocciput, giving an evaluation of PF shape. Commonly used measurements of the brainstem and surrounding area were of the pons (anteroposterior and craniocaudal diameters), 3rd ventricle and 4th ventricle.

In the context of PF assessment, there were also supratentorial measurements. The cerebral BPD and cranial BPD, and the cerebral FOD (fronto-occipital distance) and cranial FOD, along with lateral ventricular transverse diameter, were the most frequently used.

*Measurements of the posterior fossa – calculations*

Calculations were used to assess measurements in detail in a fifth of studies (13/59). Most commonly, to standardise measures against brain size, such as by creating a ratio with BPD.(18)(43)(25)(56)(54)(57) Calculations were used to assess the symmetry of different brain areas, such as comparing the surface area of the right and left cerebellar hemispheres, or for the vermis, the surface area was compared between the anterior and posterior lobe, or above and below the fastigial-declive line.(4)(7)(47) Calculations were also used to assess other brain features that are harder to measure directly, such as estimates of the CSF space.(24)(56)

*Sex*

Sex effect on fetal measurements was not commonly described. Tilea et al(29) showed a statistically significant difference by sex for the cerebral BPD, TCD and length of the corpus callosum. However, they concluded the small effect size was not clinically significant.

*Gestational age*

 GA was examined by 35 studies (Figure 3), with 34 measurements shown to correlate positively or negatively with GA in healthy fetuses, including linear, area and angle measurements. Positive correlations with GA were largely seen, with three negatively correlated including 4th ventricle angle, cerebellar primary fissure angle, and opercular measurements. The latter was shown to be positively correlated elsewhere however.(39)(18)(51) In total, 15 measurements and six angles (such as TVA) were unaffected by GA. Studies comparing CM depth, lateral ventricle transverse diameter, CSOA, and inferior vermian distance (craniocaudal) with GA have been inconsistent in their findings.(15)(21)(25)(28)(63)(18)(51)(54)(61)(44)(19)(26)(39)(52)

<FIGURE 3>

*Diagnosis*

 23 studies looked at the diagnostic use of measurements (Table 2), however interpretation was hampered by varying use of definitions and terminology, despite a drive towards anatomical descriptions.(18) TCD, vermis measurements, CM depth, brainstem/vermis angles, BPD and 4th ventricular measurements were most commonly performed.

<TABLE 2>

For five studies, this assessment compared a group of quite varied CNS abnormalities generally,(16)(22)(23)(15)(82) including PFAs. Only TVA was found to be correlated with this wide selection of diagnoses in more than one study.

Six studies looked at a diverse group of PFAs(4)(83)(47)(39)(7)(26) and compared these to controls. PFAs reported included abnormalities of the cerebellum, vermis, brainstem and cisterna magna, and cysts. Measures correlating with PFA diagnosis in more than one paper included TCD, vermis craniocaudal diameter, vermis anteroposterior diameter, vermis SA, IVD (inferior vermian distance (anteroposterior)) and CM depth.

Two papers looked at specific CNS diagnoses only, such as “Dandy-Walker malformation” or continuum, or Joubert syndrome. For these, more specific measurements proved different between the cohort and controls – PF surface area and vermis surface area for a Dandy-Walker type-diagnosis,(36) and TCD, vermis craniocaudal measurement, CM depth, and calculations using the IPF (interpeduncular fossa) for Joubert syndrome.(30) These measures make sense as useful quantitative diagnostic tools in relation to the anatomy of these conditions. In particular, Joubert syndrome was only explicitly included in one other study,(23) where TVA was correlated with pathology. For this rare condition, although measures of the IPF were only performed in a small number of fetuses, as a relevant feature for the condition, this could still be most clinically useful.

 Six studies looked at measures of the PF to diagnose neural tube defects, using a variety of different measures.(24)(32)(37)(44)(56)(63) Four of these studies went on to look at measures that differed within the neural tube defect group, including differentiating between open and closed defects, and looking at the changes pre- and post-operatively in fetal repair, and between fetal and postnatal repair cohorts. Within these studies, the CSOA, lateral ventricle transverse diameter, transverse diameter of the PF, and PF surface area were used more than once. Since the introduction of in-utero repair for neural tube defects,(84) clarity of assessment on MRI has become more crucial – the initial study used only qualitative measures of the PF. These results suggest simple measurements could be of benefit in this context.

 Four studies showed measurements of the PF correlated with a diagnosis of more systemic abnormalities compared to controls – congenital heart disease,(85) Down syndrome(66) and fetuses small for GA.(33)(86)

 Two other studies looked at measures for distinguishing within diagnostic groups. One looked at the differences between the donor and recipient twins within twin-twin transfusion syndrome – here TCD, cranial BPD and HC differed between the groups.(57) The other looked at fetuses with congenital diaphragmatic hernias, with vermis anteroposterior diameter measurements significantly different between infants who survived to discharge and those who died.(67)

*Developmental outcomes*

 Eight studies examined neurodevelopmental outcomes. Only four assessed the relationship between measurements and outcome (Table 3),(43)(85)(52)(55) with varied developmental assessments,(87)(88)(89) with the remaining four examining outcome in relation to specific diagnoses,(39)(59) or describing the range of outcomes seen.(34)(41) 8 measurements correlated with outcome, and only 3 of these in the context of PFAs – vermis craniocaudal diameter, IVD, and CM depth. Only the latter was from a study showing a specific link between a PFA, enlarged cisterna magna, with outcome.(55)

<TABLE 3>

***Discussion***

This is the first systematic review to assess 2D biometric measurements currently used for assessing the PF on fetal MRI, and how these have been used for diagnosis and relation to developmental outcomes. Our findings showed 62 different measurements currently used, including linear, area and angular measurements. These represent measures of the PF, cerebellum/vermis, brainstem, as well as supratentorial measurements. Despite the broad range of measurements, we show how few have been compared to later outcomes - only eight studies considered this area.

The use of qualitative assessments alone of the PF in fetal MRI should no longer be common practice – qualitative assessments are not completely accurate(7), and quantitative measurements can be combined with qualitative for a more thorough assessment(26)(20)(62)(37)(50)(90). The development of centile calculators (54) should make the use of quantitative measures easier. We demonstrate here the variety of measurements currently used globally, without each adding to the diagnostic picture – consistency in use is needed to standardise the evaluation of images.

*Implications for clinical practice*

 From the literature available, we propose the following flowchart for validated 2-dimensional measurements of the PF (Fig. 4). For a routine fetal MRI where an assessment of the PF is being made, 16 measurements will provide an ample evaluation, both looking at the PF and its components, as well as an assessment of the brain as a whole as a comparison. These measurements will be sufficient to highlight the most common PFAs. We propose this tool as a diagnostic tool, with suggested measurements, although not all will be possible in all patients, for example due to gestation and optimal views.

<FIGURE 4>

 The definitions used for PFAs are variable, as they are numerous and difficult to classify. However, most can be divided into those with cranial vault malformations and hindbrain malformations, with the latter further divided into those with increased fluid-filled space in the PF, and cerebellar or vermian agenesis, aplasia or hypoplasia.(91)(92)(93)(94)(95)(96) It is not possible to cover all PFAs, but here we cover some of the most common and the useful measurement findings.

 Megacisterna magna, also known as enlarged CM, is the presence of increased fluid spaces, with a normal tentorium and cerebellum/brainstem. By measurements, this would be an increased CM, with otherwise normal measurements. A “Blake’s Pouch cyst” includes additional abnormal measurements, with an increased TVA, IVD, occipital angle and 4th ventricle diameters. With an arachnoid cyst, there may simply be an increased CM depth, but when very enlarged, dimensions of the vermis/cerebellum and brainstem may be reduced by mass effect. There may also be hydrocephalus with changes to the lateral ventricle transverse diameter.

 If the CM depth, TVA, occipital angle and IVD are increased, but there are also abnormalities of the TCD, vermis craniocaudal diameter/anteroposterior diameter/surface area, then other pathology must be considered. This can include a focal abnormality such as dysplasia or as a result of previous insult (ischaemia, haemorrhage) – for these there could be unilateral abnormalities, so variations of the routine measures may be needed, such as measuring the TCD for each cerebellar hemisphere separately.

The “Dandy-Walker” malformation/variant/continuum definition becomes even more unclear, with a range including the “inferior vermian hypoplasia”. The following measurements could be abnormal: TCD, vermis craniocaudal diameter/anteroposterior diameter/surface area, TVA, CM depth, IVD, 4th ventricle laterolateral diameter, lateral ventricles, occipital angle.

 A small number of scenarios will then need specific measurements for further assessment. For these more particular situations, there are often fewer studies, so although measures may be less frequently used overall these measures are more likely to help with a certain diagnosis.

Neural tube defects cause changes in the PF through a Chiari II malformation. In this scenario, additional measurements will allow specific changes to be monitored. These include the cerebellar herniation level and brainstem kinking level, both of which are not of use to measure in most clinical situations.

 A less common scenario is investigation for possible Joubert syndrome and related disorders. The classic MRI description of the “molar tooth sign”(97) can be assessed in a quantitative way through specific measures of these features.

*Implications for research*

 The diversity and variation in 2D biometric measurements used to assess the PF on fetal MRI highlights the need for standardisation of the measurements used in clinical and research settings. Prospective studies are needed, using standardised measurements and comparing to developmental outcomes. This will improve the accuracy of antenatal diagnoses and prognoses given to families.

*Other clinical concerns*

Fetal MRIs in this review were performed across the second and third trimesters. There is some concern regarding MRI scanning in early pregnancy. This is not related to safety concerns,(98) but primarily due to technical difficulty with fetal movement and limited diagnostic value,(99)(100) for example early assessment of the PF on MRI may lead to false positive diagnoses (101). However, legal limits on the timing of pregnancy termination in some countries means clinical information is needed in a timely manner for these difficult decisions to be discussed.

MRI field strength was also variable across the studies. Safety guidance varies regarding maximal field strengths,(100) although advice is for considerations of the risks and benefits for each patient.(99)(102)

*Strengths and limitations of the study*

The strengths of this systematic review were the robust methodology for identifying studies for inclusion, assessment of data quality, and synthesis of data.

Due to the nature of the question, there was a significant degree of potential bias, with all studies being observational in approach. Another common source of bias was a lack of blinding of those performing measurements and other assessments. Many studies were also small sizes – 17 studies included less than 50 patients, and 5 studies included less than 10 patients.

Discrepancy and variation in imaging techniques meant the accuracy of measurements was likely to be different between studies. This variation in methodology, along with the small numbers of studies assessing outcomes, meant no meta-analysis was possible.

Despite approaching authors of publications/conference abstracts that provided only minimal details of relevant studies, not all responded, so additional data may have been missed. There may also be publication bias in the available studies.

***Conclusion***

 In summary, 62 2D biometric measurements have been used to assess the PF on fetal MRI. These included measures of the PF directly, and of other brain structures relevant to the PF. They have been used in a range of GAs and settings, both to identify normal growth and in the diagnosis of multiple pathologies. These included linear measurements, surface area measurements and angles. Many of them assessed similar features in slightly different ways. Although many measures have been used, those found to be valuable most consistently within the literature are starting to emerge. We propose 16 measurements for all individuals, followed by additional measures in the case of Joubert syndrome and neural tube abnormalities.

 This study provides a summary of the various measures of the PF on fetal MRI currently in use. We hope this will enable more consistency in usage, both clinically and for research, to streamline the measurements required for diagnostic and prognostic purposes.

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***Figure/table legends***

**Figure 1**. Flow chart of study selection process.

**Figure 2**. Diagrams of measurements taken – sagittal, axial and coronal slices.

*1. Vermis craniocaudal diameter, 2. Vermis anteroposterior diameter, 3. Pons anteroposterior diameter, 4. Pons craniocaudal diameter, 5. Clivus-supraoccipital angle, 6. Fourth ventricle anteroposterior diameter, 7. Vermis surface area, 8. Occipital angle, 9. Foramen magnum anteroposterior diameter, 10. Cerebellar herniation level, 11. Posterior fossa surface area, 12. Fronto-occipital distance skull, 13. Fronto-occipital distance brain, 14. Tegmento-vermian angle, 15. Inferior vermian distance, 16. Lateral ventricle transverse diameter, 17. Biparietal diameter skull, 18. Biparietal diameter brain, 19. Interpeduncular fossa anteroposterior diameter, 20. Midbrain/isthmus anteroposterior diameter, 21. Fourth ventricle lateral diameter, 22. Cerebellar surface area, 23. Cisterna magna depth, 24. Transcerebellar diameter, 25. Transverse diameter of the posterior fossa*

**Figure 3.** Measurements correlated or unchanged with gestational age.

**Figure 4**. Diagram of which measurements to take in different clinical scenarios – all fetuses should have the first measurements taken, with the additional measurements as required.

**Table 1**. Measurements taken, by most common.

**Table 2**. Measurements distinguishing a diagnosis from control.

*CM (cisterna magna), CNS (central nervous system), CSF (cerebrospinal fluid), CSOA (clivus supra-occipital angle), HC (head circumference), IVD (inferior vermian distance (anteroposterior)), PFA (posterior fossa abnormalities), SA (surface area), TCD (transverse cerebellar diameter), TVA (tegmento-vermian angle)*

**Table 3**. Measurements associated with outcomes.

*CM (cisterna magna), GA (gestational age), IVD (inferior vermian distance (anteroposterior)), MRI (magnetic resonance imaging), SGA (small for gestational age)*

***Appendices***

**Supplementary Table 1.** Publications included in final systematic review.

*BPD (biparietal diameter), CNS (central nervous system), FOD (fronto-occipital diameter), HC (head circumference), IVD (inferior vermian distance (anteroposterior)), MRI (magnetic resonance imaging), PFA (posterior fossa), PFA (posterior fossa abnormality), SGA (small for gestational age), TCD (transverse cerebellar diameter), TVA (tegmento-vermian angle), US (ultrasound)*

**Supplementary Table 2**. Quality assessment of included publications using QUADAS2.

**Supplementary Table 3**. Full table of measurements taken in each study.