Feasibility of neurosonography in CHD-fetuses and controls in a clinical tertiary setting

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ABSTRACT

Objective: Ultrasonographic examination is the first-tier test to detect abnormal development of central nervous system (CNS). In optimal conditions, neurosonography can detect all important hallmarks of CNS development. It is, however, not known how the performance of this modality is in a routine setting. We aimed to evaluate the feasibility of neurosonography in a time-limited routine setting.

Study design: We have performed a prospective study in which we have included a group of pregnant women carrying a fetus with an isolated congenital heart defect (CHD), and a control group of fetuses without structural anomalies. We have performed basic neurosonography examination according to the guideline 'how to perform a basic screening examination of the CNS', published by the international society of ultrasound in obstetrics and gynecology in both groups. In all these examinations, 9 brain structures were scored in 3 different planes, by researchers that were blinded for group allocation. A sufficient neurosonogram was performed when 7 or more out of 9 CNS structures were clearly visible during the off-line scoring of the examination.

Results: A total of 574 neurosonographic examinations were performed in 151 fetuses, 90 in the CHD-group and 61 in the control group. A sufficient neurosonogram could be performed in 79% (234/294) of cases in a clinical setting (CHD cases) and in 90% (253/280) of control pregnancies. Higher maternal BMI (>30), maternal age, fetal cephalic position, fetal gender and placental position did not significantly influence neurosonography scores.

Conclusion: In clinical setting, basic fetal neurosonography can be sufficiently performed in the majority of cases. This was not significantly influenced by maternal or fetal factors. The optimal gestational age for neurosonography is between 22 and 34 weeks.

1. Introduction

Abnormalities of the fetal CNS have a prevalence of 1–2/1000 live births. The value of prenatal detection of these defects is important for expecting parents, as malformations of the CNS can have a major impact on the quality of life of a child. It may guide the decision to undergo an invasive genetic diagnostic procedure or, in severe cases, to terminate the pregnancy within the legal constraints of the law. Dedicated neurosonography, performed by a team of well-trained ultrasonographers with a uniform protocol, has the ability to correctly diagnose 84% of the CNS-anomalies without the use of magnetic resonance imaging (MRI).[1] Additional pathology or a different diagnosis was found with MRI in only 1.3% of the cases. The diagnostic accuracy of CNS abnormalities improves when the examiner works in a center with a high volume of referrals, and together with an experienced multi-disciplinary team.[2,3] CNS abnormalities are thought to be more prevalent in fetuses and neonates with CHD, even in the absence of genetic syndromes.[4] To explore the prevalence of CNS abnormalities in isolated CHD, we have

performed neurosonography routinely to detect CNS anomalies in a group of fetuses with a broad range of CHD and a group of controls.

The aim of this study was to evaluate the feasibility of two-dimensional neurosonography in a time-limited setting. We used a limited time frame, to reflect daily clinical care and assessed quality by using a standard fetal neurosonography score. We hypothesize that an optimal score with complete visibility of all relevant structures, might not be entirely achievable in a time-limited clinical setting.

2. Material and methods

All fetal neurosonography scans were performed prior to a fetal echocardiography scan, as part of a neurological surveillance program, in the Leiden University Medical Center, a tertiary care center for pre-natal diagnosis. A group of prenatally detected CHD cases and a group of healthy control volunteers, carrying a structurally normal fetus, were prospectively included after giving informed consent. The examinations were performed by experienced fetal ultrasonographers (SE/FJ/AT), according to the HAND (Heart And NeuroDevelopment)-study protocol every four weeks from 20 weeks onwards. The in- and exclusion criteria and CHD-types for the HAND-study have been previously described.[5,6] The study protocol was approved by the local ethics committee (P13.07). In the CHD-group, cases with extracardiac structural malformations or genetic syndromes were not included. If a genetic syndrome was diagnosed in the first year of life, the data were excluded from analysis. Both groups had a neonatal cerebral follow-up scan in the first week of life. Maternal characteristics such as BMI, maternal age, parity and diabetes were recorded. Furthermore, gestational age (GA), placental position and fetal position were recorded for each scanning session. We have performed the examinations according to the ISUOG guidelines for the performance of 'basic screening' and 'fetal neuro-sonogram'.[7] To reflect daily clinical practice in a population in which normal findings were expected, time slots of 20 min were scheduled to perform all necessary planes of the ISUOG guideline for basic screening neurosonogram. Fetal echocardiography (in fetuses with (suspected) CHD) and fetal biometry were performed apart from this time slot. All examinations were performed with a RAB 6-D three-dimensional transducer on Voluson E8 and E10 systems (General Electric, Milwaukee, WI, USA). All cranial planes, including axial (trans-ventricular, trans-thalamic, trans-cerebellar planes), coronal (trans-caudate plane) and sagittal (mid- and para sagittal planes) were attempted. The neurosonographic examination starts with the axial planes, in which the lateral ventricle is visualized in the so-called transventricular plane. The third ventricle and of the cavum septum pellucidum are visualized in the transthalamic plane, just a bit lower than the transventricular plane. The fourth ventricle, cerebellum and cisterna magna are visualized in the transcerebellar plane. The transducer is then rotated to visualize the coronal plane, at around the transcaudate plane, the frontal horns are well visualized. From the coronal plane, the transducer is rotated 90 degrees to visualize the midsagittal plane in which the corpus callosum can be best visualized. Lastly: to visualize the parasagittal plane: from the transthalamic plane, the transducer was angled towards the cephalic direction in order to visualize the thalamo-occipital distance. Additional vaginal ultrasound was added, after maternal informed consent, if abdominal visibility was deemed insufficient but was not routinely added.

All fetal neurosonography examinations were stored as images and clips and were analysed offline by two researchers (SE/JvB) that were blinded for group allocation, GA and clinical outcome.

In the stored images and clips the aforementioned nine structures of brain anatomy were identified for visibility: The brain structure was scored as visible if the anatomy was clearly visible, without shadowing and in full width and length. In case of blurred vision or vague borders of the structure, the anatomic structure was scored as not visible. To avoid intra-observer variation, a set of 30 examinations were scored and compared between the two examiners. These 30 training sets were not

a part of the studied data, in this initial training period, differences were agreed upon by consensus. The intra-observer variation was calculated after the training period and the method was found to have excellent intraobserver variation with an ICC of 0.97 (95% CI, 0.95–0.98).

We developed a neurosonography score which was the composite score of the visibility of nine brain structures in three different planes, resulting in a total score of 0 in case no plane was visible to nine if all structures could be clearly visualized. In the axial plane, cavum septum pellucidum (CSP), lateral ventricle (LV), third ventricle (3 V), fourth ventricle (4 V), cerebellum (CB) and cisterna magna (CM) were scored. In the coronal plane the frontal horns (FH), and in the sagittal plane the corpus callosum (CC) and the thalamo-occipital distance (TOD) were scored (see Fig. 1). A sufficient neurosonography score was defined as a cumulative score of $\geq$ 7 points ($>77.8\%$), an insufficient score was defined as a cumulative score of < 7 ($<77.8\%$).

Analysis in categorical variables were performed with Chi-square testing, and continuous variables were analyzed with independent T-testing. All statistical analyses were performed using IBM SPSS statistics version 24.0.0.0 (IBM, Armonk, NY, USA). Statistical significance was set at $p \leq 0.05$. The results are presented as the visible percentage of structures of total number of scored structures.

3. Results

A total of 574 neurosonographic examinations were performed in 151 fetuses, 90 in the CHD-group and 61 in the control group. Baseline characteristics were comparable in each group, except for maternal age, which was slightly higher in the control group (30.2 vs 32.1 years, p = 0.01, Table 1).

The mean neurosonography score was $81.3\% \pm 11.7$ in the CHD group and $85.2\% \pm 9.0$ in the control group. Mean neurosonography score was lower for primigravidae ($78.8\% \pm 13.5$) compared to non-primigravidae ($83.1\% \pm 9.9$, $p = 0.01$) in the CHD-group. This difference was not observed in the control group. Patients with maternal diabetes (n = 2), had significantly reduced neurosonography scores in the CHD-group. Mean neurosonography score for patients with maternal diabetes was $66.7\% \pm 16.7$ and for patients without maternal diabetes $81.9\% \pm 11.7$, $p = 0.002$. There were no patients in the control group with maternal diabetes, as they were included based on their uncomplicated pregnancy. Maternal BMI negatively influenced neurosonography scores in CHD-cases, however, the difference was not statistically significant. Maternal age, fetal cephalic position, fetal gender (based on external appearance) and placental position did not statistically influence neurosonography scores in both CHD-cases and control groups (see Table 2).

In Tables 3 and 4, the evaluated brain structures are shown according to the GA at scanning. In the axial plane, for both CHD-cases and controls, more than 80% of the structures were visible. The CSP, LV and CB were visible in almost all examinations ($>94\%$) in both groups. In the coronal plane, the FH were visible in $> 80\%$ cases in both groups. In the sagittal plane, structures could be visualized in only a minority of cases; the CC was visible in 14 respectively 40% and TOD in $> 46\%$ in both groups.

Examinations in which 85–100% of the evaluated brain structures could be visualized, were performed between 22 - 34 weeks gestation.

4. Discussion

This study investigated the quality of basic ultrasound examination of the fetal brain in a large group of fetuses, by systematically scoring the scan quality for visibility of important brain structures. We have found that fetal brain structures were best visualized between 22 and 34 weeks, defining this as the optimal GA-window for fetal neurosonography. The standard neurosonogram can successfully be performed within a time limit of 20 min, in 79% (234/294) (Table 5) of cases in a clinical setting (CHD cases) and in 90% (253/280) (Table 6) of
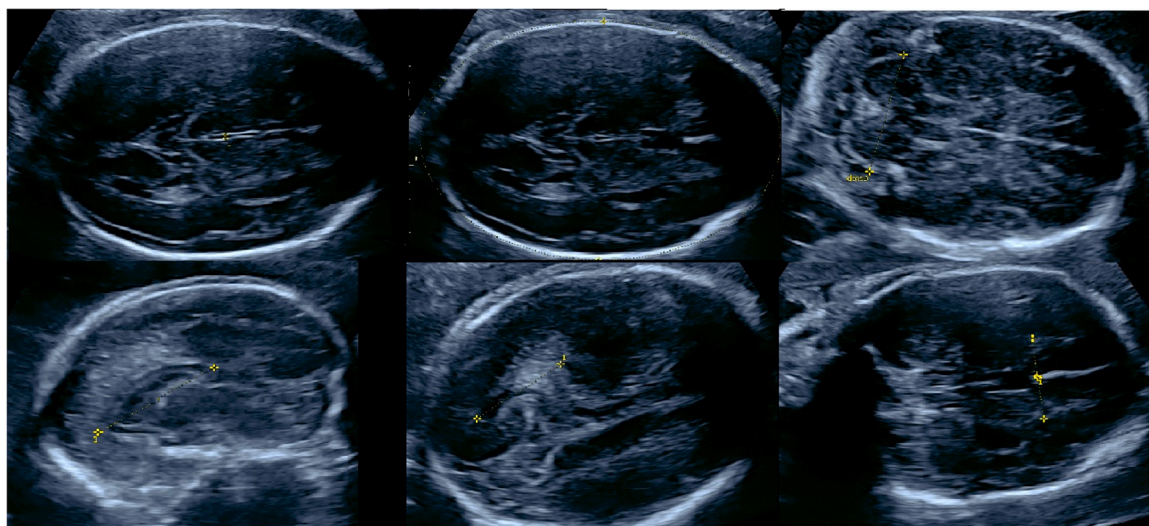
Fig. 1. Images of a neurosonography screening as described in the current study. The top three planes depict the (parallel) axial planes (transventricular, trans-thalamic and trnascerebellar) in which the following structures can be visualized: Lateral Ventricle (LV), Cavum Septum Pellucidum (CSP), Third Ventricle (3 V) and Cisterna Magna (CM). Bottom left plane: Midsagittal plane in which the Corpus Callosum (CC) is visualized. Bottom middle plane: Parasagittal plane in which the Thalamo- occipital plane is visualized. Bottom right plane: Coronal plane in which the Frontal Horns (FH) are visualized.

Table 1
Baseline characteristics (n = 574 ultrasounds).

	CHD- cases n = 294 ultrasounds 90 fetuses	Controls n = 280 ultrasounds 61 fetuses	*p-value*
Maternal age in years (Mean(SD))	30.2 (4.6)	32.1 (4.6)	0.01
Maternal Diabetes (n)	2	0	0.24
BMI	23.6 (3.9)	24 (4.6)	0.60
Primigravidae (%)	36 (40)	20 (33)	0.49
Male gender (n)	52 fetuses	28 fetuses	0.18
Fetal position (n)	Cephalic: 223	Cephalic: 213	0.63
	Breech: 52	Breech: 56	
	Transverse: 18	Transverse: 11	
Placenta position (n)	Anterior: 142	Anterior: 115	0.28
	Posterior: 129	Posterior: 133	
	Lateral: 12	Lateral: 9	
	Fundal: 11	Fundal: 23	

*p-values of < 0.05 are considered statistically significant

Table 2
Influence of confounding variables on neurosonography scores.

	Percentage of visible structures % ± SD (n)		p-value
	Normal-mid BMI (<30)	High BMI (>=30)	
CHD-cases	82.2 ± 14.4 (190)	77.0 ± 15.5 (28)	*P = 0.06*
Controls	85.7 ± 12.2 (177)	81.0 ± 8.9 (17)	*P = 0.1*
	Primigravidae	**Non-primigravidae**	
CHD-cases	78.8 ± 16.7 (115)	83.1 ± 12.2 (179)	*P = <0.01 **
Controls	86.8 ± 8.9 (88)	84.5 ± 12.2 (192)	*P = 0.1*
	Cephalic position	**Non-cephalic position**	
CHD-cases	82.3 ± 14.4 (224)	81.1 ± 1.3 (70)	*P = 0.5*
Controls	84.9 ± 11.1 (213)	86.4 ± 12.2 (67)	*P = 0.4*
	Anterior placenta	**Non-anterior placenta**	
CHD-cases	80.7 ± 14.4 (129)	82.0 ± 14.4 (165)	*P = 0.5*
Controls	84.8 ± 11.1 (133)	85.7 ± 12.2 (147)	*P = 0.5*

N = number of analysed examinations, *p-values of < 0.05 are considered statistically significant

control pregnancies. We did not find that maternal BMI, fetal cephalic position and placental position significantly influenced the visibility of brain structures.

This study used the ISUOG practice guideline: sonographic examination of the fetal central nervous system part 1, which describes the basic planes to perform a fetal neurosonographic examination. As these fetuses were not expected to have structural brain abnormalities, we aimed to perform and complete a basic screening neurosonographic exam. A previous study by Hormazabal et al. analyzed the feasibility of neurosonography in the second and third trimester by scoring the visibility of different brain structures.[8] They found higher scores (around 95%) in the performance to visualize the different brain structures. The examinations were, however, performed in a research setting without time-restriction. Presumably, in a clinical setting with time restriction, as was presented in our study, scores higher than 90% are not achievable due to clinical demands. Another study by Sripilaipong et al. analyzed the feasibility of an ISUOG screening protocol, described the learning curve of experienced and non-experienced sonographers in performing a first-trimester fetal anatomy screening.[9] These authors found that complete scans were feasible in the majority of cases as was found in our study, both experienced and non-experienced sonographers were not able to reach maximum scores for each examination. Based on our own findings, in comparison to the results of Sripilaipong, we conclude that success rates of around 90% reflect the performance of a screening neurosonogram in routine time-limited practice. If a CNS-abnormality is expected through a screening ultrasound, a broader time slot should be planned, to allow the sonographer time to produce all the necessary planes to accurately diagnose the CNS abnormality. For the purpose of diagnosing CNS-abnormalities, transvaginal ultrasound has been broadly understood to be superior to transabdominal ultrasound. We would thus recommend a broad time-slot and transvaginal ultrasound in cases with suspected CNS-abnormalities, as is already standard in our facility.

Although this is not the primary aim of our study, the differences between the control group and the CHD group were noteworthy. Mean neurosonography scores were lower in the CHD-groups as compared to control group. We suspect that the attitude of the sonographer towards maternal anxiety in the situation of an already diagnosed CHD could have played a role, as well as time pressure of the scheduled subsequent scan, since the neurosonography exam was planned prior to the echocardiography.

This study also provides a unique insight in the performance of fetal neurosonographic screening relating to maternal or fetal factors. Of the patient related factors, maternal BMI (although not significant) and the number of previous pregnancies, negatively influenced the

Table 3

Visualized brain structures in neurosonography of the **CHD-group** (n = 294 ultrasounds).

		AXIAL						CORONAL	SAGITTAL	
		CSP	LV	3 V	4 V	CB	CM	FH	CC	TOD
Gestational age	n	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
19 + 0 – 21 + 6	37	36 (97.3)	37 (100)	25 (67.6)	22 (59.2)	37 (100)	37 (100)	33 (89.2)	11 (29.7)	18 (48.6)
22 + 0 – 25 + 6	54	54 (100)	54 (100)	46 (85.2)	47 (87)	54 (100)	53 (98.1)	53 (98.1)	22 (40.7)	43 (79.6)
26 + 0 – 29 + 6	65	64 (98.5)	65 (100)	56 (86.2)	57 (87.7)	65 (100)	63 (96.9)	64 (98.5)	12 (18.5)	46 (70.8)
30 + 0 – 33 + 6	74	72 (98.6)	73 (100)	71 (97.3)	59 (80.8)	72 (98.6)	66 (90.4)	68 (93.2)	13 (17.8)	54 (74)
34 + 0 – 37 + 6	64	60 (93.8)	60 (93.8)	62 (96.9)	46 (71.9)	63 (98.4)	43 (67.2)	52 (81.3)	9 (14.1)	30 (46.9)

CSP = cavum septum pellucidum; LV = lateral ventricle; 3 V = third ventricle; 4 V = fourth ventricle; CB = cerebellum; CM = cisterna magna; FH = frontal horns CC = corpus callosum; TOD = thalamo-occipital depth

Table 4

Visualized brain structures in neurosonography of the **control-group** (n = 280 ultrasounds).

		AXIAL						CORONAL	SAGITTAL	
		CSP	LV	3 V	4 V	CB	CM	FH	CC	TOD
Gestational age	n	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
19 + 0 – 21 + 6	38	38 (100)	38 (100)	27 (71.1)	30 (78.9)	38 (100)	38 (100)	38 (100)	13 (34.2)	28 (73.7)
22 + 0 – 25 + 6	64	64 (100)	64 (100)	60 (93.8)	60 (93.8)	63 (98.4)	61 (95.3)	63 (98.4)	21 (32.8)	53 (82.8)
26 + 0 – 29 + 6	63	61 (96.8)	62 (98.4)	60 (95.2)	59 (93.7)	63 (100)	61 (96.8)	62 (98.4)	13 (20.6)	56 (88.9)
30 + 0 – 33 + 6	58	57 (98.3)	58 (100)	56 (96.6)	57 (98.3)	58 (100)	50 (86.2)	57 (98.3)	10 (17.2)	50 (86.2)
34 + 0 – 37 + 6	57	54 (94.7)	55 (96.5)	54 (94.7)	51 (89.5)	56 (98.2)	28 (49.1)	53 (93)	8 (14)	42 (73.7)

CSP = cavum septum pellucidum; LV = lateral ventricle; 3 V = third ventricle; 4 V = fourth ventricle; CB = cerebellum; CM = cisterna magna; FH = frontal horns; CC = corpus callosum; TOD = thalamo-occipital depth

Table 5

Total neurosonography-score in the **CHD group**: number of scans that performed either 'insufficient' or 'sufficient' per GA group (n = 294 ultrasounds).

Gestational age	n	Insufficient score (0-77.8%) n (%)	Sufficient score (77.8-100%) n (%)
19 + 0 – 21 + 6	37	11 (29.7)	26 (70.3)
22 + 0 – 25 + 6	54	6 (11.1)	48 (88.9)
26 + 0 – 29 + 6	65	9 (13.8)	56 (86.2)
30 + 0 – 33 + 6	74	11 (14.9)	63 (85.1)
34 + 0 – 37 + 6	64	23 (35.9)	41 (64.1)

Table 6

Total neurosonography-score in the control group: number of scans that performed either 'insufficient' or 'sufficient' per GA group. (n = 280 ultrasounds).

Gestational age	n	Insufficient score (0-77.8%) n (%)	Sufficient score (77.8-100%) n (%)
19 + 0 – 21 + 6	38	7 (18.4)	31 (81.6)
22 + 0 – 25 + 6	64	3 (4.7)	61 (95.3)
26 + 0 – 29 + 6	63	3 (4.7)	60 (95.2)
30 + 0 – 33 + 6	58	0 (0)	58 (100)
34 + 0 – 37 + 6	57	14 (24.6)	43 (75.4)

neurosonography score, this finding is in line with the prenatal detection of cardiac defects.[10–12] It is noteworthy that the mentioned factors did not seem to influence the visibility of CNS structures, as we all know from clinical practice that BMI influences image quality. A possible explanation could be that with modern ultrasound equipment that was used in this study, the image quality is stable despite scanning women with higher BMI's.

A limitation of this study, is the sparse use of transvaginal ultrasound. In the minority of cephalic presenting cases, transvaginal ultrasound was added, although it is well known that transvaginal ultrasound has a significant diagnostic value in combination with abdominal US.[13] A reason for this reserved attitude towards invasive examination at that time was the absence of suspicion of a CNS abnormality combined with sufficient visualization of the CNS anatomy by abdominal US.

The offline scoring method we have chosen could pose another limitation in this study. Since ultrasound is a dynamic examination, certain structures that are not pictured in the stored images do not necessarily mean that a structure is abnormal or absent.

In conclusion, neurosonography in a tertiary care center for the purpose of neurosonography surveillance is able to detect more than 80% of CNS structures in the axial and coronal planes in second and third trimester examinations. Structures in the axial and coronal planes are easier to visualize as compared to structures in the sagittal plane. Furthermore, maternal habitus, fetal position and placenta position did not significantly influence the visibility of brain structures.

CRediT authorship contribution statement

Teunissen Aalbertine K.: Data curation, Writing – review & editing. **Haak Monique C.:** Conceptualization, Supervision, Visualization, Writing – original draft. **Everwijn Sheila:** Data curation, Formal analysis, Methodology, Project administration, Writing – original draft, Writing – review & editing. **van Bohemen Jiska F.:** Data curation, Investigation. **Jansen Fenna A.:** Conceptualization, Data curation, Software, Writing – review & editing. **Steggerda Sylke J.:** Writing – review & editing.

Declaration of Competing Interest

none.

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