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# First trimester fetal proportion volumetric measurements using a Virtual Reality approach

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## Abstract

**Objective:** To establish feasibility and reproducibility of fetal proportion volumetric measurements, using three-dimensional (3D) ultrasound and a Virtual Reality (VR) system.

**Methods:** Within a population-based prospective birth cohort, 3D ultrasound datasets of 50 fetuses in the late first trimester were collected by three ultrasonographers in a single research center. V-scope software was used for volumetric measurements of total fetus, extremities, head-trunk, head, trunk, thorax, and abdomen. All measurements were performed independently by two researchers. Intraobserver and interobserver reproducibility were analyzed using Bland and Altman methods.

**Results:** Intraobserver and interobserver analyses of volumetric measurements of total fetus, head-trunk, head, trunk, thorax and abdomen showed intraclass correlation coefficients above 0.979, coefficients of variation below 7.51% and mean difference below 3.44%. The interobserver limits of agreement were within the ±10% range for volumetric measurements of total fetus, head–trunk, head and trunk. The interobserver limits of agreement for extremities, thorax and abdomen were −26.09% to 4.77%, −14.14% to 10.00% and −14.47% to 8.83%, respectively.

**Conclusion:** First trimester fetal proportion volumetric measurements using 3D ultrasound and VR are feasible and reproducible, except volumetric measurements of the fetal extremities. These novel volumetric measurements may be used in future research to enable detailed studies on first trimester fetal development and growth.

**KEYWORDS**
3D ultrasound, agreement, embryonic volume, fetal body parts, first trimester, reproducibility, virtual reality

## 1 | INTRODUCTION

The first trimester of pregnancy is a crucial period for growth and the initial arrangement of organs.[1] Observational studies suggest that impaired first trimester growth, measured by traditional and relatively simple two-dimensional ultrasound parameters, might be associated with increased risks of adverse birth outcomes, and adverse cardiovascular and respiratory risk profile in childhood.[2–10] Ongoing developments in obstetric two- and three-dimensional (3D) transvaginal ultrasound techniques provide opportunities for improved evaluation of early fetal growth and development.[11] Detailed studies on first trimester fetal development are needed to enable better understanding of developmental adaptation mechanisms in early pregnancy, leading to adverse outcomes in later life.

The combination of 3D transvaginal ultrasound with offline analyses using a Virtual Reality (VR) system enables more advanced measurement of first trimester volumetric markers compared to the traditional crown rump length and biometric measures.[12] Previously, embryonic volume measurements using this technique have shown to be feasible, and seem related to fetal growth and birth outcomes.[2,3,11,13] Additionally, segmentation of the various parts of the fetal body (extremities, trunk, head, thorax and abdomen) could increase the knowledge on early fetal growth and organ development in early pregnancy.[14] These novel volumetric measurements could have great potential in observational research settings in the field of Developmental Origins of Health and Disease focused on fetal developmental adaptations.

Therefore, we developed novel volumetric measurements of first trimester fetal body parts, from this stage forward *fetal proportions*, using 3D ultrasound datasets combined with a VR system. We assessed the intraobserver and interobserver reproducibility and agreement for volumetric measurements of the total fetus, extremities, head–trunk, head, trunk, thorax and abdomen of 50 fetuses in the late first trimester.

## 2 | METHODS

### 2.1 | Study population

This study was embedded in the Generation R *Next* study, a population-based prospective cohort study from preconception onwards in Rotterdam, the Netherlands. Recruitment started in August 2017 and is still ongoing. Pregnant women were invited to the research center for three appointments in the first trimester of pregnancy, from 7 to 13 weeks of gestational age, with an interval of approximately 2 weeks. During these 30-min visits 3D ultrasound datasets were obtained to assess embryonic, early fetal and placental development. Around 30 weeks of gestational age, participants were invited back to the research centre for a follow-up visit. All participating women gave written informed consent. The medical ethics committee of the Erasmus University Medical Center approved of this study (MEC-2016-589, December 2016).

For the current analysis, we focused on 3D ultrasound datasets collected in the late first trimester (during the last appointment in the first trimester of pregnancy). We selected 50 participants who visited the research center at the Erasmus MC from March 2019 to May 2019, in whom all the 3D ultrasound data according to the ultrasound study protocol was acquired.

### 2.2 | Gestational age assessment

Gestational age was calculated from the first day of the last menstrual period (LMP) in spontaneous pregnancies, or from oocyte pick-up plus 14 days in in vitro fertilization pregnancies. Gestational age was based on crown rump length in five subjects, because the LMP was unknown or gestational age determined by crown rump length differed more than 7 days from the LMP.[12]

### 2.3 | First trimester fetal ultrasound examination

All ultrasound scans were performed by three experienced ultrasonographers using a Voluson E10 System (GE Healthcare) with a 5–13 MHz transvaginal transducer (RIC6-12D). Ultrasound settings were predefined to create uniformity (gain = 0, line filter = low, persistence filter = 2, enhance = 2, dynamic contrast = 6, enhance = 2). The 3D ultrasound dataset acquisition of the total fetus was performed under a 90–110° volume angle. To assure at least one good quality 3D ultrasound dataset would be available for offline analysis, multiple 3D ultrasound dataset acquisitions were performed. The fetus was preferably facing towards the transducer in the mid-sagittal plane to provide detailed imaging of the fetal

anatomy. The ultra-sonographer ensured that the fetus was not moving during the 3D ultrasound dataset acquisition. The 3D ultrasound datasets were stored in Cartesian volume files for offline analysis.

## 2.4 | Fetal proportion volumetric measurements

We used the BARCO I-Space, a CAVE™-like VR system for offline analysis of the 3D ultrasound datasets.[15] V-Scope software enables accurate semi-automatic volumetric measurements due to improved depth perception using VR displays.[16,17] Multiple 3D ultrasound dataset acquisitions of a single fetus were stored. The dataset that was used for further offline analyses was selected by the first observer (C.W.) based on completeness and quality of the 3D dataset. In preparation of the measurements, the surrounding uterine wall and the umbilical cord were manually erased using a brusher that can be adjusted in size to enable accurate deletion of voxels. Initially, we measured the volume of the total fetus as described previously.[18] To perform the volumetric measurement of the total fetus, fully automatic segmentation of hyperechoic structures was performed using strict preset thresholds. This was followed by manual segmentation of hypoechoic parts (e.g., brain ventricles, stomach, bladder and to a minimal extent artefacts due to acoustic shadowing) to obtain a whole-body segmentation of the fetus.[17,18]

Subsequently, we performed the novel volumetric measurements of extremities, head–trunk, head, trunk, thorax and abdomen. First, we manually deselected the segmented voxels of the extremities, from hands to axillae and feet to groin using a spherical brusher with the same diameter as the extremity, to perform the volumetric measurements of the extremities and head-trunk. Second, the volumetric measurement of the head and trunk were obtained by manually deselecting the segmented voxels of the head using a brusher with the size of the occipital-frontal diameter. The base of the chin and the fourth ventricle in the midsagittal plane are used as reference points, as described previously.[19] Third, we performed the volumetric measurements of the thorax and abdomen by manually deselecting the segmented part below the diaphragm using a spherical brusher with the same diameter as the trunk. During the fetal proportion volumetric measurements, we used a transparent segmentation color to enable identification of the fourth ventricle and the diaphragm. To obtain reproducible measurements, the measurements were performed using a detailed technical measurement protocol with instructions about the size of the brusher, the alignment of the fetus and the plane in which the measurement should be performed (for a detailed description see Data S1). Figure 1 shows a step-by-step approach for the fetal proportion volumetric measurements. All fetal proportion volumetric measurements were performed independently by two researchers (C. W. and J.E.) to obtain intraobserver and interobserver reproducibility. Both researchers were experienced ultrasonographers and had previous experience with performing volume measurements in the BARCO I-Space using V-scope software. Both researchers performed the offline measurements twice, with an interval of at least one week to prevent recall bias. The measurements were performed in a blinded setting.

## 2.5 | Statistical analysis

We performed statistical analysis described by Bland and Altman.[20,21] For the intraobserver analysis, the first measurement was compared with the second measurement for each observer. For the interobserver analysis, the mean of the two measurements of the first observer was compared with the mean of the two measurements of second observer using similar calculations.

First, we plotted the measurements with the line of equality to give an initial sense of the degree of agreement.[21] Second, intraclass correlation coefficients (ICC) with a 95% confidence interval and the coefficients of variation (CV) were calculated for each measurement to evaluate consensus within each observer and between observers.[21] Third, intraobserver and interobserver variability was quantified calculating the mean difference in percentage measurement error with the 95% limits of agreement (mean difference [%] ± 1.96 SD) for all the fetal proportion volumetric measurements. Within the limits of agreement the measurements within and between observers can be assumed to be interchangeable.[12] Lastly, we plotted the mean differences in percentage measurement error with the 95% limits of agreement. These so called Bland and Altman plots were specifically provided to visualize that the agreement for the volumetric measurements does not depend on fetal size.

We consider the ICC, CV, mean difference and the limits of agreement as our main outcomes of interest. We decided that an ICC >90%, a CV <10%, a mean difference <10% and limits of agreement within ±10% were considered to be proof of good agreement.[22] Importantly, an acceptable mean difference and limits of agreement are not a statistical but a clinical and more subjective consideration.[12] To establish that the measurements are useable for future association studies, we decided that the limits of agreement should deviate a maximum of 10% from the mean difference, which indicates that 95% of all differences should be within the ±10% measurement error range.[20] Statistical analyses were performed using IBM SPSS, version 25.

## 3 | RESULTS

Participants and pregnancy characteristics are shown in Table 1. The median gestational age was 12 weeks and 3 days. Figure 2 shows the different fetal proportion volumetric measurements plotted against the fetal crown rump length.

## 3.1 | Intraobserver reproducibility analyses

Table 2 presents the mean volumes, ICCs, CVs, mean differences and corresponding limits of agreement for intraobserver agreement for volumetric measurements of the total fetus, extremities, head–trunk,
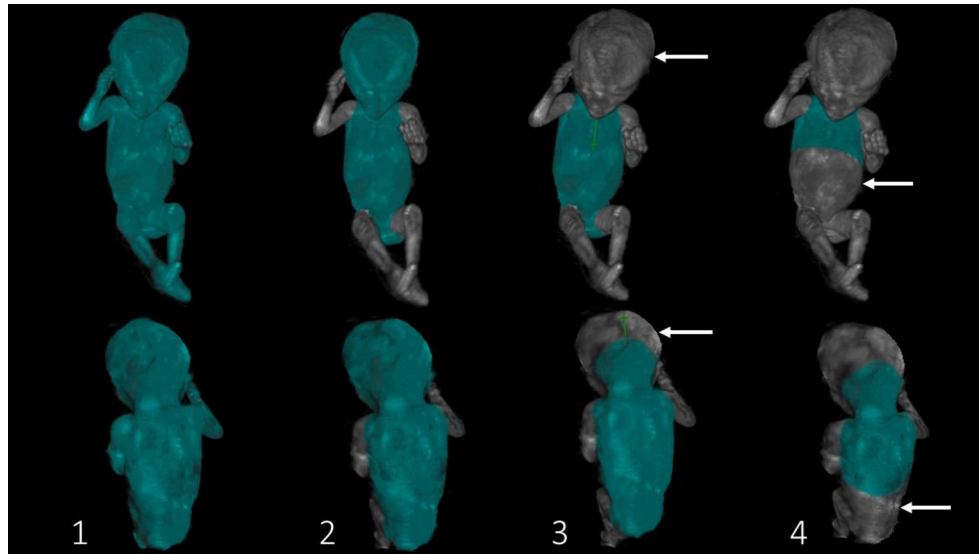
**FIGURE 1** Anterior and posterior view of a fetus at 12 weeks and 5 days of gestation in the BARCO I-Space. A step-by-step approach for volumetric measurement of the total fetus and fetal proportions is shown. Volumetric measurements from left to right: (1) Segmentation of the total fetus in cyan; (2) Segmentation of head-trunk in cyan with indirect measurement of the extremities in grey; (3) Segmentation of the trunk cyan with indirect measurement of the head in grey indicated by the arrow (reference line through chin and fourth ventricle in the midsagittal plane); (4) Segmentation of the thorax in cyan with indirect measurement of the abdomen in grey indicated by the arrow [Colour figure can be viewed at wileyonlinelibrary.com]

**TABLE 1** Participant characteristics (n = 50)

| | Median (95% range) / n (%) |
|---|---|
| Maternal age (years) | 31.5 (25.7, 38.3) |
| Maternal BMI, median (range (kg/m$^2$)) | 22.5 (18.5, 34.6) |
| Gestational age (weeks, days) | 12.3 (10.9, 13.2) |
| Crown rump length (mm) | 60.90 (44.60, 74.57) |
| Reproduction method | |
|    Spontaneously conceived (%) | 45 (90) |
|    IVF (%) | 1 (2) |
|    Ovulation induction (%) | 4 (8) |

Abbreviations: BMI, body mass index; IVF, in vitro fertilization.

head, trunk, thorax and abdomen. All measurements of both observers lie in close proximity to the line of equality suggesting small intraobserver differences, except for the volumetric measurements of the extremities (Figures S1 and S2). Intraobserver ICCs were higher than 0.980, and CVs were below 9.43% for each measurement. The observed mean differences ranged from −0.76% to 0.04 for intraobserver differences of Observer 1 and from 1.44% to 1.07% for Observer 2. Figures S3 and S4 depicts the Bland and Altman plots for intraobserver agreement for each measurement of both observers, in which the mean difference is plotted against the mean of the assessments accompanied with the limits of agreement. We observed that the limits of agreement for volumetric measurements of the total fetus, head–trunk and trunk were within ±10% for both observers, but slightly exceeded the ±10% limits of agreement for

volumetric measurements of thorax and abdomen. Limits of agreement for volumetric measurement of the extremities ranged between −17.42% and 18.94%.

## 3.2 | Interobserver reproducibility analyses

Table 3 presents the mean volumes, success percentage, ICCs, CVs, mean differences and corresponding limits of agreement for volumetric measurements of the total fetus, extremities, head–trunk, head, trunk, thorax and abdomen. Not all measurements could be performed by both observers due to the lack of visibility of anatomic landmarks, and thus measurements were incomplete in 10 fetuses. The plots with the line of equality suggest small interobserver differences, but larger interobserver differences for the volumetric measurement of the extremities (Figure S5). Interobserver ICCs for all measurements were higher than 0.951. CVs ranged from 3.35% to 6.44%, except for the volumetric measurements of the extremities (CV = 10.86%). The observed mean differences were <10% and ranged from −3.44 to 2.84, except for the volumetric measurements of the extremities (mean difference = −10.66%). Figure S6 depicts the Bland and Altman plots for interobserver agreement. We observed good agreement for volumetric measurement of the total fetus, head-trunk volume, head and trunk with limits of agreement within ±10%. Interobserver limits of agreement for the volumetric measurements thorax and abdomen exceeded the ±10% limits of agreement slightly (lower limit of agreement, upper limit of agreement: −14.14%, 10.00%; −14.47%, 8.83%, respectively). Limits of agreement for the volumetric measurement of the extremities were −26.09% and 4.77%.
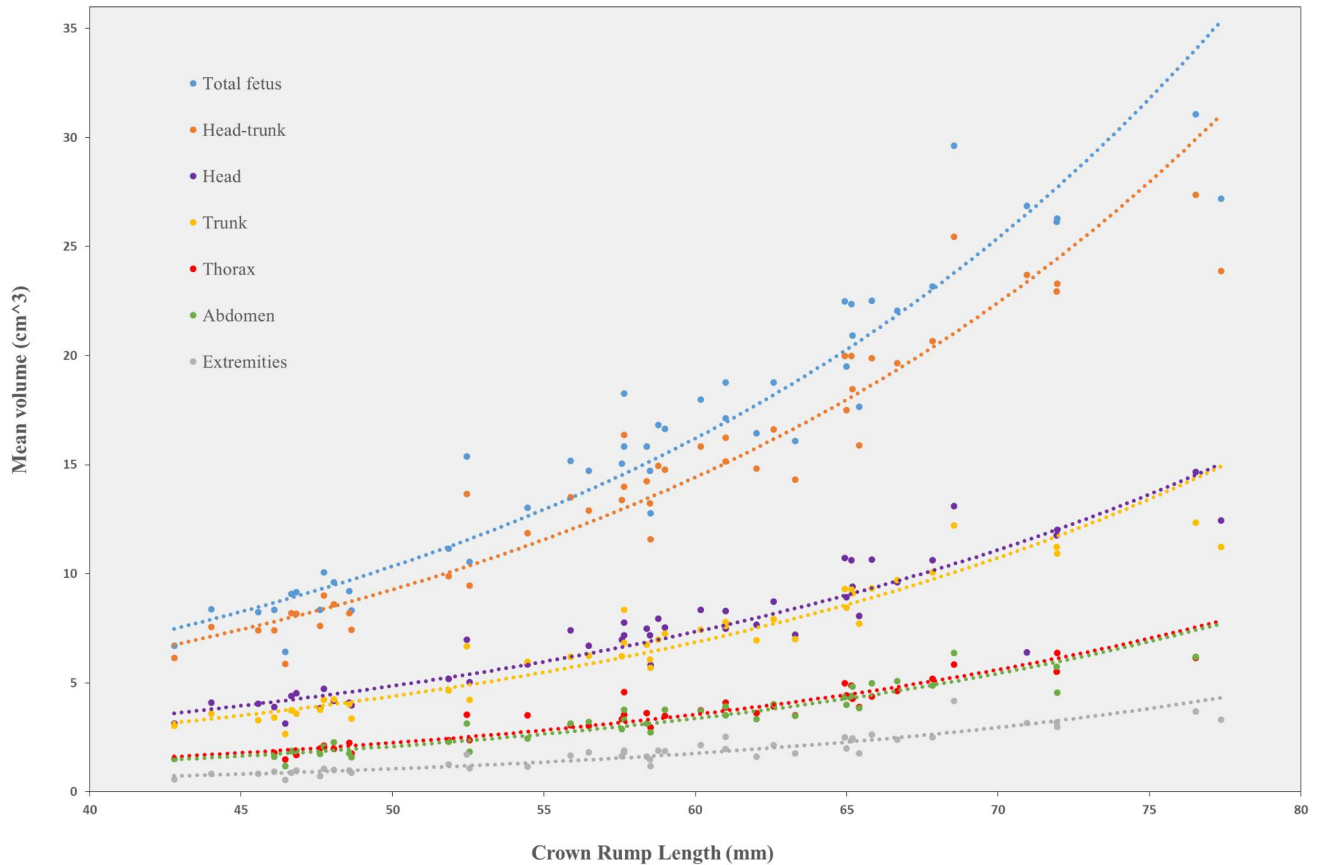
**FIGURE 2** Fetal crown rump length and fetal total and body proportion volume measurements. In the graph the colored dots indicate the measurements, the mean value is indicated by the accompanying colored dotted line [Colour figure can be viewed at wileyonlinelibrary.com]

**TABLE 2** Intraobserver agreement of fetal proportion volumetric measurements for both observers ($n = 50$)

| Volumetric measurement | Observer | ICC (95% CI) | CV % | Mean difference cm³ | Mean difference (LLOA, ULOA) % |
|---|---|---|---|---|---|
| Total fetus | 1 | 0.998 (0.996, 0.999) | 2.70 | 0.01 | 0.04 (−4.60, 4.67) |
| | 2 | 0.999 (0.999, 1.000) | 1.34 | −0.01 | −0.16 (−2.99, 2.67) |
| Extremities | 1 | 0.980 (0.982, 0.994) | 9.43 | 0.03 | 0.76 (−17.42, 18.94) |
| | 2 | 0.983 (0.97, 0.991) | 8.88 | −0.01 | −0.89 (−16.77, 14.98) |
| Head–Trunk | 1 | 0.998 (0.996, 0.999) | 2.67 | −0.02 | −0.00 (−4.61, 4.52) |
| | 2 | 0.999 (0.998, 0.999) | 1.71 | −0.00 | −0.11 (−3.04, 2.82) |
| Head | 1 | 0.996 (0.994, 0.998) | 3.29 | −0.03 | −0.00 (−6.70, 5.89) |
| | 2 | 0.996 (0.994, 0.998) | 3.38 | −0.01 | −0.13 (−6.09, 5.83) |
| Trunk | 1 | 0.996 (0.993, 0.998) | 3.34 | −0.02 | −0.00 (−6.42, 6.25) |
| | 2 | 0.997 (0.995, 0.998) | 3.08 | −0.01 | −0.17 (−6.23, 5.89) |
| Thorax | 1 | 0.989 (0.980, 0.994) | 5.48 | −0.03 | −0.01 (−11.19, 8.85) |
| | 2 | 0.991 (0.983, 0.995) | 5.08 | −0.06 | 1.07 (−8.90, 11.03) |
| Abdomen | 1 | 0.992 (0.992, 0.985) | 5.04 | −0.01 | 0.01 (−10.44, 11.47) |
| | 2 | 0.985 (0.973, 0.992) | 7.06 | −0.06 | −1.44 (−12.44, 9.56) |

**TABLE 3** Interobserver agreement of fetal proportion volumetric measurements (*n* = 50)

| Volumetric measurement | Mean volume (SD) cm³ | n (%)[a] | ICC (95% CI) | CV % | Mean difference cm³ | Mean difference (LLOA, ULOA) % |
|---|---|---|---|---|---|---|
| Total fetus | 16.32 (6.51) | 46 (92) | 0.991 (0.944, 0.997) | 3.95 | −0.58 | −3.44 (−8.79, 1.91) |
| Extremities | 1.82 (0.86) | 46 (92) | 0.951 (0.697, 0.983) | 10.86 | −0.19 | −10.66 (−26.09, 4.77) |
| Head–Trunk | 14.50 (5.67) | 46 (92) | 0.993 (0.973, 0.997) | 3.75 | −0.39 | −2.57 (−7.90, 2.77) |
| Head | 7.41 (2.89) | 45 (90) | 0.991 (0.977, 0.996) | 4.51 | −0.19 | −2.51 (−10.00, 4.98) |
| Trunk | 6.89 (2.69) | 45 (90) | 0.995 (0.984, 0.998) | 3.35 | −0.15 | −2.14 (−8.76, 4.46) |
| Thorax | 3.57 (1.34) | 40 (80) | 0.979 (0.960, 0.989) | 7.51 | −0.08 | −2.07 (−14.14, 10.00) |
| Abdomen | 3.40 (1.33) | 40 (80) | 0.985 (0.971, 0.992) | 6.44 | −0.07 | 2.82 (−14.47, 8.83) |

Abbreviations: CI, confidence interval; CV, coefficient of variation; ICC, intraclass correlation coefficient; LLOA, lower limit of agreement; ULOA, upper limit of agreement.

[a]Number and percentage of datasets in which both observers could perform the measurement.

## 3.3 | Feasibility

A total of 112 3D ultrasound datasets of the whole-body fetus were available for offline analysis, on average 2.4 3D ultrasound datasets per participant. Table 3 shows the number and percentage of late first trimester fetuses, in which both observers could perform the fetal proportion volumetric measurements. Volumes of the total fetus, extremities and head-trunk could be obtained in 46 of 50 (92%) late first trimester fetuses. Success percentages were 90% for volumetric measurements of head and trunk, and 80% for volumetric measurements of thorax and abdomen.

## 4 | DISCUSSION

### 4.1 | Main findings

Using 3D ultrasound datasets acquired in the late first trimester of pregnancy, combined with a VR system, we observed good intraobserver and interobserver reproducibility for volumetric measurements of the total fetus, head–trunk, head, trunk, thorax and abdomen. We observed that volumetric measurements of extremities were feasible but with lower intraobserver and interobserver reproducibility.

### 4.2 | Interpretation of main findings

Currently, first trimester growth is assessed by crown rump length and biometric measurements, which are relatively simple two-dimensional ultrasound parameters. Advanced ultrasound techniques such as 3D ultrasound in combination with VR volumetric measurements can lead to more accurate first trimester growth parameters when compared to the routine two-dimensional ultrasound measures.[11] The use of VR, enables depth perception in 3D ultrasound datasets and therefore offers the possibility to reliably conduct complex volumetric measurements. Due to detailed measurement protocols with predefined ultrasound and VR settings, this technique is highly reproducible.[23] Assessment of 3D ultrasound datasets with a VR system has previously shown feasible and reproducible for several first trimester measurements, including the measurement of embryonic volume.[18,19,24] As the increase in volume during the first trimester is much larger than the increase in length, it is suggested that these volumetric measurements may have higher sensitivity to assess deviations in first trimester growth compared to customary biometric measurements.[18]

As the relative growth rate of the fetus is highest during the first trimester of pregnancy, the fetus is most vulnerable during this period for stressors that can lead to early developmental adaptations. These developmental adaptations might translate into dissimilar growth rates of the different organ systems and fetal body parts.[1] We developed novel volumetric measurements of the various parts of the fetal body as an addition to already existing techniques for volumetric measurement of the total fetus and head using V-scope software.[18,19] We believe that these novel measurements could increase the knowledge on fetal growth and development in early pregnancy, when applied in research settings focused on fetal developmental adaptations.

Before a novel measurement technique is introduced, it is important to assess the reliability of the measurements. To this purpose, we used a combination of statistical methods to allow a good impression of the reproducibility and agreement of fetal proportion volumetric measurements.[20] We found good intraobserver and interobserver agreement as indicated by a high ICC accompanied by a low CV.[12] As expected, we found slightly lower interobserver ICCs and higher interobserver CVs when compared to the intraobserver values. This indicates that different observers measure slightly different. Except for the volumetric measurements of the extremities, we found no bias between the observers as the mean differences were <10%, and the Bland and Altman plots do not show a larger measurement error with increasing volumes. The consideration to require limits of agreement within the ±10% measurement

error was made to ensure that these novel measurements would be useful for future association studies within an observational setting, but these limits remain arbitrary. Therefore, we consider the reproducibility of the volumetric measurements of thorax and abdomen as good.

The volumetric measurements of the extremities had slightly lower ICC and CV values when compared to the other measurements. As the measurements of the extremities separate from the fetal body also had a mean difference >10% and limits of agreement exceeding ±10%, we consider the current reproducibility of these volumetric measurement as suboptimal. The lower reproducibility can be explained by poorer visualization of the extremities when compared to other parts of the fetus. This is caused by the presence of acoustic shadowing caused by calcification of the bones in the upper and lower extremities that is visible during this stage of fetal development. Although these artefacts are minor, they can compromise the 3D interface between the fluid and fetal surface in such a way that the V-scope software cannot automatically recognize the interface at the level of the artefact. If the extent of the artefacts is only minor, the researcher can decide to manually extrapolate these parts of the segmentation of the extremities. We think this approach gives a slightly larger interobserver differences when compared to the automatic segmentations. Importantly, the small absolute volumes of the extremities only allow for very small absolute measurement errors. We hope to improve these measurements in the future.

Within our study, the success percentages ranged from 92% for volumetric measurement of the total fetus to 80% for volumetric measurements of the thorax and abdomen. Some of the measurements could not be performed due to the inability to identify the anatomical landmarks that are necessary for the proposed measurements. The quality of the 3D ultrasound data is of extreme importance for feasibility of the fetal proportion volumetric measurements. To enable collection of high quality 3D ultrasound data, the data collection was done by three experienced ultrasonographers using a high-frequency transvaginal transducer, and 3D acquisition was done in the midsagittal fetal plane while the fetus was not moving. Unfortunately, factors such as maternal adiposity or fetal movements can still negatively influence ultrasound quality, leading to a lower success percentage of the fetal proportion volumetric measurements. Despite these limitations, we consider the success percentages in our study to be sufficiently high. Thus, we conclude that the fetal proportion volumetric measurements are feasible for application in research projects.

The observed reproducibility and agreement was similar to previous VR studies for volumetric measurement of the embryo and head.[18,19] Previously, one other study attempted to reconstruct volumes of extremities in early fetuses, using specialized software that allows to estimate volumes by drawing contours.[25] Within this study it was found feasible to measure the extremities separately from the fetal body, but as in our study the measurement agreement seemed poor. To our knowledge, no previous studies have been conducted to assess volumetric measurements of the abdomen and thorax. In large scale population-based research settings like the Generation R Next Study, these measurements could be used for research within the field of Developmental Origin of Health and Disease research. The Generation R Next Study, is a population-based prospective cohort study from preconception onwards. The study has a specific focus on the consequences of maternal and paternal preconception lifestyle, diet and health, and embryonic development in relation to childhood growth, development and health. In the future, we will measure the fetal proportion volumetric measurements in a larger study sample and assess whether early fetal growth is influenced by preconception and early prenatal lifestyle, diet and health related factors. We will also investigate whether early fetal growth is related to adverse birth outcomes, and unfavorable outcomes in children. Volumetric measurements are expected to have higher sensitivity to assess deviations in early fetal growth compared to the traditional crown lump length that is used in earlier research investigating first trimester growth restriction and adverse outcome. Thus, these novel measurements might give further insights in the influence of periconceptional exposures on early fetal growth, and the consequences for later health. The measurements of the thorax and abdomen can be used as surrogate markers for organ development of the cardiopulmonary system and the gastrointestinal system. Also, volumetric measurements of organs in first trimester fetuses could provide further and more specific knowledge on developmental adaptations and should be the focus of future studies.

## 4.3 | Strengths and limitations

The technique we propose can be used on a large scale in research settings.[16] It is an easily comprehensible technique that is conducted following a detailed protocol. To ensure that the measurements are conducted according to protocol and in a reproducible manner, both researchers practiced the measurement method in a rehearsal setting. This training program is approximately 20 h in duration and could be used to train other researchers within Generation R *Next* in the future. There are some limitations to this measurement approach. We compared the mean of the two measurements to achieve good interobserver reproducibility. This implies that in research settings with multiple observers, measurements have to be conducted twice by the same observer. Approximately 20–30 min are needed to conduct the fetal proportion volumetric measurements in a single 3D ultrasound dataset, which could be considered as time-consuming. In the current study, we only used 3D ultrasound datasets collected in the Generation R *Next* study during the visit in the late first trimester. Because the proposed aim of these novel measurements is to give insights in early fetal growth and development within research settings, we do not think the narrow range of gestational age within our study influenced the generalizability of our findings.

## 5 | CONCLUSION

In conclusion, we found that fetal proportion volumetric measurements in the late first trimester using 3D ultrasound in combination with a VR system are feasible and reproducible, except for volumetric measurements of the fetal extremities. These novel volumetric measurements may be used in future research to enable detailed studies on first trimester fetal development and growth. These studies may lead to better understanding of early developmental adaptation mechanisms leading to adverse birth outcomes, and unfavorable cardiovascular and respiratory risk profiles in later life.

### CONFLICT OF INTEREST

No relevant financial, personal, political, intellectual or religious conflicts of interest are declared.

### AUTHOR CONTRIBUTIONS

Clarissa J. Wiertsema, Jan S. Erkamp, Anton H. J. Koning, Annemarie G. M. G. J. Mulders, Romy Gaillard, and Vincent W. V. Jaddoe were responsible for design and planning of the study. Clarissa J. Wiertsema, Jan S. Erkamp, and Anton H. J. Koning were responsible for the development of the fetal proportion volumetric measurements. Clarissa J. Wiertsema and Jan S. Erkamp were responsible for the data collection. Clarissa J. Wiertsema, Jan S. Erkamp, Romy Gaillard, and Vincent W. V. Jaddoe had full access to all of the data and take responsibility for the integrity of the data and the accuracy of the data analysis. Clarissa J. Wiertsema wrote the main manuscript text. Jan S. Erkamp, Annemarie G. M. G. J. Mulders, Eric A. P. Steegers, Liesbeth Duijts, Anton H. J. Koning, Romy Gaillard, and Vincent W. V. Jaddoe were responsible for critical review of the manuscript. All authors approved the final manuscript and agree to be accountable for all aspects of the work.

### DATA AVAILABILITY STATEMENT

The data that support the finding of this study are available from the corresponding author (VWVJ) upon reasonable request.

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## SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.