Evaluation of first trimester physiological midgut herniation using 3D ultrasound

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Fetal Diagn Ther. 2018 Aug 15:1-7 [Epub ahead of print]

Abstract

Introduction: The aim of the study was to investigate the development of the midgut herniation in vivo using 3D ultrasonographic volume- and distance measurements and to create reference data for the physiological midgut herniation in ongoing pregnancies in a tertiary hospital population.

Material and Methods: Transvaginal 3D ultrasound volumes of 112 women, seen weekly during first trimester of pregnancy, were obtained and subsequently analysed in a virtual reality environment. The width of the umbilical cord insertion, the maximum diameter of the umbilical cord and the volume of the midgut herniation were measured from 6 until 13 weeks gestational age (GA).

Results: All parameters had a positive relation with the GA, crown-rump length and abdominal circumference. In approximately 1 in 10 volumes no midgut herniation could be observed at 9 and 10 weeks GA. In 5.0% of the foetuses at 12 weeks GA the presence of a midgut herniation could still be visualised.

Discussion: Reference charts for several different dimensions of the physiological midgut herniation were created. In future, our data might be used as a reference in the first trimester for comparison in case of a suspected pathological omphalocoele.

Introduction

A congenital omphalocoele, defined as the presence of visceral contents in the umbilical cord, can be detected from 12 weeks GA onwards.[1-3] Before 12 weeks there is a temporary physiological midgut herniation. There is an increasing interest in detecting structural abnormalities in the first trimester of pregnancy.[4, 5] Although a large congenital omphalocoele can be detected before 12 weeks GA,[6] false positive diagnosis may be as high as 32% during the first trimester[7] and small omphalocoeles may disappear later in pregnancy.[8] Kagan et al. even described a spontaneous resolution at 20 weeks in 92.5% of first trimester diagnosed omphalocoeles in euploid foetuses.[9] Three-dimensional (3D) imaging may be helpful in confirming the diagnosis and counselling patients.[10]

Between 7 and 12 weeks gestational age (GA) the midgut herniates into the umbilical cord. This midgut herniation (sometimes called physiological omphalocoele) is caused by a relatively rapid growth of the midgut, accompanied by a 270^0 anticlockwise midgut rotation in the abdominal cavity. Return into the body is caused by a rapid growth of the body or a decrease in the length of the mesentery. Failure may result in a (pathological) congenital omphalocoele. Since this does not explain the possible herniation of other organs like the liver, Achiron et al. differentiated between an omphalocoele caused by a failure to form the primitive umbilical ring and a failed return of the midgut from the umbilical cord.[11] This would also explain the spontaneous resolution of small omphalocoeles. Herniation was already observed in an in vitro study at Carnegie stage 16 (about 7 weeks and 2 days GA) and at 11 weeks GA the herniated intestine was still present in half of the cases.[2]

Technical developments in three-dimensional (3D) ultrasound techniques, including 3D virtual reality (3D VR) have resulted in progress in visualisation of the foetus and foetal volume measurements as well.[12] The aim of this study was to investigate the presence and size of the midgut herniation in a normally developing foetus using 3D ultrasonographic volume- and distance measurements and to develop reference charts for the dimensions of the midgut herniation during organogenesis.

Material and Methods

Study population and samples

This study has been conducted in a periconception cohort study at a university hospital for which women were enrolled for first trimester longitudinal 3D ultrasound measurements to evaluate foetal growth and development using new imaging techniques. Pregnant women who participated were enrolled between 6 and 8 weeks GA via the outpatient clinic of the department of Obstetrics and Gynaecology and local midwifery practices. All women received once weekly 3D ultrasound scans between 6^{+0} and 12^{+6} weeks GA. Only women less than eight weeks pregnant with a singleton pregnancy entered the study for further analysis.

We selected from the cohort 141 women who were enrolled in 2009 and from whom at least one volume was obtained. Two pregnancies complicated with trisomy 21 and three with congenital anomalies were excluded. Three multiple pregnancies, three drop outs, 16 miscarriages and two cases with an intrauterine foetal demise had to be excluded as well, leaving 112 inclusions for analysis (**Figure 1**).

Since an exomphalos is a common feature of Edwards syndrome, after finishing the study we also looked at available ultrasound volumes of trisomy 18 cases that have been described before.[13]

Ethical approval

All participants signed a written informed consent form and the local medical and ethical review committee approved the study protocol (METC 232.394/2003/177, METC 323.395/2003/178, MEC 2004–227).

Pregnancy dating

The GA was calculated according to the first day of the last menstrual period (LMP) in case of a regular menstrual cycle of 28 days and adjusted for a longer or shorter cycle.[14] In case of a discrepancy in GA of more than seven days between crown rump length (CRL) and the last menstrual period

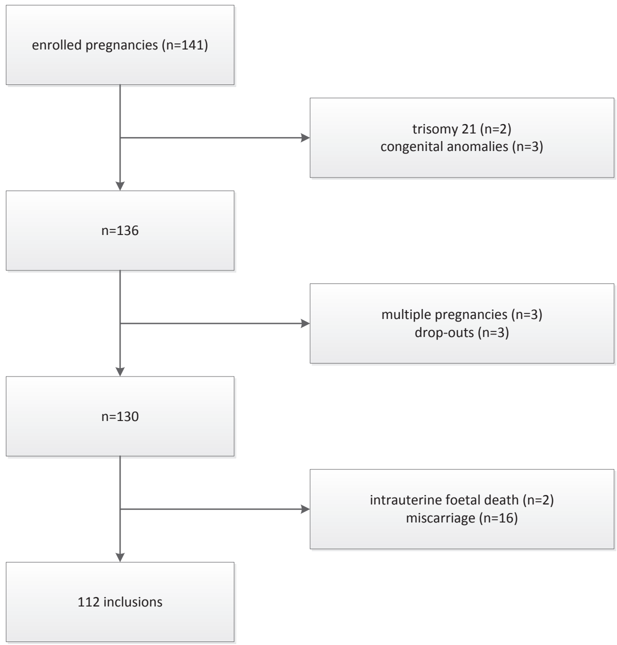

Figure 1: flowchart illustrating inclusions and exclusions of the study population

(LMP), or an unknown LMP, the GA was calculated by using CRL according to Robinson[15] at the end of the first trimester using the latest available measurement. In case of assisted reproductive technology, GA was determined by the date of oocyte retrieval plus 14 days in pregnancies conceived via in vitro fertilisation with or without intracytoplasmic sperm injection (IVF/ICSI) procedures, from the LMP or insemination date plus 14 days in pregnancies conceived through intrauterine insemination, and from the day of embryo transfer plus 17 or 18 days in pregnancies originating from the transfer of cryopreserved embryos, depending on the number of days between oocyte retrieval and cryopreservation of the embryo.

Material

The sonographic volumes were acquired using a Voluson E8 ultrasound machine (GE Medical Systems, Zipf, Austria) and obtained with a transvaginal scan (GE-probe RIC-6-12-D [4.5–11.9 MHz]). With regard to the safety aspects of first trimester ultrasound the thermal index (TI) and mechanical index (MI) were kept below 1.0, the examiners were qualified and experienced, and the as-low-as-reasonable-practicable (ALARP) principle was respected: the duration of the examination did not exceed 30 minutes, and 3D images were stored for offline evaluation in order to reduce the exposure to ultrasound as much as possible.[16] The 3D volumes were converted to a Cartesian format and visualised in the BARCO I-Space (Barco N.V., Kortrijk, Belgium). This is a four-walled CAVE™-like (Cave Automatic Virtual Environment) virtual reality system.[12] The V-Scope volume rendering application is used to create a 'hologram' of the ultrasound volume that is being investigated, floating in space in front of the observer.[17] For our study the 3D volumes were resized (enlarged), rotated and cropped when necessary and grey-scale and opacity values were adjusted for optimal image quality.

Measurements

Using the 3D VR wireless joystick, we first determined whether we could observe the midgut to protrude in the umbilical cord. If so, just above the level of the insertion we measured in a midsagittal plane the anteroposterior diameter of the abdomen (APD), perpendicular to the spine. In an axial plane we measured perpendicular to this diameter the transverse diameter of the abdomen (TD) in order to calculate the abdominal circumference (AC): $AC = \pi[0.75(APD+TD)-\sqrt{(APD*TD)}/4]$. Then, we measured the maximum width of the midgut herniation and the width of the cord insertion in an axial plane as well (**Figure 2**). After these measurements we erased all voxels surrounding the midgut herniation. The volume of this free floating midgut herniation could be determined semi-automatically by placing a seed point in the midgut herniation and using the region growing segmentation algorithm implemented in the V-Scope application (**Figure 2**).

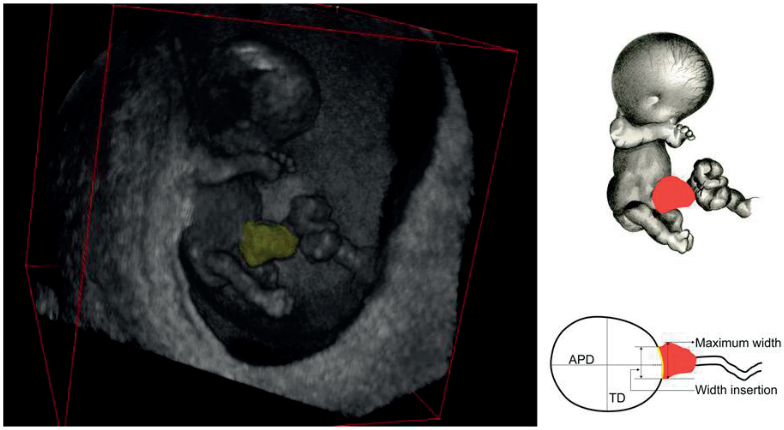

Figure 2: semi-automatic volume measurement of the free floating midgut herniation in the BARCO I-Space (left) and schematic representation of measurements (right); APD: anteroposterior diameter of the abdomen, TD: transverse diameter of the abdomen

All measurements were performed offline. Measurements of 31 foetuses were randomly repeated once by the same examiner (LB) and once by another examiner (HB) to study the reproducibility by determining the intraobserver and interobserver variability.

Statistical analysis

We created references curves for the maximum width of the midgut herniation and the width of the cord insertion, and the volume of the midgut herniation. These parameters were plottedagainst the GA, AC and CRL. This was done using the GAMLSS (generalised additive models for location scale and shape) methodology using the eponymous R-package.[18] It is assumed that the responses follow a (truncated) normal distribution after applying a Box-Cox transformation. The parameters of this distribution are modelled as a spline function of the independent variable.

The intraobserver and interobserver variability was depicted with Bland Altman plots indicating the bias (the systematic of mean difference between two measurements, with 95%CI) and the upper and lower limits of agreement (LOAs, with 95%CIs). The Repeatability Coefficient and Intraclass correlation coefficients (ICCs, two way mixed, single measures, absolute agreement) of intraobserver and interobserver measurements were added.

Results

From the 112 pregnancies 699 volumes were obtained for evaluation (mean: 6.24, median: 6, range: 4-8 volumes per patient). Patient characteristics are presented in **Table 1**. Of these 699 volumes, a midgut herniation was

Characteristic		**Median (range) or percentage**
Singleton pregnancies (n=112)		
Maternal age (years)		32.9 (18.9-42.7)
Gravidity		2 (1-10)
Parity		
	0	62.5%
	1	27.7%
	≥ 2	9.8%
Miscarriages ≥ 2		25.9%
Conception mode		
	Natural	70.5%
	IVF or IVF/ICSI	27.7%
	Intrauterine insemination	1.8%
Gestational diabetes		5.4%
Hypertensive disorders		8.9%
Small-for-gestational age		3.6%
Newborns (n=112)		
Female		52.7%
Birth weight (grams)		3390 (450-4700)
GA at delivery (weeks)		39^{+4} (26^{+4} – 42^{+0})

Table 1: general characteristics of the study population

present in 305 volumes. Measurements could be performed in 181 out of 305 volumes (59.3%). Besides one foetus (with very low quality of all the acquired volumes), in all foetuses at some moment a herniation was seen. In our data set in approximately 1 in 10 ultrasound volumes no midgut herniation could be observed at 9 and 10 weeks GA. The earliest and latest GA we were able to measure a midgut herniation was 7 weeks and 3 days and 12 weeks and 1 day respectively (**Table 2**). Reference values of the width of the cord insertion, the maximum width and the volume of the herniation are provided in **Table 3**, **4** and **5** respectively. In **Figure 3** the width of the cord insertion is plotted against the GA, CRL and AC. Although there is a positive linear relation with all parameters, this effect is most prominent at an early GA and smaller CRL and AC. The same results were obtained regarding the maximum width and the volume of the midgut herniation - plotted against the GA, CRL and AC.

We found six cases of trisomy 18 between 12 weeks and 0 days and 13 weeks and 1 day, more or less immediately following the time period of study of our current manuscript (7 weeks and 3 days - 12 weeks and 1 days). Volume measurements in these six cases were much larger (median:

Week	Number of volumes	Midgut herniation absent	%	Midgut herniation present	%	Success rate	%
6	65	65	100.0	0	0.0	-	-
7	101	91	90.1	10	9.9	3/10	30.0
8	106	47	44.3	59	55.7	29/59	49.2
9	107	10	9.3	97	90.7	62/97	63.9
10	110	12	10.9	98	89.1	67/98	68.4
11	109	73	67.0	36	33.0	17/36	47.2
12	101	96	95.0	5	5.0	3/5	60.0
Total	699	394	56.4	305	43.6	181/305	59.3

Table 2: absolute and relative numbers of absent and present midgut herniations and success percentages of measurements (measurement/number of volumes with discernible midgut herniation; %) by gestational age (expressed in complete weeks)

GA	p5	p50	p95	number of volumes measured
8^{+0}	1.67	2.21	2.87	29
9^{+0}	2.03	2.70	3.52	62
10^{+0}	2.42	3.26	4.27	67
11^{+0}	2.46	3.33	4.39	17
12^{+0}	2.45	3.35	4.44	3

Table 3: reference values of the width of the cord insertion (mm); GA: gestational age

GA	p5	p50	p95	number of volumes measured
8^{+0}	2.22	3.23	4.19	29
9^{+0}	2.89	4.04	5.14	62
10^{+0}	3.55	4.79	5.97	67
11^{+0}	3.84	5.01	6.14	17
12^{+0}	3.89	4.94	5.96	3

Table 4: reference values of the maximum width of the midgut herniation (mm); GA: gestational age

GA	p5	p50	p95	number of volumes measured
8^{+0}	17.76	27.16	37.95	29
9^{+0}	21.07	44.19	73.07	62
10^{+0}	30.68	67.76	114.65	67
11^{+0}	42.51	82.02	130.34	17
12^{+0}	75.99	90.01	104.89	3

Table 5: reference values of the volume of the midgut herniation (mm^3); GA: gestational age

182.6 mm^3; range: 71.4 - 995.6 mm^3) as compared to our reference data (median: 59.0 mm^3, range: 13.9 - 146.1 mm^3).

The mean differences, the 95% limits of agreement and the intraclass correlation coefficients (ICC) of intra- and interobserver variability are shown in **Table 6**. ICC's were all >0.9 indicating excellent reproducibility.

	Mean difference (95%CI)		Lower LOA (95%CI)		Upper LOA (95%CI)		Repeatability Coefficient		ICC	
	intra	inter	intra	inter	intra	inter	intra	inter	intra	inter
width of insertion	0.037 (-0.56 ; 0.130)	0.008 (-0.081 ; 0.097)	-0.469 (-0.630 ; -0.308)	-0.478 (-0.633 ; -0.324)	0.543 (0.382 ; 0.703)	0.494 (0.340 ; 0.649)	0.506	0.486	0.920	0.917
maximum width	0.020 (-0.075 ; 0.115)	0.037 (-0.043 ; 0.118)	-0.500 (-0.665 ; -0.335)	-0.401 (-0.540 ; -0.262)	0.540 (0.375 ; 0.705)	0.475 (0.336 ; 0.615)	0.520	0.438	0.951	0.962
volume	0.703 (-0.056 ; 1.463)	0.285 (-0.456 ; 1.025)	-3.438 (-4.753 ; -2.122)	-3.753 (-5.035 ; -2.470)	4.844 (3.529 ; 6.159)	4.322 (3.040 ; 5.605)	4.141	4.038	0.997	0.997

Table 6: intra- and inter observer variability; LOA: limits of agreement, ICC: intraclass correlation coefficient

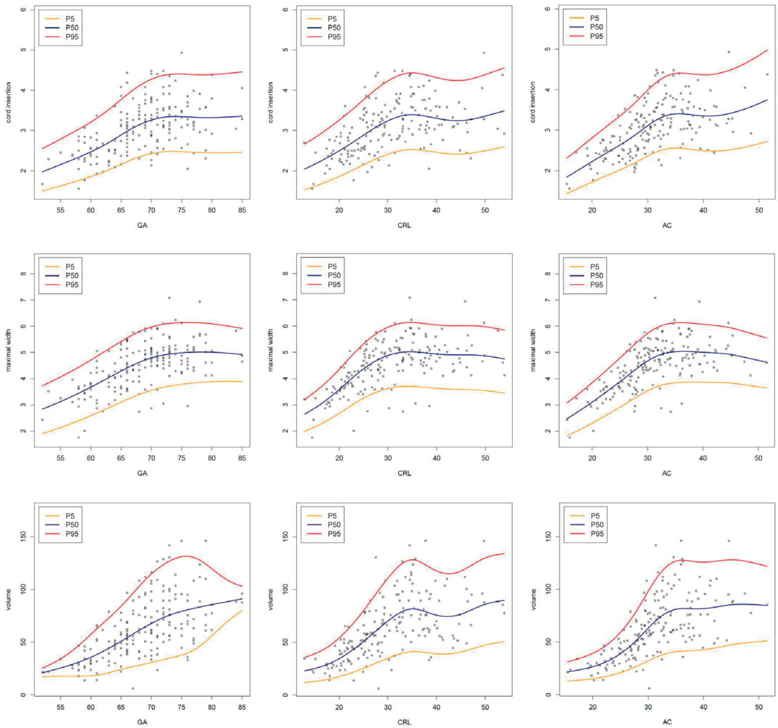

Figure 3: the width of the cord insertion (mm), the maximum width of the midgut herniation (mm) and the volume of the midgut herniation (mm^3) as a function of respectively gestational age (GA; days), crown-rump length (CRL; mm) and the abdominal circumference (AC; mm)

Discussion

We investigated the early foetal development of the umbilical cord insertion by means of 3D ultrasound. The midgut herniation could be measured reliably and reference curves were constructed for the volume and maximum width of the midgut herniation and the width of the umbilical cord insertion. Although we are not the first to investigate the midgut herniation by means of ultrasound, all these studies had been performed in relatively few foetuses. Furthermore, most of these were done using 2D sonography.[1, 3, 6, 19]

In 1987 Schmidt et al. studied fourteen women weekly between 7 and 12 weeks GA.[1] The mean herniated mass was larger at 8 weeks GA (or 17-20 mm CRL) than at 9 weeks (or 23-26 CRL), which appears to be in contrast with our findings (**Figure 3**). The authors, however, found a noticeable variation in size of the mass at the same GA.

Blaas et al. investigated the development of several structures including the midgut herniation.[3] 29 women were seen five times from 7 to 12 weeks GA to measure - among others - the thickness of the umbilical cord at the insertion and its thickness in a free loop. At 7 weeks GA a thickening of the cord containing a slight echogenic area was seen, progressing to a large hyperechogenic mass during 9 and 10 weeks GA. The thickness of the umbilical cord at the insertion appeared to be increased between 8 and 11 weeks GA compared with the thickness in a free loop. From 10 weeks and 4 days the gut retracted and from 11 weeks and 5 days in none of the foetuses any herniation could be seen. In contrast, we observed at 12 weeks GA still a midgut herniation in a small minority of foetuses.

Bowerman investigated in 48 foetuses the midgut herniation.[19] From 11 weeks and 2 days GA no herniated midgut could be observed. In all cases but one scanning was performed transabdominally. The significant gap between his and our findings might be caused by the fact that we used high-resolution transvaginal instead of transabdominal ultrasound, most likely resulting in higher image quality.

The circumference of the midgut herniation was investigated weekly in 18 women by Van Zalen-Sprock et al.[6] between 7 and 12 weeks GA. The circumference of the midgut herniation appeared to be greatest at 10 weeks GA, with a maximum 24.5 mm, measured at the level of the insertion. Herniation could be observed in all foetuses at 10 weeks GA and in none of these at 12 weeks GA which is in contrast with our findings (98% and

5% respectively). This may be due to a relatively small number of cases in comparison to the present study. The different findings in the present study may be due to a much larger number of cases (18 vs 110 and 101).

3D evaluation of the midgut herniation has been investigated previously without performing measurements. Yonemoto et al. and Hata et al. compared in 5-11 weeks GA and 8-13 weeks GA respectively the visualisation rate of - among others - the midgut herniation. They showed 3D examination to be non-inferior to 2D examination, although this was not scientifically tested.[20, 21] Soffers et al. who investigated the rotation of the midgut in histological specimens used another novel 3D visualisation technique.[22] They used a technique in which serial sections of historical collections of embryos and foetuses were digitised using a scanning microscope. Subsequently these images were converted and aligned to create a 3D reconstruction. The several loops of the midgut appear to develop in a hierarchal manner and move independently of each other, facilitating phased return into the abdominal cavity. The authors state that the width of the hernia neck does not appear to determine the time window for intestinal return, which is supported by our finding that the width of the insertion does not increase after 10 weeks GA (**Figure 3**).

To our best knowledge, we are the first to perform volume measurements of the herniation. Another strong point of our study is the number of volumes that could be analysed, although this was somewhat limited by the success rate of the measurements. This could be due to the fact that in our study only non-targeted 3D sweeps of the entire foetus were stored. Movement artefacts of the foetus could have impeded accurate visualisation. Furthermore, the parameters were measured offline on stored data. All these aspects contributed to the suboptimal success rate.

In 5 out of 101 (5.0%) foetuses a midgut herniation could be observed at 12 weeks GA. Unfortunately we have only data available until 13 weeks GA. Further research in this period of gestation is necessary. The steeply decreasing number of foetuses with a midgut herniation from 11 weeks GA and the data from the literature however suggest a rapid disappearance after 12 weeks GA. In the careful postnatal follow up of our study group no congenital omphalocoeles have been reported. The larger measurements in the trisomy 18 cases at least supports the hypothesis that volume measurements may become a valuable diagnostic tool in diagnosing pathological omphalocoeles at the end of the first trimester. One should remain cautious however as spontaneous resolution of omphalocoeles have been described and a pathological omphalocoele during this period can easily be mistaken for a physiological midgut herniation. Since in only 5% of the foetuses at 12 weeks GA a midgut herniation was observed and the latest GA we could measure a herniation was 12 weeks and 1 day, we advise to repeat the examination when a herniation is observed at 12 weeks GA for this may be a pathological finding.

The proposed volume measurement technique cannot be done on conventional ultrasound machines with a 2D display, limiting its applicability. However, specialised 3D software is available to perform volume measurements on ultrasound machines or desktop computers. Also a user friendly 3D VR desktop system has been developed for routine use of diagnostic 3D VR ultrasound in an outpatient clinic, allowing precise length, volume and angle measurements.[23] By means of this system the volume measurements can easily be performed.

Conclusion

We created reference data for the midgut herniation in ongoing pregnancies. Our data may be used in future for studies on aetiology of abdominal wall defects and for comparison in foetuses in which at the first trimester ultrasound scan a congenital, pathological omphalocoele is suspected. Since in only 5% of the foetuses at 12 weeks GA a midgut herniation was observed and the latest GA we could measure a herniation was 12 weeks and 1 day, we advise to repeat the examination when a herniation is observed at 12 weeks GA for this may be a pathological finding.

Acknowledgements

We would like to thank Mr Hans Kneefel for helping creating **Figure 2**.

References

1. Schmidt W, Yarkoni S, Crelin ES, Hobbins JC. Sonographic visualization of physiologic anterior abdominal wall hernia in the first trimester. Obstet Gynecol. 1987;69(6):911-5.
2. Kim WK, Kim H, Ahn DH, Kim MH, Park HW. Timetable for intestinal rotation in staged human embryos and fetuses. Birth Defects Res A Clin Mol Teratol. 2003;67(11):941-5.
3. Blaas HG, Eik-Nes SH, Kiserud T, Hellevik LR. Early development of the abdominal wall, stomach and heart from 7 to 12 weeks of gestation: a longitudinal ultrasound study. Ultrasound Obstet Gynecol. 1995;6(4):240-9.
4. Syngelaki A, Chelemen T, Dagklis T, Allan L, Nicolaides KH. Challenges in the diagnosis of fetal non-chromosomal abnormalities at 11-13 weeks. Prenat Diagn. 2011;31(1):90-102.
5. Chaoui R, Nicolaides KH. Detecting open spina bifida at the 11-13-week scan by assessing intracranial translucency and the posterior brain region: mid-sagittal or axial plane? Ultrasound Obstet Gynecol. 2011;38(6):609-12.
6. van Zalen-Sprock RM, Vugt JM, van Geijn HP. First-trimester sonography of physiological midgut herniation and early diagnosis of omphalocele. Prenat Diagn. 1997;17(6):511-8.
7. Lakasing L, Cicero S, Davenport M, Patel S, Nicolaides KH. Current outcome of antenatally diagnosed exomphalos: an 11 year review. J Pediatr Surg. 2006;41(8):1403-6.
8. Blazer S, Zimmer EZ, Gover A, Bronshtein M. Fetal omphalocele detected early in pregnancy: associated anomalies and outcomes. Radiology. 2004;232(1):191-5.
9. Kagan KO, Staboulidou I, Syngelaki A, Cruz J, Nicolaides KH. The 11-13-week scan: diagnosis and outcome of holoprosencephaly, exomphalos and megacystis. Ultrasound Obstet Gynecol. 2010;36(1):10-4.
10. Anandakumar C, Nuruddin Badruddin M, Chua TM, Wong YC, Chia D. First-trimester prenatal diagnosis of omphalocele using three-dimensional ultrasonography. Ultrasound Obstet Gynecol. 2002;20(6):635-6.
11. Achiron R, Soriano D, Lipitz S, Mashiach S, Goldman B, Seidman DS. Fetal midgut herniation into the umbilical cord: improved definition of ventral abdominal anomaly with the use of transvaginal sonography. Ultrasound Obstet Gynecol. 1995;6(4):256-60.

12. Rousian M, Hop WC, Koning AH, van der Spek PJ, Exalto N, Steegers EA. First trimester brain ventricle fluid and embryonic volumes measured by three-dimensional ultrasound with the use of I-Space virtual reality. Hum Reprod. 2013;28(5):1181-9.

13. Baken L, Benoit B, Koning AH, Willemsen SP, van der Spek PJ, Steegers-Theunissen RP, et al. First-trimester hand measurements in euploid and aneuploid human fetuses using virtual reality. Prenat Diagn. 2014;34(10):961-9.

14. Steegers-Theunissen RP, Verheijden-Paulissen JJ, van Uitert EM, Wildhagen MF, Exalto N, Koning AH, et al. Cohort Profile: The Rotterdam Periconceptional Cohort (Predict Study). Int J Epidemiol. 2016;45(2):374-81.

15. Robinson HP, Fleming JE. A critical evaluation of sonar "crown-rump length" measurements. Br J Obstet Gynaecol. 1975;82(9):702-10.

16. Knez J, Day A, Jurkovic D. Ultrasound imaging in the management of bleeding and pain in early pregnancy. Best Pract Res Clin Obstet Gynaecol. 2014;28(5):621-36.

17. Koning AH, Rousian M, Verwoerd-Dikkeboom CM, Goedknegt L, Steegers EA, van der Spek PJ. V-scope: design and implementation of an immersive and desktop virtual reality volume visualization system. Stud Health Technol Inform. 2009;142:136-8.

18. Stasinopoulos DM, Rigby RA. Generalized additive models for location scale and shape (GAMLSS) in R. J Stat Softw. 2007;23(7).

19. Bowerman RA. Sonography of fetal midgut herniation: normal size criteria and correlation with crown-rump length. J Ultrasound Med. 1993;12(5):251-4.

20. Yonemoto H, Yoshida K, Kinoshita K, Takeuchi H. Embryological evaluation of surface features of human embryos and early fetuses by 3-D ultrasound. J Obstet Gynaecol Res. 2002;28(4):211-6.

21. Hata T, Aoki S, Manabe A, Hata K, Miyazaki K. Three-dimensional ultrasonography in the first trimester of human pregnancy. Hum Reprod. 1997;12(8):1800-4.

22. Soffers JH, Hikspoors JP, Mekonen HK, Koehler SE, Lamers WH. The growth pattern of the human intestine and its mesentery. BMC Dev Biol. 2015;15:31.

23. Baken L, van Gruting IM, Steegers EA, van der Spek PJ, Exalto N, Koning AH. Design and validation of a 3D virtual reality desktop system for sonographic length and volume measurements in early pregnancy evaluation. J Clin Ultrasound. 2015;43(3):164-70.