Chapter 1

General introduction

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GENERAL INTRODUCTION

Congenital heart disease

Congenital heart disease (CHD) is the most common congenital malformation, affecting approximately 6 to 8 of 1000 live born children. The prevalence in miscarriages and stillbirths is even higher. The mortality rate from CHD in children ranges between 3 to 20%, with a large difference between industrialized (3 to 7%) and third world countries (20%). In the Netherlands congenital malformations are part of the ‘Big Four’ risk factors (congenital malformations, small for gestational age, asphyxia, preterm delivery) which are held responsible for the vast majority of the perinatal mortality.

Most of CHD develops during cardiac morphogenesis in the early embryonic period. Already in the third week of development the heart tube starts pulsating and morphogenesis is completed in the eighth week. During this period a process of looping, septation and valve formation takes place in which the heart tube is remodeled into a four chambered heart. Errors at any stage of embryological development can result in a defect of the anatomy of the heart.

Prenatal detection of congenital heart disease

Prenatal diagnosis of CHD reduces neonatal morbidity and mortality through determining location of delivery for immediate adequate neonatal care. Additionally, early knowledge of CHD provides the possibility of invasive testing to detect associated chromosomal anomalies. Moreover, it allows time for adequate counseling and, in severe cases, the opportunity to terminate a pregnancy on request of the parents.

Ultrasound as a diagnostic tool was developed in the late 1940’s, however, it was not until the early 1960’s that ultrasound equipment became available commercially. An important development in the late 1970’s, was real-time ultrasonography which increased the implementation of ultrasound in the obstetric care units. In the 1980’s ultrasound screening programs were introduced gradually in many countries, aiming to detect congenital anomalies at an early stage of pregnancy. Despite the high prevalence of cardiac defects, these anomalies are still the most commonly overlooked lesions in prenatal screening programs. The four-chamber view, which is a transverse plane through the four heart chambers, has been used as the primary plane to screen for CHD. The addition of the outflow tract views has increased the detection rate of cardiac defects. Unfortunately, the overall sensitivity in screening programs remains low, but varies widely (25-59.7%). The deviation in detection rates is mainly explained by the different levels of training of ultrasonographers. The quality of acquired images may depend on fetal position and maternal conditions like obesity and oligohydramnios. In early pregnancy the fetal heart is about 10 times smaller compared to a newborn heart and visualization is complicated by the high fetal heart rate.
The accuracy of prenatal diagnosis in third-level centers after referral has increased over time up to 87%²³-²⁸. Although the performance of ultrasound machines and the operators experience have improved, it can still be a challenge to diagnose complex anomalies. The interpretation of the images must be done in real-time, making it time consuming and operator dependent.

**Two-dimensional ultrasound**

Real-time two-dimensional ultrasound (2DUS) is the conventionally used tool for fetal echocardiography. Although continuous improvements in the hardware and post-processing software have resulted in a good image quality even in late first trimester, 2DUS still has its limitations. A well-known difficulty in echocardiography is capturing and interpretation of the outflow tracts by 2DUS, especially when there is a cardiac malformation with stenosis or atresia. Specific features of the heart like the surface of the ventricular septum and the anteroposterior view of the atrioventricular annuli (mitral and tricuspid valves) are difficult to visualize in detail in 2DUS planes. This hinders the detection or correct diagnosis of cardiac defects.

**Three-dimensional ultrasound**

Over the past decades, development of ultrasound systems and the processing software led to the introduction of dynamic three-dimensional (3D) image sequences. The acquired data are available as a real-time volume dataset rather than a time dependent series of planar 2D images. Three-dimensional ultrasound has potential advantages over the conventional 2DUS. Volumetric scanning is less dependent on the angle of acquisition, and thus less dependent on fetal position or operator expertise. However, since the heart is a beating organ, non-gated acquisition produces artifacts in the reconstructed volume data²⁹. Therefore, spatiotemporal image correlation (STIC) has been developed.

**Four-dimensional ultrasound and spatiotemporal image correlation**

STIC is a software modality which is developed to analyze a cine sequence of a moving fetal heart³⁰. A mechanical transducer acquires a volume dataset with a single sweep. The automated 3D volume acquisition consists of multiple 2DUS slices. The STIC software determines the fetal heart rate based on the rhythmic movements within the volume dataset. All recorded 2DUS slices are rearranged according to their appearance in the cardiac cycle in the 3D datasets. This process results in multiple serial 3D volume datasets, which are combined according to their appearance in time to create one complete moving real-time 3D cardiac cycle, which is called a 4D volume dataset. The fourth dimension is time. This loop can be played in slow motion or stopped at any time for analysis. Each of the planes can be moved and rotated while maintaining
the synchronized cardiac loop\textsuperscript{22,30-32}. With several post-processing rendering capabilities, an unlimited number of ‘virtual planes’ of the fetal heart can be obtained. STIC technology can be combined with power-Doppler, color-Doppler and B-flow ultrasound. Earlier studies demonstrated good reproducibility of echocardiographic planes acquired by STIC\textsuperscript{33-35}.

**To record a STIC volume**

To record a STIC volume, it is best is to start with a four-chamber view\textsuperscript{32}. This is the acquisition plane from which the sweep will be recorded symmetrically cranially and caudally. A complete volume should include the entire heart with outflow tracts and the abdominal situs. Before making a sweep optimal settings should be acquired. Best images are retrieved from a fetal position with the spine posterior (at six o’clock), to reduce rib shadowing to a minimum. The examiner places the region of interest (ROI) box around the heart. Best resolution and frame rate is achieved if the heart covers the majority of the box\textsuperscript{22}. Acquisition time of the sweep can be varied and ranges usually between 7.5 and 15 seconds. The best resolution is achieved with a long acquisition time, however, the chance of artifacts due to fetal movements is high if more than 10 seconds is selected. A short acquisition time reduces the risk of fetal movements but the higher speed of the sweep results in decreased resolution of the volume. Thus the acquisition time should be as long as possible, but adjusted to the behavioral state of the fetus. The sweep angle can be set between 20 and 40 degrees. The angle of the sweep should cover the entire heart and aortic arch. If the angle is too large, the resolution of the images of the heart decreases and the acquisition time is unnecessary long, which results in a higher chance of movement artifacts. In the first trimester usually 20 to 30 degrees is sufficient, and 30 to 40 degrees is required later in pregnancy. The frame rate during the acquisition of the volume is 150 frames per second, which results in 1500 frames in 10 seconds\textsuperscript{22}. Thus 20 to 30 cardiac cycles are included in one volume. The success rate of STIC acquisition varies between 75.7 and 96.2\%\textsuperscript{29,36}. The highest success rates are achieved during the second trimester. The first-trimester fetus causes difficulties for acquisition because of frequent fetal movements. In the third trimester STIC acquisition is complicated by shadowing of the ribs, which increases with gestational age due to increased calcification of the bones.

**Pitfalls and artifacts**

Only few studies address the pitfalls of 4DUS. Comparable to 2DUS, artifacts can originate in 4DUS. Similar like in conventional ultrasound, drop-out artifacts and reverberations occur frequently. In a STIC volume this can result in a volume with artifacts like rib shadowing in the rest of the volume which were not visible at the initial recording at the level of the four-chamber view. As a STIC volume consists of multiple 2DUS slices, conditions which are known to create suboptimal
2D image quality like oligohydramnion or maternal obesity, will result in a suboptimal 3D volume. In addition, 4DUS may show artifacts specifically created during the sweep. Fetal breathing and other fetal movements during the acquisition will result in dislocation of the structures and abrupt transitions. Furthermore, gating errors have been described due to the lack of sufficient echogenic voxels in the volume to detect the rhythmic movement of the myocardium properly. This will result in incorrect arrangement of the images. This was demonstrated in an ‘in vitro’ study. Therefore, examination with STIC should always be combined with a 2DUS examination. A STIC volume is recorded with one direction angle. To overcome insonation problems, it is advisable to record multiple volumes, each from another direction (transversal, sagittal, coronal). However, this will not solve all possible difficulties like resolution problems because of a high BMI or shadowing of the ribs, especially in the third trimester.

Functions of 4DUS using STIC

The functions of STIC to visualize the fetal heart have been described in several studies. The imaging modalities will first be described and then their application regarding cardiac anatomy and function.

Imaging and render modalities in 4DUS

The multiplanar mode provides visualization of the heart in three directions (transversal, sagittal and coronal) which can be visualized separately or together in one screen (plane A, B, C). When the transverse plane of the heart with the four-chamber view is visualized in panel A, panel B shows the sagittal plane and panel C the coronal plane of the heart. A reference dot represents the intersection between the panels (Figure 1). By moving the volume around the X, Y and Z axes the heart can be manipulated in all three dimensions and can be viewed in every desirable plane. Cine loop allows to visualize the planes through the cardiac cycle. The cine loop can be slowed down or stopped to examine the heart in a specific phase of the cardiac cycle. By moving the image in panel B from left to right or vice versa almost a complete cardiac examination can be performed by visualizing the stomach and the diaphragm upwards to the heart and the outflow tracts. Measurements of distance and area can be performed.

The render mode is a virtual visualization of the fetal heart with all three dimensions combined. Lights and shadows are added to create a 3D effect. This view illustrates the surface area within the heart with visualization of the depth in a more realistic image (Figure 2). The ROI box should be placed around the intended structure with the green line corresponding to the side from where the structure should be visualized. The screen can be divided in four panels with the multiplanar and render planes in one screen to manipulate the volume.
**Figure 1. Multiplanar mode**

The three panels show a fetal four-chamber view visualized using STIC with multiplanar mode. The left upper panel shows the four-chamber view, the upper right panel the sagittal view of the heart and the lower left panel the coronal view. Ao indicates aorta, LA left atrium, LV left ventricle, RA right atrium, RV right ventricle.

**Figure 2. Render mode**

The four panels show the fetal heart visualized using STIC with multiplanar mode. The left upper panel shows the four-chamber view with a render box placed around the atrioventricular valves. The upper right panel shows the sagittal view of the heart, the lower left panel the coronal view. The lower right panel shows the render mode of the heart with the opening of the atrioventricular valves visualized from the atria. LA indicates left atrium, LV left ventricle, RA right atrium, RV right ventricle.
**HDLive** is a render technique with possibilities for the examiner to adjust the lighting of the images to create more depth effects\(^1\).

**Tomographic ultrasound imaging (TUI)** provides sequential analysis of the fetal heart and outflow tracts in one screen. The heart can be divided in parallel planes, which are depicted in a sequential order. In the left upper panel a view of the fetal heart is visualized. The vertical lines in the panel correspond to the orthogonal planes which are visualized in the same screen\(^{39,42}\). This allows visualization of the heart from the outflow tracts to the lower part of the heart and the stomach (Figure 3). A nearly complete fetal cardiac examination can be performed in one screen, comparable to the sequential slices of a Computed Tomography scan.

**Inversion mode** projects echolucent structures as echogenic structures and visa versa based on gray scale levels. This method allows visualization of the fluid filled structures (water or blood) in the heart like the vessels and heart chambers. This technique does not distinguish blood from other hollow structures\(^{38}\).

**Virtual Organ Computer Aided AnaLysis (VOCAL)** provides volume analysis based on 2D contour measurements in planes of a structure which is rotated around a selected rotation angle\(^{40}\).
Sonographic Automatic Volume Calculation (Sono-AVC) identifies echolucent structures based on edge recognition in 3D and fills them with color to create casts of the same structures\(^44\). The number and volume of the structures in the dataset are automatically calculated. This software was originally designed for ovarian follicular volume estimation\(^48,49\).

Applications of 4DUS

Morphology of the fetal heart
Each imaging technique has its own specific application. For each cardiac structure it will be discussed which imaging modality can be useful.

Atria
With the \textit{multiplanar mode} the atria can be visualized in three directions in one screen. Identification of the atrial appendages using 2DUS is challenging. The \textit{render mode} shows a virtual surface of the atria, however identification of the atrial appendages with the render mode has not been described. Only one study analyzed the atrial appendages with Sono-AVC in a retrospective design. Twenty-two fetuses with cardiosplenic syndromes were examined\(^50\). They reported correct visualization of the atrial appendages in all cases in which a volume with adequate quality was available. This might help to diagnose cardiac anomalies with heterotaxy, however the authors described several technical limitations like over-projection of the color outside the cardiac chambers because of shadowing from ribs or limbs\(^50\).

Atrioventricular valves
The atrioventricular valves can be examined using the \textit{multiplanar} and \textit{render mode}. \textit{Multiplanar mode} allows examination of atrioventricular valves and their spatial relationship with the great vessels. The tricuspid and mitral valves can be visualized together in the anteroposterior view, although experienced examiners are able to achieve this plane using 2DUS as well. For an optimal view, the plane exact parallel to the atrioventricular valves can be achieved through rotation of the volume around the three axes with the multiplanar mode. This is important, as the tricuspid and mitral valve have different angles with the ventricular septum. The \textit{render mode} displays the atrioventricular annuli (Figure 2) and the arterio-ventricular alignments, their size and connections. A high success rate, up to 93\%, of the visualization of these structures has been described in normal hearts\(^45\). However, the feasibility to visualize the morphology, like the valve leaflets, has not been studied.

Ventricles
\textit{Multiplanar mode} allows visualization of the ventricles in three directions together in one screen. Using the \textit{render mode} small heart structures like the papillary muscles can be visualized as three
dimensional structures. Developmental failure of the papillary muscles can result in tricuspid valve dysplasia. Identification of the papillary muscles in the four-chamber view was possible in 89.3% of the women with good interobserver reproducibility. The volume of the ventricles can be assessed with inversion mode, VOCAL and sono-AVC which is discussed below in the heart function section.

**Ventricular septum and foramen ovale**

Using 2DUS only a small portion of the ventricular septum can be examined, which is probably the reason why ventricular septal defects (VSDs) are the most commonly overlooked cardiac defects during prenatal examination. A VSD can vary in size and the position can be at any level in the interventricular septum. Blood flow across these lesions can be intermittent or absent due to the equal pressure in both fetal ventricles. STIC, with the use of render mode, has the potential to image the complete interventricular septum, including the interatrial septum and the foramen ovale. The lateral view of the septum can be visualized from the left or right ventricle. The ROI box should be placed around the ventricular septum in the four-chamber view in panel A with the green line at the site of one of the ventricles. For optimal image quality, the insonation angle of the septum should be more than 45 degrees. Yagel et al. presented successful visualization of the interventricular and interatrial septum in 96.3% of 136 normal fetuses in a third-level ultrasound center. VSD evaluation was improved by the interventricular septum plane in 13 (out of 35) abnormal cases, including two cases where it excluded a VSD. In the other 11 cases the VSD was visualized using 2DUS, however, render mode increased the accuracy of the size and functionality of the VSDs. There were two small isolated VSDs which were missed by 2DUS as well as by the render mode. In four cases the interatrial septum plane contributed to foramen ovale evaluation like restriction of foramen ovale flap in case of a transposition of the great arteries without VSD. Reference values for the area of the interventricular septum are developed to detect septal changes such as septal hypertrophy.

**Outflow tracts including aortic arch**

Measurement of the aortic and pulmonary valve diameter is a simple measurement using 2DUS and STIC. Multiplanar mode may be helpful in determining the exact plane and phase of heart cycle to measure the diameter precisely, although experienced sonographers can achieve this with 2DUS as well. Therefore no additional clinical value of 4DUS for this measurement can be expected. A potential addition could be the examination of the area and morphology of the valve. The render mode enables visualization of the morphology of the semilunar valves (Figure 4) which is difficult using 2DUS. The valve opening can be visualized in almost every STIC volume (93% in normal hearts). However, the feasibility to visualize the morphology, like the valve leaflets, has not been studied before.
Inversion mode allows examination of the spatial relationship of the great vessels and other heart structures\cite{38,41}. In addition, inversion mode can be useful to detect an interrupted aortic arch or a coarctation of the aorta. Fetal and maternal movements may create artifacts which might give a misrepresentation of the vessels\cite{59}.

Heart function

Adjusting color Doppler to the STIC volume provides information of the blood flow dynamics and intracardiac flow\cite{59}. Visualization of the four-chamber view and the three-vessel view with color Doppler volumes is feasible, with a success rate of 90\%\cite{59}. As with 2DUS, color Doppler will generate poor signals with a perpendicular insonation angle. In a 3D image, which can be rotated in any direction, the insonation angle is not always easily recognizable and an examiner should realize that these artifacts can be present. Furthermore, the quality of acquisition is dependent on the fetal movements.

Several studies reported assessment of the fetal cardiac function using STIC\cite{40,60-71}. Assessment of the cardiac function is of importance for fetuses with CHD, intra-uterine growth restriction, twin-to-twin transfusion syndrome and hydrops. Reference values for the ventricle volume, stroke volume, cardiac function and ejection fraction are developed using Virtual Organ Computer...
Aided Analysis (VOCAL)\textsuperscript{61-63,65}. Other methods are 3D slice method\textsuperscript{66} and inversion mode\textsuperscript{71}. VOCAL can be useful in analysis of the heart function by examination of the heart ventricles during systole and diastole (stroke volume = diastolic volume – systolic volume), ejection fraction (ejection fraction = stroke volume / diastolic volume) and cardiac output (cardiac output = stroke volume x heart rate)\textsuperscript{69}. Hamill et al. presented good inter- and intraobserver reliability for measurements of the ventricle volumes using VOCAL, while Schoonderwaldt et al. showed wide limits of interobserver agreement for measurements of the left ventricle volume and ejection fraction\textsuperscript{72}. Assessment of the cardiac function is useful to understand the fetal hemodynamics in utero, however, this method is time consuming\textsuperscript{70} and dependent on the operators experience\textsuperscript{69}. Therefore, evaluation of the cardiac function using STIC has not been incorporated in daily practice.

Telemedicine and offline analysis
Another application of STIC is evaluation of the fetal heart in absence of the patient. The offline 4D analysis allows manipulation of the volume to acquire images comparable to the planes used in neonatal examination. Another advantage is the possibility of ‘telemedicine’. This means that STIC data can be acquired by an examiner at a remote site and reviewed offline by experts at great distance. ‘Telemedicine’ allows a worldwide multidisciplinary evaluation of a fetal heart. This can be extremely helpful in developing areas without expertise in fetal echocardiography. It has been shown that sonographers without specific experience in fetal echocardiography, are able to record a good STIC volume\textsuperscript{36,73}. Good results with internet links have been reported, even in the first trimester\textsuperscript{73,74}. The ‘Collaborative Study on Four-dimensional Echocardiography for the Diagnosis of Fetal Heart Defects (COFEHD)’ analyzed the agreement in diagnosis between seven centers with expertise in 4D echocardiography. They reported an excellent inter-center agreement (k = 0.97)\textsuperscript{75}. However, if details required for planning of postnatal care can be obtained using solely STIC is still unknown.

Training and research
Manipulation of the heart in a STIC volume helps to understand the fetal anatomy and the spatial relationships of the different structures. Inexperienced sonographers can get insight in the alignment of the four-chamber view with the outflow tracts. Especially multiplanar mode and TUI are useful tools to understand the relationships between the cardiac structures and help in training to perform a complete cardiac examination. Trainees can learn how to diagnose CHD by practicing in STIC volumes. The interpretation and understanding of rendered images can be valuable for the implementation of new 3D/4D technologies. Furthermore, STIC can provide information for research regarding fetal anatomy.
Accuracy of 4DUS in prenatal diagnosis

Numerous case reports have been published to describe the extra details which can be visualized using STIC. Only several studies address the accuracy and additional value of STIC in comparison to 2DUS. Bennasar et al. evaluated the accuracy of 4DUS to diagnose fetal CHD in a selected high-risk population. STIC overall accuracy, sensitivity, specificity, positive and negative predictive value were 91.6, 94.8, 88.1, 89.7, 94.0% respectively. They described absolute concordance in 80.1% in normal fetuses and 74.3% in CHD, while 2DUS showed 84.8 and 81.7% respectively. However, recollection bias might have played a role, because both the bedside recording of the volumes as well as the offline analysis were performed by the same examiner. The earlier mentioned COFEHD study analyzed the accuracy of 4DUS for the diagnosis of CHDs in seven centers with expertise in 4D echocardiography. They presented a sensitivity of 93% (range 77-100%) and a specificity of 96% (range 84-100%)75.

The additional clinical value of STIC is still topic of current debate77-79. One large study of Yagel et al. addressed the added value of 4DUS versus 2DUS in the prenatal diagnosis of CHD. The aim of this study was to determine whether 3D/4D ultrasound improved diagnostic accuracy in cases of CHD. This study assessed 13101 ultrasound examinations with 181 diagnosis of CHD. In 6.6% (12/181) additional details of the cardiac defect, which were important for prenatal counseling, were detected79. Anomalies that were missed in 2DUS but were diagnosed in 4DUS were VSDs (4), total anomalous pulmonary venous connection (2), right ventricle aneurysm (1), transposition of the great arteries with pulmonary atresia with intact ventricular septum (1), right aortic arch with Kommerell’s diverticulum (1), segmental interrupted aortic arch (1), and portosystemic shunt to coronary sinus (2). The authors dedicated the extra details mainly to B-flow imaging in blood flowing in anomalous vessels and the multiplanar mode to compare orthogonal planes of the STIC volume.

Value of 4DUS in screening setting

The additional value of STIC has only been reported in third-level centers. For incorporation of STIC in a screening setting inexperienced sonographers need to be able to acquire a STIC volume and to detect if the heart is normal or abnormal. STIC acquisition by sonographers without experience in 4DUS is feasible29,36,74. However, the success rate of inexperienced sonographers is lower compared to experienced sonographers (experienced vs. less experienced, 88.4% vs. 70.5%, P = 0.02)36. Only one study analyzed if inexperienced sonographers were able to examine the heart using STIC80. The aim of this study was to asses whether sonographers with low-to-intermediate scanning experience are able to detect major abnormalities of the outflow tracts by reviewing the A-plane of cardiac datasets acquired with STIC80. Fourteen inexperienced sonographers analyzed 26 volumes after a two-hour briefing. They were asked to define if
the outflow tracts were normal or abnormal. Although the sensitivity and specificity of this preliminary study were good (83 and 87%, respectively), the individual diagnostic accuracy ranged from 66 to 100% (median 85.5%) and the individual detection rate from 50 to 100% (median 85%). Unfortunately, no other studies regarding the additional value of STIC in a screening setting have been reported. New screening tools are desired to increase the (low) prenatal detection rate of CHD in screening centers.

**AIM OF THIS THESIS**

An accurate and reproducible method for the examination of the fetal cardiac anatomy, with offline analysis, may be extremely valuable in cases with a suspected cardiac anomaly. Four-dimensional ultrasound with STIC was introduced as a new ultrasound method to increase the detection rate of CHD\(^{22,29}\). Storage of the volume provides the possibility of offline analysis. Numerous studies have been developed to describe the various functions of STIC\(^{22,31,38-41,44,45,47,59,71,74,81}\). The examination of the cardiac morphology has, however, not been systematically investigated before. This thesis explores if this highly specialized diagnostic tool proves to be clinically relevant in this aspect. Especially, the usefulness of 4DUS with regards to the examination of the valves of the fetal heart is evaluated.

In this thesis the following questions are addressed:

- Is visualization of the area and the morphology of the valves (atrioventricular valves, semilunar valves, differential insertion of the atrioventricular valves) feasible using 4DUS?
- Is the differential insertion of the atrioventricular valves a useful tool to detect congenital heart disease like AVSDs? Can 4DUS play a role to gain additional information about this cardiac structure?
- Are experienced sonographers able to diagnose cardiac defects in detail using spatiotemporal image correlation?

**OUTLINE OF THIS THESIS**

A large prospective study was conducted to study several morphological items of the fetal heart with STIC. Healthy low-risk pregnant women were asked to participate in this prospective research project concerning the utilization of STIC in fetal echocardiography. Seventy-four women pregnant with fetuses with a structural normal heart were examined four to six times between the 15\(^{th}\) and 36\(^{th}\) week of pregnancy. At each visit a STIC volume was recorded and fetal biometry was performed. Follow-up was done by postpartum questionnaires.
Two imaging studies were performed that explore if the fetal heart valves can be examined morphologically using STIC. In chapter 2 we evaluated the morphology and area of the atrioventricular valves in normal fetuses and fetuses with cardiac defects using rendered views of the atrioventricular valves using STIC.

In chapter 3 we studied the feasibility of visualization of the morphology and area of the semilunar valves in normal fetuses and fetuses with cardiac defects using STIC.

In chapter 4 the echocardiographic feature ‘differential insertion of the atrioventricular valves’ (DIAVV) was addressed. This feature of the four-chamber view represents the more apical attachment of the tricuspid valve to the septum compared to the mitral valve. Reference values were developed using 4DUS with STIC. We explored if measurement of the DIAVV could differentiate between normal hearts and hearts with cardiac defects. Earlier developed reference ranges for the DIAVV differed widely from each other. Therefore, we performed an in-depth study of this specific region of the fetal heart (atrioventricular valves and crux of the heart) in chapter 5. We compared the findings of 4DUS to anatomical specimens. The fibrous skeleton and attachment of atrioventricular valves to the septum were studied in STIC volumes and histological sections of normal hearts and hearts with an AVSD and Down syndrome.

In chapter 6 the atrioventricular septum and atrioventricular valves were examined and measured in STIC volumes and histological sections of fetuses and infants with Down syndrome without AVSD, Down syndrome with AVSD and normal hearts.

In chapter 7 the clinical accuracy of STIC in the detailed prenatal diagnosis of CHD in a telemedicine setting is evaluated.

Finally, in the general discussion the current clinical value of 4DUS is evaluated. The future implications for clinical practice and research are discussed (chapter 8).

In Chapter 9 we summarize the results of the studies presented in this thesis in both English and Dutch.
REFERENCES


