SUMMARY

Congenital heart disease (CHD) represents the most common birth defect and is the leading cause of infant mortality if premature births are excluded. CHD affects approximately 6 to 8 per 1000 live-born children. Despite the high prevalence of CHD, these anomalies are the most commonly overlooked lesions in prenatal screening programs. A timely and accurate prenatal diagnosis provides the possibility of appropriate neonatal care, like planning of the place and moment of delivery. Ultrasound systems continue to improve and nowadays four-dimensional ultrasound (4DUS) imaging of the fetal heart is possible. This thesis investigates new developments in fetal echocardiography, especially 4DUS with spatiotemporal image correlation (STIC). STIC is an automated volume acquisition, recording one single 3D volume dataset, which allows the fetal heart to be viewed in three dimensions during one complete heart cycle. Storage of the volume provides the possibility of offline analysis. The method was introduced in fetal echocardiography with the prospect to increase detection rates of CHD. Various functions have been described in current literature. The examination of the cardiac morphology has, however, not been investigated before. This thesis explores if this highly specialized diagnostic tool proves to be clinically relevant in this aspect.

A large prospective study was developed to study several morphological items of the fetal heart. Healthy low-risk pregnant women visiting the VU University Medical Center for an appointment 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 15th and 36th week of pregnancy. At each visit a STIC volume was recorded and fetal biometry was performed. Follow-up was done by postpartum questionnaires.

Two STIC imaging studies were performed, and these explore if the fetal heart valves can be examined morphologically. 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. Sufficient quality was encountered in 82.5% of 355 STIC volumes of normal fetuses. Reference values for the area of the valves were developed. The tricuspid valve leaflets were visualized in 200 (68.3%) volumes and the mitral valve leaflets in 219 (74.7%) volumes. A rectangular valve opening is normal, which was visualized in about one third of the normal fetuses. Fifty fetuses with cardiac defects were examined. As expected, most heart defects with stenosis showed an area below the 5th percentile.

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. Visualization of
the valve opening succeeded in 96.1%, visualization of the leaflets in 52.6%. From 19 to 24 weeks gestational age the leaflets could be visualized best (72.1% normal hearts). In 58 STIC volumes of cardiac defects, visualization of the valve opening and valve leaflets was feasible in 97.4% and 43.1% respectively. In cardiac defects with stenosis, abnormal areas were found. With these studies we showed that prenatal examination of the morphology and area of the atrioventricular and semilunar valves using 4DUS with STIC is feasible.

The tricuspid valve is attached to the ventricular septum more apical than the mitral valve. If visualized with ultrasound, this is called differential insertion of the atrioventricular valves (DIAVV). This echocardiographic feature of the four-chamber view was studied in chapter 4. A linear insertion is present when both valves form a linear continuum and is suggested as a marker for atrioventricular septal defects (AVSDs). To increase the detection rate of CHD, reference values were developed for normal fetuses using 4DUS with STIC. We explored if measurement of the DIAVV could differentiate normal hearts from hearts with a cardiac defect. The DIAVV was measured in 70 fetuses with cardiac defects. The DIAVV of fetuses with double outlet right ventricle, truncus arteriosus, AVSDs, Ebstein’s anomaly and tetralogy of Fallot all differed from normal fetuses.

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), comparing findings with 4DUS to anatomical specimens. In chapter 5, the fibrous skeleton and the attachment of atrioventricular valves to the septum were studied in histological sections of 17 normal hearts and four hearts with an AVSD and Down syndrome (10+0 weeks GA to 3 days postpartum). In addition, STIC volumes of 10 normal hearts and eight hearts with an AVSD (13+6 to 35+5 weeks GA) were examined. It appeared that the distance between the valves is dependent on the plane in which the DIAVV is measured. Remarkably, normal hearts as well as hearts with an AVSD showed both a differential and linear insertion, dependent on the plane in which the four-chamber view is visualized. This might explain the differences in the earlier developed reference values. Measurement of the DIAVV is a promising tool; however, a well-defined measurement protocol should be followed to accomplish the correct plane and exact moment in the cardiac cycle.

In addition, the atrioventricular septum and atrioventricular valves in Down syndrome (DS) without AVSD (DS no-AVSD), DS with AVSD (DS AVSD) and normal hearts (controls) were examined. Congenital heart disease is present in 44 to 56% of fetuses with DS. There are, however, signs that hearts in DS without overt structural CHD, differ from the normal population. In chapter 6 the muscular ventricular septum, membranous part of the atrioventricular septum and atrioventricular valves were examined and measured in histological sections of 15 DS no-
AVSD, 8 DS AVSD and 34 control hearts (10 weeks GA to 3 days postnatally). The ventricular septum length was measured on ultrasound images (acquired from STIC volumes) of fetal hearts (6 DS AVSD, 9 controls, 19+4 to 32+2 weeks GA) and infant (10 DS no-AVSD, 10 DS AVSD, 10 controls, 1 day to 15 years) hearts. DS no-AVSD hearts have a larger membranous septum, a shorter ventricular septum and show dysplasia of the atrioventricular valves compared to normal hearts. These findings may indicate that a careful cardiac follow-up is warranted in these patients.

STIC proved its usefulness by giving insight in fetal anatomy in a research setting. Furthermore, STIC can be extremely useful for education. Training inexperienced sonographers to examine the fetal heart using STIC gives them the opportunity to get familiar with the anatomy of the fetal heart, the rendered views and the spatial relationships of the heart structures. Furthermore, offline analysis is helpful in multidisciplinary consultation and to obtain an opinion from an expert at a distance. In chapter 7 the clinical accuracy of STIC in the detailed prenatal diagnosis of CHD in a telemedicine setting is evaluated. Ten second-trimester STIC volumes (9 cardiac defects, 1 normal heart) were sent to three examiners in different tertiary care centers. They were asked to provide the diagnosis. The results were compared with neonatal echocardiography or postmortem findings (‘gold standard’). In two cases all examiners correctly diagnosed all details of the volume datasets. The best examiner reached perfect agreement in six cases and nearly perfect agreement in three. In a telemedicine setting using STIC volumes, fetal cardiac anomalies can be diagnosed correctly by an expert. However, details required for planning of postnatal care and adequate counseling were missed, even by an experienced sonographer. Therefore STIC is not accurate enough for exclusive use in clinical decision making regarding treatment, prognosis or termination of pregnancy.

In chapter 8, all the above findings of this thesis are discussed. An overall conclusion of this thesis is that 4D ultrasonographic imaging tools are of limited clinical importance and that well-established intra-cardiac measurements (DIAVV) lack good measurement protocols. A new measurement protocol for DIAVV is proposed. Abnormal DIAVV values are found in several congenital heart defects. The use of DIAVV as a screening tool, still remains to be investigated in a prospective manner, but this finding gives insight in abnormal cardiac developmental processes. STIC by telemedicine is a promising modality, although at this moment not accurate enough for exclusive use to decide treatment, prognosis or termination of pregnancy in clinical decision making. With the anticipated increasing use of real-time 4D probes in the future, together with the help of navigation techniques, the interpretation and understanding of rendered images can be valuable for the implementation of these new technologies.