CHAPTER 8
General Discussion
GENERAL DISCUSSION

The actual effects of ultrasound screening programs in pregnancy have always been challenging to study, due to the gradual and heterogeneous introduction of prenatal screening worldwide, improvements in neonatal care and the continuous technical developments. The standard anomaly scan (SAS) is, however, part of routine prenatal care in almost every developed country. It is known that the SAS is capable to detect a large variety of congenital malformations, ranging from severe malformations like anencephaly to subtle ventricular septal defects.

Congenital heart defects are the most common congenital defects in neonates, occurring in 6-8/1000 live births. One third of these (2-3/1000) are severe CHD, commonly defined as being potentially life threatening and requiring surgery in the first year of life. Severe CHD are the leading cause of non-infectious neonatal mortality in at term born neonates. Only 10% of CHD cases occur in pregnancies with identifiable risk factors, such as fetal extracardiac malformations. Therefore, it is impossible to select all pregnant women that are at ‘high risk’ for having a child with CHD and ultrasonographic screening is required for prenatal detection.

Infants with congenital heart defects (CHD) benefit from a prenatal diagnosis. Prenatal detection facilitates an accurate diagnosis without the rush and anxiety a life threatening circulatory condition of the newborn would create. Moreover, it provides time for additional prenatal ultrasonographical and genetic testing. In some cardiac diagnosis, the risk for an aneuploidy or genetic syndrome is substantial and these conditions do not only affect the prognosis of the child in general, but can also influence the results of cardiac surgery in a negative manner. Research shows that the long-term prognosis of the physical quality of life is very important for the parents and this should be included in the counselling.

All the information combined, prepares the parents for the time to come and provides a fundament to make a deliberate decision on continuation of the pregnancy. This decision is influenced by the kind of congenital defect(s), religion, family circumstances and life experiences. The process of understanding, accepting and decision making should be supported by the medical team and it is essential that parents have a freedom of choice.

Increasing evidence shows that a prenatal diagnosis can prevent mortality in several types of severe CHD, due to prompt and appropriate treatment of the neonate in a specialised care centre. This effect is probably most essential in transposition of the great arteries, because this specific heart defect is almost always isolated, and when treated in time, has a very favourable prognosis. Besides a reduction of the mortality, there are
indications that a prenatal diagnosis of severe CHD results in a more favourable long-term outcome in terms of morbidity in the first years of life. Current screening programs show disappointingly low prenatal detection rates, around 35-50%. Detailed data on detection rates stratified per diagnosis were lacking so far. The defined and uniform national introduction of the SAS for all pregnant women in the Netherlands in 2007 provided the unique opportunity to study the effect of the 20 weeks anomaly scan on the detection of heart defects, which was the primary aim of this thesis. Unlike most countries, in which ultrasound screening is not regulated and uniform, the program in the Netherlands was strictly regulated from the beginning onwards, with education and volume requisites for the ultrasonographers and a well-defined uniform scanning protocol.

The most important findings of this thesis are that the screening program in the Netherlands resulted in high detection rates for CHD (60% in general) in an unselected population in the Netherlands. A strong relation between the prenatal DR and the severity of the heart defect was present. The prenatal detection of CHD at the severe end of the spectrum (univentricular hearts) is above 90%. Yet, some defects like coarctation of the aorta remain difficult to detect in pregnancy. There is still room for improvement for conotruncal defects in particular (DR around 30-60%). The size of the cohort provided the opportunity to study the pregnancy outcome in sufficient detail. We found that fetal demise (3.6%) and preterm birth occur more frequently in isolated CHD pregnancies compared to the general, unselected population.

When a CHD is diagnosed prenatally and appears to be isolated (without any other structural anomalies) on the ultrasound, in 79% of the cases it was confirmed after birth. An aneuploidy was found in 11% and a genetic syndrome in 6% of the cases. Finally, when a CHD is suspected and the woman is referred for a fetal echocardiography in a tertiary care center, the diagnostic accuracy is high.

**FUTURE PERSPECTIVES**

**Implications for current screening program**

The detection rates for congenital heart defects of the current screening program in the Netherlands are relatively good. Albeit we found that approximately 40% of severe CHD are prenatally missed, and almost all univentricular and other complex heart defects are detected. These results are far better than other studies reporting on regional cohorts, in which detection rates do not exceed 40%. The studies described in this thesis did not aim to explore the underlying reasons for the screening performance of the SAS, but we hypothesize that the well-organized program...
can be held responsible for the good results. From the start in 2007 onwards, a national standardized scanning protocol, executed by uniform trained ultrasonographers, was the main principle of the program. Quality is maintained through bi-annual assessments of the scans and volume requirements. The degree of organisation, standardisation and defined prerequisites are substantially different from other countries, and must therefore contribute for a large part to the encountered result.

The results of these studies were collected through the assessment of several sources, like fetal databases, OR and catheterisation registries, emergency ward admission registries and post-mortem examination databases. This was a time consuming process and implicates a risk on missing data because of the partly retrospective approach. The monitoring of the national screening program through assessment of true-positive, false-negative and false positive cases is a very focussed way of reporting on test performance, and thus of the delivered quality of the individual health care workers. Therefore the reported figures in this thesis, which are currently not part of the quality monitoring, are essential, and need to be incorporated in the monitoring program. To achieve this, the database PERIDOS, which registers all prenatal SASs, should be enabled to link the screening results with the results of the subsequent diagnostic scans and the postnatal outcome up to the age of one. Findings after unexpected neonatal death should be incorporated in such registries. Following the example of Scandinavian countries all patients should be registered and traceable by their BSN number and mother and child should be linked to each other. Besides the monitoring of the full program, such a system would allow individual ultrasonographers to get informed about detected or missed anomalies, to directly learn from these cases. Such a registry also provides in the need for a long-term follow-up. The long term outcome, in terms of morbidity, quality of life and reproductive outcomes of infants with congenital malformations is a research subject that is still not elucidated in fetal medicine.

The current prenatal screening program is embedded in the national public health programs of our country. It started with the aim to detect neural tube defects for historical reasons. With the current available results, combined with results of other study groups in our country, the objective of the SAS should be changed into the prenatal detection of congenital defects in general. Preferably the screening should be performed around 19 weeks’ gestation, in order to allow reasonable time for additional diagnostics and counselling the parents, since in the Netherlands the law allows to terminate pregnancy up to 24 completed weeks’ gestation. Especially since the possibilities of genetic testing will evolve, which currently takes several weeks to achieve a result.
As the prenatal detection of CHD still carries a vast amount of false negatives, combined with the fact that we encountered a strong relationship between detection rates and the severity of the heart defect, we believe that the detection rates of heart defects would be a very suitable quality indicator of the SAS. The high prevalence of heart defects makes it furthermore a feasible quality indicator, with the opportunity of a relatively fast identification of deviations in quality.

In the era of Non-Invasive Prenatal Testing, discussion is raised whether the nuchal translucency screening at 12-13 weeks’ gestation should remain to identify cases at risk for heart defects. The reported incidence of CHD amongst fetuses with an NT >99th percentile is, however, only 6-7% \(^{29}\), and a relationship between increased nuchal translucency and the severity of the cardiac defect is absent. Considering the screening performance of the SAS, the nuchal translucency measurement as a screening tool to identify cardiac defects cannot be upheld, especially if the costs of such a program are taken into consideration.

**Scope for further research**

The detection rate of conotruncal anomalies needs further improvement, especially because these infants may benefit most from a prenatal diagnosis. As a start, the addition of the three vessel view, \(^{30}\) Incorporating as an obligatory item in the Dutch screening protocol since 2012, is expected to increase the detection rates of conotruncal defects further. \(^{31}\) The effect of training of sonographers is only sparsely studied, but increased detection rates after training were reported. \(^{32}\) Further research could focus on repetitive training, the effect of on-line availability of image libraries and the use of modern teaching tools like apps or web-based courses and platforms. Furthermore it is unclear if tele-consulting of a fetal medicine specialist, without actual referral of the patient, could help in selecting cases that need expert level real-time echocardiography. Finally, it is unknown what influence personal characteristics and beliefs of the ultrasonographers have on their performance. What makes them doubt and what makes them decide to refer? The importance of these factors seem to play a role, as is proven in breast and lung cancer screening, \(^{33}\) but it is unknown if these factors can be controlled and guided in obstetric ultrasound.

Besides research to study instruments that improve the screening quality, more knowledge is needed about long-term outcome of children with congenital heart defects. Counselling of future parents that are faced with a prenatal diagnosis is hampered by the lack of availability of large series that describe what the outcome is in their specific situation. The available literature on long-term outcome usually starts at the OR table, which is essentially different from cases that are identified at 20 weeks of gestation. The positive effect of a prenatal diagnosis on the morbidity, through the
prevention of asphyxia and circulatory collapse by the timely started measures after birth, should be investigated more extensively, including long-term neurological follow up. In several countries, as well as in our study region, the value of postnatal saturation measurement in screening for CHD is currently evaluated. With the current and expected future improvements in prenatal detection of CHD, postnatal screening will probably be superfluous. On the other hand, postnatal saturation measurement can have a value in regions with a lower quality of prenatal screening, and for other indications such as sepsis or persistent pulmonary hypertension. Finally, the possibilities of genetic testing in pregnancy are increasing rapidly. With the developments in non-invasive prenatal testing, a future scenario could be that a test with panels of gene expressions associated with CHD become available for women early in pregnancy or even before pregnancy. Future research will probably demonstrate what the implications will be for the outcome of the pregnancy and the morbidity of the unborn child.

In conclusion, this thesis provides an overview of prenatal screening for fetal heart defect in the current era. The goal should be further improvement of prenatal detection rates of CHD and the reduction of mortality and morbidity of the affected infants.
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