Chapter 9

Summary, general discussion and future recommendations
SUMMARY

This thesis presents the results of a number of studies on the efficacy of the 20-week scan in detecting severe congenital anomalies. In chapter 1 the history and organization of prenatal screening in the Netherlands is described. A license for prenatal ultrasound screening was granted under the Dutch Population Screening Act in 2007, which was relatively late compared to the neighboring European countries. From that moment on, first trimester screening for chromosomal anomalies and second trimester screening for congenital anomalies, with the focus on neural tube defects, became available for all pregnant women. At the same time uniform educational and quality requirements as well as protocols were introduced.

In chapter 2 results of a retrospective study on the prenatal detection of open spina bifida during the period 2003 – 2011 are described. During the four years after the 20-scan was introduced (2008 – 2011), diagnosis of open spina bifida before 24 weeks’ gestation increased significantly compared to the four-year period before (2003 – 2006): 88% vs. 43%. Most cases of open spina bifida are diagnosed after visualization of a lemon-shaped axial view of the skull or a banana-shaped cerebellum. Despite the increased prenatal detection rate, the number of children born alive with open spina bifida did not change significantly. We concluded that pregnancies affected by open spina bifida that were previously destined to end in perinatal loss were terminated whilst pregnancies with a less severe prognosis were frequently continued.

Anencephaly is the most severe form of neural tube defect with high prenatal and perinatal mortality. The prenatal detection rate of anencephaly cases is reported in chapter 3. This study showed that the majority of the anencephaly cases are visualized prior to the 20-week scan: in the period 2008 – 2011 69% of the anencephaly cases were diagnosed before 18 weeks’ gestation. Factors determining successful early diagnosis were competence level of the sonographers, with a significantly higher detection rate when scans were performed by a sonographer licensed by the Fetal Medicine Foundation (FMF) for nuchal translucency measurement (p = 0.001), and gestational age at or beyond 11 weeks of gestation (p = 0.024).

In chapter 4 the prenatal detection during the period 2009 – 2013 of two abdominal wall defects (exomphalos and gastroschisis) are presented. As is the case with anencephaly cases, abdominal wall defects are also amenable to detection in early gestation. Overall the majority (74%) of the exomphalos and almost half (48%) of the gastroschisis cases are diagnosed before the 20-week scan. In the group with exomphalos, the number of cases with additional anomalies is high (84%) and more than 50% has an underlying genetic cause. In the exomphalos group the pregnancy termination rate significantly increased from 35% prior to 2007 to 63% in the period after 2007, whilst in the gastroschisis group this rate remained low and stable. The majority of the gastroschisis cases do result in a live birth and the mortality rate in this group is low.
Results on the study with regards to the prenatal detection of cleft lip cases with or without cleft palate ("CL±P"; isolated cleft palate cases not included) during the years 2008 – 2012 are described in chapter 5. Approximately 80% of the CL±P cases are visualized at the time of the 20-week scan, making the 20-week scan an important tool in the prenatal diagnosis of CL±P. CL±P is rarely diagnosed during the first trimester. The number of cases that were detected before 24 weeks’ gestation increased during the study period, while the rate of termination of pregnancy did not change significantly. This illustrates that prenatal detection, contrary to dreaded consequences, is not necessarily associated with an increase of the termination rate. During the study CL±P was an isolated finding in 66% of the cases. An abnormal karyotype was found in 21% of the CL±P cases. In 5% of the cases where a cleft lip seemed isolated during the 18-23 week anomaly scan, postnatal array-CGH analysis revealed an abnormal karyotype and in 50% of these cases major additional anomalies were present. Based on the facial cleft data it was examined to what extend structural anomalies are recorded in the Netherlands Perinatal Registry. In the case of cleft lip, 37% of the cases were not recorded. This indicates that currently data from the Netherlands Perinatal Registry cannot be relied on to monitor the prevalence of birth defects.

Congenital heart defects (CHD) are the most common type of congenital anomaly. In chapter 6 the results of a study on the diagnostic accuracy of CHDs are presented. This study was done in cooperation with the Academic Center of Utrecht and included the years 2008 – 2013. More than 60% of the cases included in this study were diagnosed prenatally. Overall a correct or a minor discrepancy in the prenatal diagnosis occurred in 81.1% of the cases with rates ranging between 45.5% and 97.3%, depending on the type of CHD involved. In 5.5% of the cases, postnatal findings revealed a different type of CHD that was of comparable severity. In 13.4% of the cases the type and severity of CHD did not match the prenatal findings. Prenatal diagnosis as well as accuracy of the prenatal diagnosis depends on the type of CHD involved and the presence of additional anomalies. In the group with major additional anomalies the prenatal detection rate was highest, but diagnosis was more accurate in the group with isolated CHD. The mortality rate is highest in the group diagnosed prenatally, which can be explained by the higher prenatal detection rate of the more severe types of CHD. Accuracy of prenatal diagnosis is especially important in reducing morbidity of children with a CHD.

During the 20 week scan soft markers can be detected. Soft markers are anatomical variants not pathological in itself, but occurring more frequently in abnormal fetuses (2-4). Examples of soft markers are a single umbilical artery (SUA), echogenic bowel (EB) and ventriculomegaly (VM). Results of a systematic review on the relationship of an isolated single umbilical artery with fetal growth, aneuploidy and perinatal mortality is described in chapter 7. Out of 449 articles, 7 studies were eligible for inclusion in the study. No statistically significant evidence that fetuses with isolated SUA have an increased risk of aneuploidy was found. Fetuses with
an apparently isolated SUA potentially have an increased risk of impaired fetal growth and perinatal mortality. However, even in meta-analysis the results were not statistically significant and large studies showed smaller differences than small studies, suggesting publication bias. As part of the study, prospective data on the prevalence and outcome of cases with an isolated single umbilical artery was collected and the results are described in chapter 8.

Uptake of the 20-week scan and the number of referrals for an advanced diagnostic ultrasound scan, based on prospectively collected data of pregnant women residing in the North of the Netherlands (provinces Groningen, Friesland and Drenthe), is described in chapter 8. Furthermore, the prevalence and outcome for specific groups of soft markers as well as the detection rate for specific structural congenital anomalies was examined. Overall uptake of the 20-week scan was 93%. During the study 4.3% cases were referred for an advanced diagnostic scan within two weeks after a 20-week scan. A third of the cases were referred because of a suspected anomaly, while a third was referred because of the presence of one or more soft markers. Of the women that were referred, a third could be reassured as no abnormal findings were found during the subsequent advanced diagnostic scan. The prevalence of an isolated SUA was comparable to the rate reported in the literature whilst the prevalences of isolated EB and VM were lower than expected, most likely due to underreporting. Based on the literature and findings of our study, it is recommended that the current policy of referring for an advanced diagnostic ultrasound scan in case of an isolated EB should be reevaluated and the current management protocol should include tighter criteria for referrals.

More than sixty percent of the selected severe congenital anomalies were diagnosed at the time of the 20-week scan. This overall prenatal detection rate of increases to almost 80% taking into account only those cases not diagnosed during the first trimester. Congenital heart defects and cleft lip are most often missed during the 20-week scan. If sonographers who perform dating scans are trained in assessment of the fetal anatomy, the majority of severe congenital anomalies can be diagnosed prior to the 20-week scan. However, it remains important to stress that some anomalies are not amenable for early diagnosis since they develop later in pregnancy (5).

**GENERAL DISCUSSION AND FUTURE RECOMMENDATIONS**

**Prenatal detection of neural tube defects**

In 2007 a prenatal screening program was introduced in the Netherlands, consisting of first trimester screening (the combined test) for chromosomal anomalies and second trimester screening (the 20-week scan) for structural anomalies. Our study is the first reporting on the efficacy of the 20-week scan in diagnosing serious congenital anomalies after the implementation of this national screening program in the Netherlands. The high uptake shows that the 20-week scan is valued by women. Furthermore, our study shows that second-
trimester screening is effective in detecting structural anomalies. The main focus of the 20-week scan in the Netherlands is the detection of neural tube defects. Results of this study show that the introduction of the national prenatal screening program in 2007 has resulted in almost a 100% prenatal detection rate of neural tube defects. It is important to note that mainly open spina bifida is detected at the 20-weeks scan. In contrast, anencephaly, a more serious neural tube defect, is often detected in the first trimester at the dating scan or at the scan performed as part of the combined test. Our study shows that an important prerequisite for early detection of anencephaly is that the first trimester scan is not performed before 11 weeks of gestation and that the sonographer is trained in first trimester fetal investigation and in recognizing the defect.

Uptake of second trimester screening
More than 90% of the women in the North of the Netherlands choose for second trimester screening, which is more than three times the number of women that choose first trimester screening (6-10). This difference in uptake may be explained by differences in costs and purpose: only women aged 36 and older or with a medical indication are reimbursed for first trimester screening, while second trimester screening is included in the Basic Health Insurance package. (Note: as of January 1, 2015 only women with a medical indication are reimbursed for first trimester screening.) The focus of first trimester screening is the detection of chromosomal anomalies, while second trimester screening is aimed at the detection of neural tube defects and other major structural anomalies. However, our study shows that serious structural anomalies like anencephaly and abdominal wall defects are also detected in the first trimester.

Early diagnosis of structural anomalies
The main focus of this study was the prenatal detection of a selected number of serious structural anomalies during the 20-week scan. Results of our study showed that a certain percentage of cases are detected prior to the 20-week scan. In addition, results indicated that early detection of structural anomalies is dependent on the timing of the scan (it should not take place before 11 weeks’ gestation) as well as the level of training and experience of the sonographer. Sonographers performing nuchal translucency measurements are also trained in assessing early fetal anatomy. Many of these accredited sonographers also perform dating scans (ideally between 10 and 13 weeks’ gestation), which is the preferred method of establishing gestational age according to a guideline of 2010 (11). In contrast, not all sonographers performing the dating scan are trained to measure nuchal translucency and/or to assess the fetal anatomy. Many sonographers working in extra-mural practices also offer to their clients non-medical “scans for fun”, for instance for fetal sexing at around 16 weeks’ gestation, which are not subject to quality assessment or standardization for both technical...
skills or equipment used. This means that although most women currently have at least one scan before the 20-week scan (in reality they have on average 2), there is unequal access with regards to the quality of the early scans.

Given the results of our study it is recommended that information about the dating scan as well as the combined test is updated to include the true “coverage” of the investigation. Based on the Dutch Medical Treatment Act (WGBO), a women has the right ‘not to know’ which means that before providing information on medical conditions and investigations parents (in this case) should be able to decline information on items they not want to be informed about (such as screening for chromosomal anomalies or other incurable diseases in the fetus). Moreover, information must be provided in a language which is accessible to the vast majority of women and can be understood correctly. In the information brochure on the first trimester combined test the test characteristics are explained. It is also explained that “an excessive nuchal edema may also indicate other chromosomal and physical disorders in children, such as heart defects. If the test results show a nuchal edema of 3.5 mm or more, you will automatically be offered an extended additional ultrasound examination”. (12) Before the nuchal translucency measurement or dating scan parents should be made aware about the type of structural anomalies that can be found during a first trimester scan. Based on the result of this thesis, parents should be informed that almost all cases of anencephaly and most abdominal wall defects can already be visualized in the first trimester, together with other severe types of structural anomalies (which did not fall within the scope of this thesis).

Prenatal diagnosis in relation to pregnancy outcome

Overall, 62% of the structural anomalies examined in this thesis were detected at the 20-week scan. The number of pregnancy terminations for open spina bifida, anencephaly, congenital heart defect, exomphalos and gastrochisis, all defects associated with a high level of mortality and/or morbidity (13-19), increased together with the improvement in prenatal detection. This finding is in line with a study by Stoll et al., who concluded that the introduction of routine prenatal screening and diagnosis results in a significant fall in the birth prevalence of children with congenital anomalies, varying according to the type of congenital anomaly (20). In our study we also noted that in the group with open spina bifida an increase in pregnancy terminations was accompanied by a decrease in the number of infants that died after birth (21). This was not the case for exomphalos, where an increased prenatal detection rate resulted in significantly fewer live births, without significant changes in the perinatal death rate in the live born infants. Although improved prenatal diagnosis of severe structural anomalies affects the number of pregnancy terminations, the overall number of terminations (for social and medical reasons) remained stable since the year 2000 and even showed a slightly declining trend since 2008. In fact, in the period 2012-2014 the percentage of pregnancy terminations following prenatal diagnosis of anomalies was less
than 5% (22). With regards to congenital heart defects, the mortality rate was higher in the
group of live born children diagnosed prenatally compared to the group that was diagnosed
postnatally. This finding can be explained by the fact that especially the more severe types of
CHD are detected prenatally and that diagnosis does not necessarily leads to termination of
pregnancy (23).

**Peridos**

Data available from the national screening database Peridos cannot yet be used to measure
the effect of the prenatal screening program on timing of diagnosis of congenital anomalies
and impact on pregnancy outcome. Although Peridos has been specifically developed in
order to “potentially improve the primary process of prenatal screening” (24), it was not until
2012 (5 years after the screening program had been introduced!) that indicators addressing
quantitative issues on uptake after counseling and number of examinations became available.
The main reasons for incomplete registration in the first years were that not all counselors
and sonographers uploaded their data, as well as problems of missing data such as social
security numbers. These issues were addressed and in the course of the years additional
data was added: per January 1, 2014 advanced diagnostic scans and cytogenetic findings
were added. Currently, pregnancy outcome (type of birth; intrauterine death, termination
of pregnancy, live birth, and the presence or absence of congenital anomalies) is not fully
registered. During our study we found that the biggest challenge in collecting outcome data
is that retrieval of missing data is often complicated by the lack of identifying information or
because women move out of a specific region and/or change their caregiver. The strength of
a database like Peridos is that women are identified based on their own unique social security
number, limiting the number of cases without follow up. In order for Peridos to be able to
provide useful information, registration at the source has to be improved: the social security
number should always be registered. In order to facilitate future studies on the prenatal
detection of structural anomalies and improve quality and reliability, fetal anomalies should
always be registered at birth in a uniform way.

**Isolated soft markers**

The detection of soft markers (or sonomarkers) causes considerable short-term anxiety (25).
Isolated soft markers therefore pose a specific challenge, since informing parents about the
presence of soft markers found during a routine ultrasound examination may cause more
harm than good (3). An isolated Single Umbilical Artery ("SUA") and Echogenic Bowl ("EB")
have a very low association with structural or chromosomal anomalies (26,27). Based on the
results described in chapter 8 it is recommended that the policy of referring for an advanced
diagnostic ultrasound scan after the detection of an isolated EB should be reevaluated. It is
clear that more studies are necessary to reach a better distinction between the EB cases that
have a favorable prognosis and those that definitely need to be referred for an advanced diagnostic scan and additional investigation. This would save unnecessary costs and anxiety. Referral for an advanced diagnostic scan in the case of isolated Ventriculomegaly (“VM”) measuring at least 11 mm and an isolated SUA seems warranted, whereas genetic testing should only be offered in case of isolated VM. In order to monitor the prevalence and implications of isolated soft markers, the presence (or absence!) of isolated soft markers as well as pregnancy outcome has to be registered more accurately. In case of VM, we suggest that future research focusses on the relationship between lateral ventricles measurement, corrected by fetal gender and biparietal diameter. This data combined with outcome details may lead to a better definition of “true” ventriculomegaly cases and reduce the number of false positive diagnosis.

FUTURE DEVELOPMENTS

Although a gestational age between 18 and 22 weeks is considered to be the optimal time for a full structural assessment of the fetal anomaly (5), at least for some anomalies detection in the first trimester is feasible. Preliminary results from a still unpublished study from our group examining the yield of the 12-13 week scan in detecting congenital anomalies show that almost half of the prenatally detected structural anomalies can be diagnosed at this early scan, confirming the findings of this thesis. The reported false positive diagnosis rate (0.02%) is lower compared to the 20-weeks scan (0.6%). Recent developments however might impact the exposure of sonographers to nuchal translucency measurement and assessment of the fetal anatomy during the first trimester, with the risk of declining experience. In April 2014 the TRIDENT study was started in the Netherlands to evaluate the use of the Non Invasive Prenatal Test (NIPT) as an alternative to chorionic villus sampling or amniocentesis (28). The test can be performed from 10 weeks onwards and screens for aneuploidies by searching cell-free fetal DNA in maternal blood and does not include an ultrasound scan, besides for dating. The NIPT specifically targets trisomy 13, 18 and 21, which have a prevalence of 2, 5 and 22 per 10,000 births respectively (29,30). This means that the NIPT is aimed at approximately 10% of the 2-3% of the children born with a congenital anomaly. In July 2016 the Health Council recommended that a license within the Screening Population Act should be granted to use NIPT as the primary test in prenatal screening for trisomy 21, 13 and 18 (31). As per April 2017 a pregnant women has the option to choose either for the combined test or NIPT and the cost for both tests are equal (€ 168 and € 175 respectively). If the NIPT will replace the combined test, it can be expected that severe congenital anomalies will more often elude first trimester detection to be diagnosed only at the 20-week scan. The advantage of diagnosis before the 20-week scan is that earlier diagnosis provides more time for additional diagnostic testing. This provides more time for follow-up scans and gives parents more time to understand the
information they receive and to consider their options. Should they choose to terminate the pregnancy, the pregnancy is less advanced compared to cases where an anomaly is found at the 20-week scan. The legal term of 24 weeks’ gestation for termination of pregnancy in the Netherlands provides parents with little time to make such a major decision. Termination of pregnancy in case of a congenital anomaly affects parents deeply; it causes posttraumatic stress and depressive feelings (32). Advanced gestational age at the time of the termination is associated with more psychological distress (33).

We recommend that every pregnant woman should have the option for a detailed assessment of the fetal anatomy during the first trimester, in addition to the 20-week scan. For this purpose, after an early vitality scan at 8-10 weeks, a proper dating scan might be postponed to after 12 weeks, since a physiological bowel herniation within the umbilical cord (which may mimic an exomphalos) might still be present before this time (34). Furthermore, ossification of the skull normally occurs at or after 11 weeks of gestation, making the diagnosis of anencephaly less reliable before 11 weeks’ gestation (15). It is advisable that this scan is performed by sonographers who have undergone a formal training in evaluating first trimester anatomy and who are subject to regular quality controls.

Owing to the continuous technical improvement of medical imaging we also suggest that the 20 weeks scan should be scheduled at 18 weeks rather than 20 weeks’ gestation, in order to reduce the number of cases where the decision to terminate the pregnancy due to severe structural anomalies has to be taken under pressure.
REFERENCES


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