# PRENATAL ULTRASOUND SCREENING FOR CONGENITAL HEART DISEASE; AN EPIDEMIOLOGIC PERSPECTIVE

E. Buskens

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# PRENATAL ULTRASOUND SCREENING FOR CONGENITAL HEART DISEASE; AN EPIDEMIOLOGIC PERSPECTIVE

PRENATAAL ULTRAGELUIDSONDERZOEK NAAR AANGEBOREN HARTAFWIJKINGEN; EEN EPIDEMIOLOGISCH PERSPECTIEF

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Just because man no longer understands his place in the universe, don't let him assume all God's creatures have become equally confused and trivial.

*Bill Tarrant: Hey Pup, Fetch It Up!*

*Voor Sylvia*

*Voor mijn ouders*

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Errata

page 124, bottom line; 31 should be 32

page 125, line 6 from bottom; 31 should be 32

page 126, title of table 1; 70 should be 67

page 131, line 5 from bottom; not have been

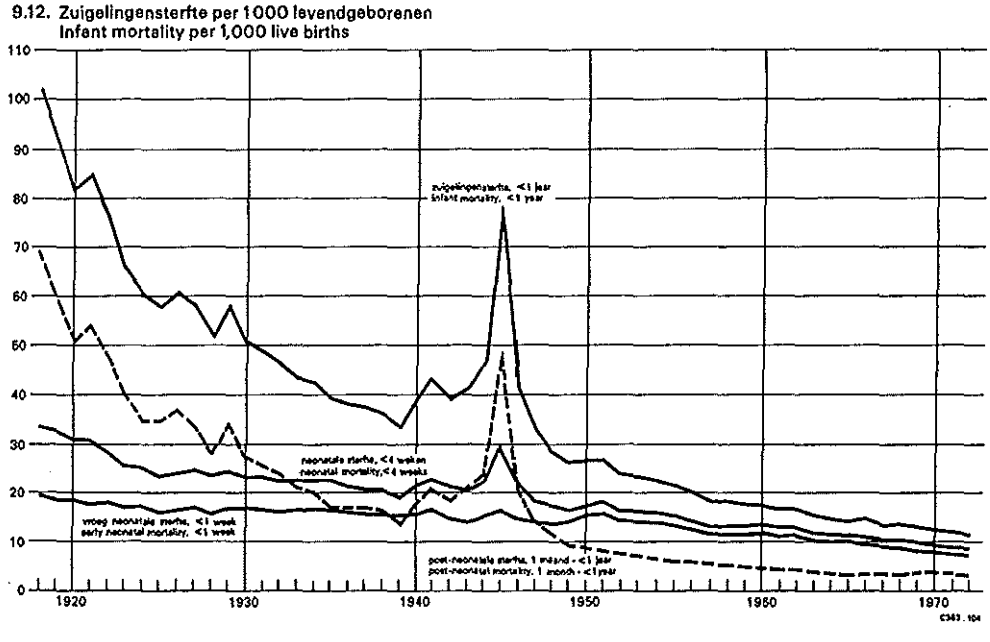
# CHAPTER 1

# INTRODUCTION

## INTRODUCTION

In Western societies infant mortality has decreased substantially this century. Improved hygiene and water supply, improved nutrition, vaccination and availability of treatment for many infectious diseases have contributed highly to this evolution. With improved hygiene and vaccination schemes the spread of infectious agents is prevented. Generally improved health, nutritional status, again vaccination and availability of antibiotics avert a serious course of illness once the child is infected. In particular, the success of primary prevention has been tremendous as demonstrated by the sizable decrease in infant mortality during this century (figure 1) (1).

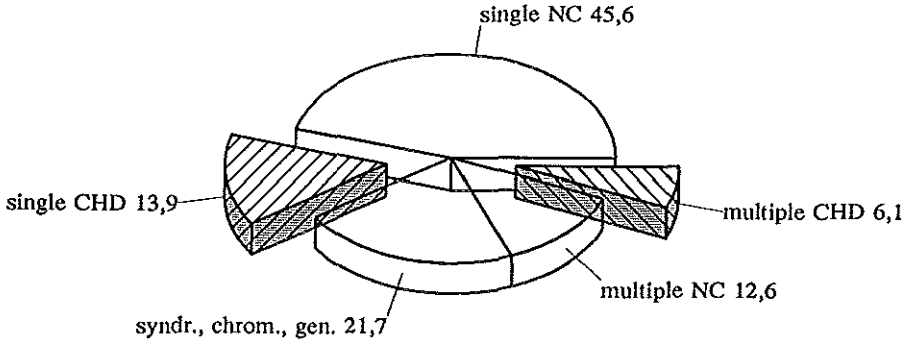
Figure 1




In contrast, no obvious trends in occurrence of congenital malformations have appeared. The birth of a malformed infant has a great impact. Parents, society and science feel a strong need to provide an explanation for such an event. However, causes of congenital

malformations remain as yet unknown in the majority of cases, precluding large scale primary prevention. Consequently, despite increased options and improved possibilities for treatment of these cases, the relative contribution of congenital malformations to infant mortality has increased (2). As illustrated in figure 2, congenital heart disease constitutes a major part of congenital malformations and, accordingly, has a sizeable impact on children's health (3).

Figure 2 Proportional distribution of congenital anomalies




NC = non-cardiac, CHD = congenital heart disease, syndr. = syndromes, chrom. = chromosomal disorders, gen. = genetic disorders.

A concise review of current knowledge and research on the aetiology of congenital heart disease discloses that, at present, information on causal factors for the occurrence of congenital heart disease is limited. In fact, an accurate estimate of the number of cases of congenital heart disease that occur in the general population seems lacking at present also. Estimates of the prevalence of congenital heart disease appear to vary widely across studies. Seemingly, an accurate estimate of the size of the problem can not be easily

obtained. Moreover, the (birth) prevalence of congenital heart disease does not provide any information on the impact and implications cardiovascular anomalies may have prenatally. Accordingly, the various congenital malformations of the cardiovascular system need further assessment with regard to possible consequences for the neonate as well as for the fetus. In this respect, possibilities for prenatal detection and subsequent implications are of importance also.

Nevertheless, the potential for prenatal detection of congenital heart disease during routine screening and its supposed potential to improve the status for neonates and parents has been enthusiastically described, and indeed been introduced in several countries. Adoption of such a policy has also been suggested in the Netherlands. It appeared, however, that the efficacy of the proposed screening test had not been firmly established. Still, in view of currently impossible primary prevention, the possibility of secondary prevention following a prenatal screening test for congenital heart disease merits additional study. Also, a decision to set up a routine prenatal ultrasound screening program should only be based on reliable research data. Consequently, a prospective cohort study on 6,922 fetuses scanned was designed and conducted to assess the performance of prenatal ultrasound screening as a method of early detection of congenital abnormalities.

Irrespective of the efficacy of routine screening, once a fetal anomaly is suspected referral for additional examination is needed for verification. These cases then are part of a so-called high risk population. In contrast to a policy of routine screening offered to an entire population, a high risk approach implies that only pregnancies or women deemed at risk for fetal anomalies are offered (extensive) structural ultrasound examination. Clearly, suspicious findings during previous examination justify extensive evaluation. However, as knowledge on causes and risk factors for the (re)occurrence of congenital heart disease is constantly expanding, indications for extensive examination, particularly anamnestic risk factors, may require updating.

Subsequently, combining the information on routine screening and subsequent extensive examination once an anomaly is suspected, may provide a quantitative estimate of the impact of current clinical practice of prenatal ultrasound screening in an unselected or low-risk population. A decision analysis model designed to reflect the options and chances future parents and clinicians face, allows such a comprehensive evaluation. Finally, all

data and conclusions warrant overall inference and possibly even have implications for a public health policy.

The magnitude of the problem and a common interest in occurrence and prevention of diseases of the cardiovascular system engendered a successful collaboration of the Division of Paediatric Cardiology, Department of Paediatrics, the Department of Epidemiology & Biostatistics and the Division of Prenatal Diagnosis, Department of Obstetrics and Gynaecology of Erasmus University Medical School Rotterdam. With the specific input of these disciplines the efficacy of routine fetal ultrasound screening and additional aspects of congenital heart disease have been evaluated and are reviewed in the research described in this thesis.

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# CHAPTER 2

# ASPECTS OF THE AETIOLOGY OF CONGENITAL HEART DISEASE

## 2.1 CAUSES AND RISKS OF CONGENITAL HEART DISEASE

The evolution of an individual human being from a single fertilised ovum is a complicated process of which we are largely ignorant to date. A failure of this development in utero has always had great impact on the parents and on the community in general. Reactions of fear, mourning and guilt can be expected if a family is confronted with affected offspring. Explanations for the occurrence of congenital malformations have been sought in various domains and have engendered many theories on the causes of congenital malformations. However, despite a long history of attention and research relatively little is known. This is also true for congenital heart disease.

Recent reports on congenital cardiac anomalies still cite that approximately 80 to 90% of the cases encountered at birth have a multifactorial origin (1,2). This implies that for the majority no single causative mechanism or agent is known. Rather, a general interaction model of genetic susceptibility and environmental factors is proposed based on empirical (re)occurrence data (3). Ergo, the risk for siblings if one case has occurred has been estimated to be in the range of 2 to 4 %. In the event of two affected siblings this risk increases to 6 to 12 %. In case one of the parents is affected there is also an increased risk for their offspring. Moreover, the sex of the affected parent appears to influence the risk. The paternal risk is comparable to that of one affected sibling, whereas the maternal risk has a range approximately equal to that of two affected siblings (4). This disparity in risk is largely unexplained. It may be that in fact what is currently called multifactorial, including specific maternal teratogens, actually constitutes an aetiologically heterogeneous group. For instance, it may be that affected males are less likely to start a relation as compared to affected females and subsequently may not reproduce. Alternatively, a monogenic disorder with imprinting, that is parental sex affects the expression of genetic material, can be considered. Lately, inheritance of cytoplasmatic or mitochondrial DNA, which is derived exclusively from maternal cells, has been added as yet another possibility. Thorough examination of extended pedigrees may enable distinction of specific patterns of inheritance. Furthermore, a striking resemblance of the type of anomalies or an identical embryological origin has been reported in over 50% of the recurring cases, which may point out a common pathogenetic process running in families (2,5). The

estimates of recurrence rates mentioned above are currently used in counselling of parents for the risk they carry for bearing affected offspring in the future.

The efforts of researchers up until now have indicated that 10 to 20 % of cases may be associated with specific factors that have been identified. Approximately 6 to 10% is brought about directly by a chromosomal anomaly. Down's syndrome, for instance, has a strong association with cardiovascular anomalies; approximately 40 % of trisomy 21 cases are affected (6). Similar associations have been reported in other structural or numerical disorders of autosomal or sex chromosomes, with percentages of affected individuals ranging from 100 % for trisomy 18 to less than 25% for some chromosomal deletions like cri-du-chat syndrome, del(5p) (6,7). The type of anomalies encountered in the various syndromes is not as similar in the anomalies determined by chromosomal anomalies as they are in those determined by multifactorial origin. However, clustering of certain malformations in a particular syndrome has been described and may be an indication of a common embryologic origin or, perhaps more important, point at the chromosome(s) involved in the development of the organ(-structures).

A further 5 to 10% of the cardiovascular malformations can be attributed to a genetic (Mendelian) disorder (1,2). A sizeable number of syndromes has been described with specific patterns of inheritance. Autosomal dominant inheritance has a 50% recurrence risk for the offspring of an affected parent. Autosomal recessive inheritance bears a 25% recurrence risk for siblings of affected individuals and sex-linked inheritance a 50% recurrence risk for male offspring of a carrier female.

About 1% of the cardiovascular malformations can be attributed to maternal diseases (8). Maternal type I diabetes, which carries an estimated 2% risk of affected offspring, and maternal phenyl ketonuria, which presents an increased risk for the fetus if not treated adequately, are well known. In addition, systemic lupus erythematosus, which may carry a risk for structural malformations besides conduction disorders, should be considered (Frohn-Mulder, in print).

Finally, approximately 1% is caused by teratogen exposure (8,9). Excessive maternal alcohol consumption may carry a risk of almost 1 in 3 for congenital heart disease and other disorders. Maternal anticonvulsants use also increases the risk for the fetus to 2 to 3 %. Use of lithium and retinoic acid (vitamin A) increase the risk too. The importance of

female sex-hormones and narcotics like cocaine, heroin etc. has not yet been established completely. Nevertheless, it is obvious that drug use during pregnancy should be avoided because of potential teratogenic effects.

## 2.2 RESEARCH ON THE AETIOLOGY OF CONGENITAL HEART DISEASE

Traditionally, in embryology observations derived from autopsy series on embryos of human origin and infants were accumulated either after normal or abnormal development. Subsequently theoretical models on the pathogenesis of cardiovascular malformations were deduced. However, several drawbacks of this type of research appear. Though apparently readily available for examination, it is difficult to gather cases as only a limited number of parents approve of having an autopsy performed on the abortion material or on their deceased baby. Furthermore, a fetus may be otherwise lost during abortion. Case ascertainment will not be complete and, subsequently, as a number of cases will not be identified a genuine occurrence rate can not be established. Therefore, the impact of possible pathogenetic factors may be (considerably) underestimated. In addition, as the cases are provided by occasional abortions and not systematically gathered during follow-up of high risk pregnancies or exposed pregnancies, actual pathogenesis can not be studied.

A research model to evaluate possible teratogenic agents and pathogenetic mechanisms is required to enhance the yield of embryology. Despite potential differences between human embryology and pathogenesis, chick embryos, among other species, are frequently used and appear to be a satisfactory animal model (10-12). Cardiac outflow tract defects comparable to those seen in DiGeorge and Sphrintzen syndrome have been shown to occur in chick embryos after ablation of parts of the neural crest (10) and administration of all-trans retinoic acid (12).

A further field of research in progress on the aetiology of congenital heart disease are genetics and molecular biology. Recently chromosome 22 has been identified as the chromosome involved in DiGeorge syndrome, Sphrintzen syndrome and possibly other types of (familial) malformations of the cardiac outflow-tracts (13). Small deletions in genes located on chromosome 22 coding for the development of structures

embryologically derived from the pharyngeal arches may cause a wide variety of phenotypes ranging from minor anomalies to full blown syndromes. Future research in genetics and molecular biology applying cytogenetic and DNA techniques may add a great deal to the knowledge on the aetiology of (familial) congenital heart disease and other malformations.

The above findings originating from two distinct areas of research, both showing a causal relation with a common defect, may be explained by interference of various pathogenetic mechanisms with a common stage of embryogenesis. Apparently, normal development of the cardiovascular system involves many interactive steps that all have to be taken to result in a normal heart. Conversely, a presumption that several or possibly many pathogenetic mechanisms may cause identical malformations should be accepted. The link with the timing of embryogenesis is evident. In order for an incident to act on the development of an organ or structure it would have to occur at the time of interest. For congenital heart disease a gestational age of 14 to 60 days has been proposed as the most vulnerable period (8).

Genetics, molecular biology and embryology focus on the identification of a particular pathogenetic mechanism in individuals deemed to be at risk for having affected offspring. Subsequently, adequate counselling and diagnostic tests may be performed.

Epidemiology, on the other hand, may identify populations at risk. Especially, widespread exposure to "low-level" risk factors, which must have a pathogenetic basis and thus may be considered teratogens, can be expected to have a major impact on the occurrence of congenital malformations. A small increase in risk of affected progeny may lead to a significant increase of cases if the exposure-rate is high. A major problem in this type of research will be ascertainment of the exposure and of the cases (8). First of all it may be difficult to assess the exposure of cases to an agent of interest. Second, finding control-subjects not exposed and excluding flaws like bias (recall bias) and co-existing risk-factors (or even other teratogens) may be complex. As mentioned above, another important issue is the timing of exposure to the presumed teratogen. If the time frame does not coincide with the embryogenesis or vulnerable period of the organ or structures of interest one may well miss any teratogenic effect. Time specific information on exposure and analysis according to specified and rational time periods is therefore necessary.

Case ascertainment is yet another crucial and problematic issue. The cases that present at birth are but a selection of cases that occur during embryogenesis. Fetal wastage may have a great impact on the birth prevalence and should be accounted for. Preferably by means of complete ascertainment of all cases prospectively, including cases resulting in intra-uterine death. Moreover, complete case ascertainment implies rigorous case definition and diagnostic criteria applied to both early aborted fetuses and newborns. Catheterisation, autopsy and possibly neonatal ultrasound data are to be preferred as conclusive diagnostic procedures for congenital heart disease. A final point that needs the attention of the researcher is the study-size. In order to achieve sufficient (statistical) power the number of participants included should be deduced from the number of cases anticipated over the background prevalence or incidence. In turn, of course, the number of extra cases will depend on the teratogenic capacity of the agent. The apparent difficulties awaiting future epidemiologists should not discourage, but rather challenge them as the potential yield could be sizeable. If widespread risk factors are identified and can subsequently be averted effectively at population level the number of infants with congenital heart disease may decrease drastically. Examples of possible low level, yet widespread, teratogenic agents are viruses, substances commonly applied in decontamination and electromagnetic fields. Especially viral infections, which are very common and often occur subclinically must be considered in this respect. Moreover, combinations of agents may potentiate each other or become teratogenic when taken or occurring in combination.

Teratogens carrying a high risk for the individual with well known examples like thalidomide, retinoic acid (and the rubella virus) are important to bear in mind when prescribing drugs to people at reproductive age, in particular pregnant women. Currently, the principle of non-prescription during pregnancy is well recognised and a lengthy process of studies assessing the safety of drugs precedes marketing. Similarly, if available, vaccination preceding childbearing age prevents infections with known teratogenity during pregnancy in most Western societies. Therefore, the number of cases originating, and hence potentially preventable, from prenatal exposure will be small. Furthermore, it seems likely that high level teratogens that women are currently exposed to have not already been discovered.

In summary epidemiologic studies with complete data on large series of early abortions,

including karyotyping, extensive post-mortem examination, clinical data on prenatal (or even pre-conceptional) exposure and clinical data on relatives are a source of information currently neglected but with a great potential. A concerted action of epidemiologists, clinicians, geneticists, pharmacologists and fetal or paediatric pathologists should be encouraged and may also add to the current 10 to 20 % of cardiovascular anomalies explained by a specific factor rather than by the repository of multifactorial causes.

## 2.3 POSSIBILITIES FOR PREVENTION OF CONGENITAL HEART DISEASE.

Emanating from the fact that at present we are largely unaware of the aetiology of congenital malformations of the cardiovascular system it is not feasible to pursue large scale primary prevention. That is, it is not possible to avert the occurrence of malformations in the offspring at a population level. However, for individual couples with known risk factors for affected offspring preventive measures can be adopted. For instance a young woman with type I diabetes trying to conceive should have an optimal insulin regimen to normalise blood glucose levels even before ovulation. Similarly, once the genetic basis of the condition of familial heart disease has been elucidated, e.g., the gene(s) involved has been recognised, it may be possible to develop diagnostic tests to identify individuals at risk. A next step may be to offer treatment to those individuals by means of gene-therapy or offer prenatal diagnosis to the couples at risk. It is likely that in the near future a number of specific monogenic disorders giving rise to congenital malformations of the cardiovascular system will be identified.

Alternatively, secondary prevention may be an option in those cases where we are aware of increased risk but have not identified the causative agent. If already a child is born with congenital heart disease the risk for future siblings is increased. This is an indication for extended fetal echocardiography during future pregnancies. Upon prenatal detection of a cardiovascular anomaly the obstetric policy may be adapted, or termination of pregnancy can be offered in case a fatal anomaly is detected. Thus the outcome, the birth of a critically ill neonate due to a congenital malformation, is prevented rather than the occurrence of a malformation. Genetic counselling is part of this strategy as the geneticists determine the recurrence risk and set the indication for extensive fetal ultrasound

examination or other modes of prenatal detection. However, this strategy has little impact numerically as it can only be offered to the small subgroup of parents known to be at risk. Secondary prevention at a population level by means of routine fetal ultrasound, e.g. the fetal four chamber view at 18 to 20 weeks gestation, has been proposed as an adequate and efficient procedure (14,15). Upon detection of an anomaly during a routine ultrasound evaluation, extended examination in a referral setting should follow in order to confirm the diagnosis, offer counselling and adapt the obstetric policy if required. In theory population screening may have a potential yield for the fetus and parents. However, we feel that before general introduction several issues have to be clarified.

The efficacy of the procedure has not been proven beyond doubt. Furthermore, the natural history of a number of anomalies is not known. Therefore, the consequences and impact of prenatal diagnosis should also be addressed. Large-scale state of the art epidemiologic studies can address the issue of need and utility of population screening by establishing the yield, efficacy and safety of the procedure proposed. Although not displaying the aetiology of congenital heart disease secondary prevention of congenital heart disease should be evaluated as it may reduce neonatal distress due to congenital heart disease or even lower the birth prevalence of some fatal or severe anomalies as a result of termination of pregnancy in affected cases (16).

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# CHAPTER 3

# PREVALENCE OF CONGENITAL HEART DISEASE; A CRITICAL ASSESSMENT

## INTRODUCTION

The birth prevalence of congenital malformations is estimated at about 2 to 3 per 100 live births (1,2). Anomalies of the cardiovascular system, detected in about 8 per 1000 live births, either isolated or in combination with other birth defects, account for a large proportion of this number (3). Many reports on the number of children born with congenital heart disease in various populations have appeared, offering a considerable range in frequency in the human conceptus. Variation in factors such as method of diagnosis, or examination of liveborn infants versus spontaneously aborted fetuses, have led to estimates of frequency between 2 and 680 per 1000 (4,5). Irrespective of the exact frequency of occurrence, congenital heart disease still causes considerable morbidity and mortality. While perinatal and childhood mortality related to, for instance, infectious diseases has decreased dramatically in the latter half of this century (6,7) the proportion of newborn children with congenital heart disease has remained more or less stable. Thus, congenital cardiovascular malformations have gained relative importance in contributing to mortality despite major advances in paediatric cardiology and cardiac surgery. For instance, 18.2% of 4390 infants with congenital heart disease registered in the Baltimore Washington Infant Study from 1981 to 1989 did not survive their first year (8). Equally, a significant proportion (20 to 35%) of perinatal mortality and childhood mortality due to congenital anomalies is associated with cardiovascular malformations (6,9,10).

As the aetiology of congenital heart disease still is largely unknown (11), prevention based on intervention at a causal level remains an elusive goal. As a consequence, paediatric cardiologists and, increasingly, geneticists and obstetricians, remain faced with a variety of clinical conditions which consume a large amount of the available resources for child health care. In this paper we will review the literature reporting data on the occurrence of congenital heart disease. In addition, possible explanations for the variability in the figures reported will be examined and, finally, recommendations for further study will be provided.

## APPROACH

Papers and books, published over the last 4 decades, on the occurrence of congenital heart disease in humans were studied. Primary papers on studies, describing the methods in sufficient detail, were selected. Subsequently, characteristics of study design, e.g., period of case ascertainment, length of follow-up, procedures of case ascertainment, diagnostic procedures applied, composition of the study population, case definition and study size were extracted, together with the final prevalence figures. Finally, with these guidelines, comparable data on various populations, nations, and era were available.

Our aim was to assess the influence of various characteristics of study design on the reported prevalence, rather than to establish an ultimate overall point estimate of the prevalence of congenital heart disease. Accordingly, if sufficiently detailed information was available the data were pooled, under the assumption of one general prevalence, according to categories of design features. Proportions, with a 95 % confidence interval, were calculated.

## FINDINGS

The various characteristics of study design, potential sources of variability, will successively be assessed. In table 1 the principal methodological characteristics and the results of the studies reviewed are summarised. Striking differences in the reported prevalence of congenital heart disease appear. For instance, Fyler et al. have reported the lowest prevalence of congenital heart disease in a very large hospital-referral based study (2.08 $\pm$ 0.086 per thousand) whereas Mészaros et al., in a much smaller population-based study, reported the highest prevalence (11.9 $\pm$ 2.8 per thousand)(4,22).

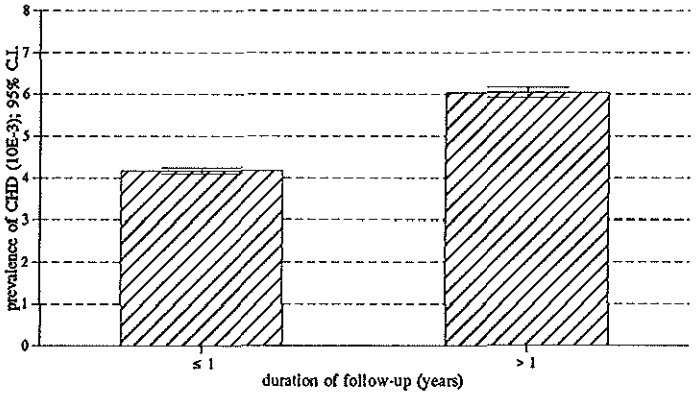
*period of case ascertainment*

The selected reports cover a period of ascertainment of cases from 1940 to 1989. A chronological representation of the prevalence figures reported does not reveal a systematic variation over time. That is, no specific trend can be detected.

*duration of follow-up*

The duration of follow-up, on the other hand, has a direct impact on the prevalence estimates. A comparison of studies with a maximum follow-up of one year (prevalence 0.417%; 95% C.I.: 0.409 - 0.424) to studies with a follow-up of over one year (prevalence 0.604%; 95% C.I.: 0.592 - 0.617) shows that a longer period of follow-up is likely to yield a larger proportion of children with congenital malformations. This is illustrated in figure 1.

Figure 1 Prevalence of congenital heart disease in relation to duration of follow-up




CHD = congenital heart disease; C.I. = confidence interval

*methods of ascertainment*

The methods of ascertainment used may be another source of variability of the prevalence of congenital heart disease reported. Comparing the results of studies applying routine examination of all children (prevalence 0.717%; 95% C.I.: 0.691 - 0.743) to the results of studies using information retrieved from pre-existing medical records for case finding (prevalence 0.448%; 95% C.I.: 0.441 - 0.455) demonstrates that routine examination yields a larger proportion of cases of congenital heart disease (figure 2).

Table I. Prevalence of congenital heart disease as reported from 1953 to 1993.

| author | place of study | birth cohort | follow up period (yrs) | method of ascertainment | diagnostic procedures | study population | definition of CHD | # of births | # of CHD | prevalence $10^{-3}$ | # of septal defects ASD (%) | VSD (%) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| MacMahon et al.[12] | Birmingham, UK | '40 - '49 | 2 - 11 | school medical records + death certificates + clinical and autopsy records | 9,10,11 | stillborn (no specification) and live born | not specified | 199418 | 633 | 3,17 | 121 not specified (19,1) | |
| Carlgren et al.[13] | Gothenburg | '41 - '50 | 7 - 16 | routine examination by health care professionals + clinical and autopsy records | 1,2,3,4,5,6,7,10 | live born | not specified | 58105 | 369 | 6,4 | 19 (5) | 99 (27) |
| Richards[14] | New York, USA | '46 - '53 | 1 | routine examination of all live born + autopsy records | 1,2,3,10 | product of conception > 500 g. | not specified | 6053 | 50 | 8,3 | 18 not specified (36) | |
| Feldt et al.[15] | Olmsted County Minnesota, USA | '50 - '69 | 1 - >10 | clinical records | 0,1,2,6,7,9,10,11 | live born | not specified | 32393 | 186 | 5,74 | 13 (7) | 62 (33,4) |
| Michaëlsson[16] | Upsala, Sweden | '52 - '61 | 4 - 13 | clinical records | not specified | live born | not specified | 48500 * | 291 | 6,0 | (9,3) | (22,4) |
| Bound et al.[17] | Blackpool, UK | '57 - '71 | 3 (10% >3) | routine examination of all live born + clinical and autopsy records | 6,7,9,10,11 | stillborn (no specification) and live born | Mitchell[20] + ISC; CHDC | 57979 | 395 | 6,8 | 41 (10,3) | 110 (27,8) |
| Kerrebijn[18] | Leiden, Netherlands | '58 | 2 - 15 months | referral by health care professionals + general health screening + clinical records | 0,1,2,3,4,5,6,7,10 | live born | not specified | 1817 | 15 | 8,25 | 1 (6,6) | 8 (53,3) |
| Hoffman et al.[19] | East Bay, Cal, USA | '59 - '66 | 5 - 13 | routine examination of all live born + clinical and autopsy records | 6,7,9,10,11 | live born | Mitchell[20] | 19044 | 168 | 8,8 | 10 (6,1) | 52 (31,5) |
| Mitchell et al.[20] | 12 centres, USA | '59 - '67 | <9 | register of CHD + clinical records | 6,7,9,10,11 | product of conception > 20 weeks gestational age | functional definition for study of CHD, no specification | 56109 | 457 | 8,14 | 34 (7,4) | 133 (29,1) |
| Dickinson et al.[21] | Liverpool & Boodle,UK | '60 - '69 | not specified | register of congenital malformations + clinical records | 6,7,9,10,11 | live born | functional definition, no specification | 160480 | 884 | 5,51 | 52 (5,9) | 287 (32,5) |
| Mészaros et al.[22] | Szolnok County, Hungary | '63 - '65 | 6 - 9 | routine examination of 81 % of the children + clinical and autopsy records | 0,1,3,4,6,7,9,10 | live born | ISC; CHDC | 5644 | 67 | 11,9 | 11 (16,4) | 18 (26,9) |
| Laursen[23] | Denmark | '63 - '73 | 15 | hospital records (not specified) + death certificates | 1,2,,3,6,7,10 | live born | ISC; CHDC | 854836 | 5249 | 6,14 | 494 (9,4) | 1259 (24,0) |
| Fyler[4] | New England, USA | '68 - '74 | 1 | death certificates + clinical and autopsy records | 6,7,9,10 | live born | functional definition (not specified) | 1083083 | 2251 | 2,08 | 70 (2,9) | 374 (15,7) |
| Bleuer et al.[24] | Bern region, Switzerland | '75 | 8 | register of CHD + information obtained from health care professionals and-/or parents on children referred | 11 | live born | not specified | 27100 * | 271 | 10 | 26 (10, including ODB) | 101 (37) * |
| Borman et al.[25] | New Zealand | '78 | 1 | birth notification form + death certificates + clinical and autopsy records | 10,11 | live born | not specified | 51777 | 181 | 3,5 | 6 (3,3) | 35 (19,3) |
| Fischer et al.[26] | Tyrol, Austria | '79 - '83 | 5 | routine examination of all children + clinical and autopsy records | 3,4,6,7,8,9,10,11 | live born | Mitchell[20] (with inclusion of bicuspid aortic valves) | 41725 | 341 | 8,2 | 43 (12,6) | 144 (42,2) |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Stoll et al.[27] | Bas - Rhin, France | '79 - '86 | 1 | 1st routine post partum examination + clinical and autopsy records | 0,1,6,7,8,9,10 | product of conception > 26 weeks gestational age | ISC; CHDC | 105374 | 801 | 7,60 | 137 (13,5) | 393 (38,7) † |
| Samánek et al.[28] | Bohemia, Chechoslovakia | '80 | 4 | routine examination of all children + clinical and autopsy records | 0,1,6,7,8,9,10,11 | live born | specified functional definition | 91823 | 589 | 6,42 | 67 (11,4) | 185 (31,4) |
| Calgren et al.[29] | Sweden | '81 | 1 | 4 independent registers including death certificates and a CHD registry either using ICD or ISC; CHDC | 6,7,8,9,10,11 | live born (it is not clear if stillborn are included) | ICD; VIIIth revision and ISC; CHDC | 94778 | 853 | 7,6 | 32 (12,5) | 78 (30,5) ‡ |
| Ferencz et al.[8,30] | Baltimore-Washington, USA | '81 - '89 | 1 | death certificates + clinical and autopsy records | 6,7,8,9,10 | live born | ISC; CHDC | 906624 | 4390 | 4,84 | 340 (7,7) | 1411 (32,13) † |
| Grabitz et al.[31] | Northern and Central Alberta, Canada | '81 - '84 | 1 | clinical and autopsy records | 6,7,8,9,10 | live born | Mitchell[20] + ISC; CHDC | 103411 | 573 | 5,54 | 60 (10,5) | 197 (34,4) |
| Sung et al.[32] | Hong Kong | '87 - '89 | 2 months | routine examination in 95 % of all children + clinical and autopsy records | 0,1,2,3,6,7,8,9,10 | live born | not specified | 20928 | 133 | 6,3 | 5 (3,8) | 60 (45,1) |
| Gerlis[5] ‖ | Leeds, UK | '75 - '83 | - | spontaneous abortions | 10 | product of conception < 24 weeks gestational age | not specified | 274 | 38 | 154 | 1 | 29 (including 4 AVSD) |
| Chinn et al.[33] ‖ | Seattle, Washington, USA | '77 - '87 | - | spontaneous abortions | 10 | product of conception 9 - 40 weeks gestational age | not specified | 400 | 52 | 130 | 1 | 12 |

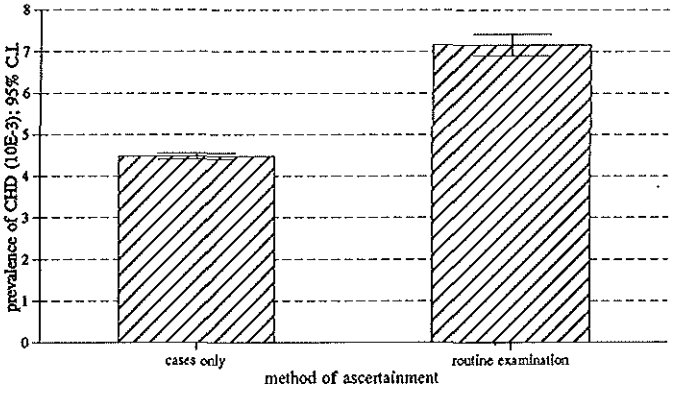
Footnotes:

Abbreviations: CHD = congenital heart disease; ASD = atrial septum defect; VSD = ventricular septum defect; ISC; CHDC = International Society of Cardiology; Classification of heart disease in Childhood; ICD = International Classification of Diseases; ODB = open ductus Botalli; AVSD = atrio-venticular septal defect

Diagnostic procedures: 0 = history taking; 1 = physical examination; 2 = chest X-ray; 3 = ECG (electro cardiogram); 4 = phonocardiogram; 5 = electromycogram; 6 = cardiac catheterization; 7 = angiography; 8 = echocardiography; 9 = surgery; 10 = autopsy; 11 = clinical evaluation (not specified)

Symbols: * = estimated population; † = isolated CHD; ‡ = calculated from the information available in the CHD register (256 births); § = series on spontaneous abortions < 24 wks; an inverse relation between fetal size and prevalence of CHD is found, range 1 - 68%; ‖ = series on spontaneous abortions between 9 and 40 weeks gestational age; a direct relation between fetal size and prevalence of CHD is found, range 0 - 30%

Figure 2 Prevalence of congenital heart disease in relation to method of ascertainment

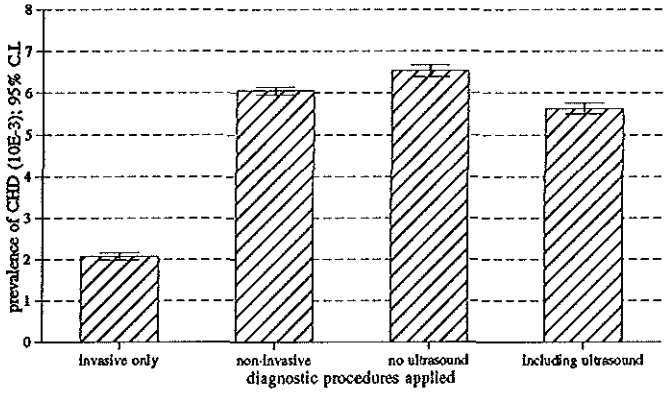



CHD = congenital heart disease; C.I. = confidence interval

*diagnostic procedures*

Additional factors in ascertainment-variability are the diagnostic procedures employed. The results of the studies classified according to use of invasive methods only (prevalence 0.208%; 95% C.I.: 0.199 - 0.216), as opposed to additional use of non-invasive methods (prevalence 0.605%; 95% C.I.: 0.596 - 0.615) clearly shows that adoption of non-invasive procedures yield more cases (figure 3). With respect to the nature of the malformations detected in the different studies, the column in table 1 concerning septal defects indicates that the proportion of minor lesions encountered increases with the use of non-invasive diagnostic procedures like physical examination, chest X-ray, ECG and ultrasound. Figure 3 also demonstrates the effect of introduction of ultrasound diagnosis; a lower prevalence appears in studies applying ultrasound (prevalence 0.563%; 95% C.I.: 0.550 - 0.595) versus studies relying on other non-invasive procedures (prevalence 0.653%; 95% C.I.: 0.639 - 0.668).

Figure 3 Prevalence of congenital heart disease in relation to diagnostic precedures applied

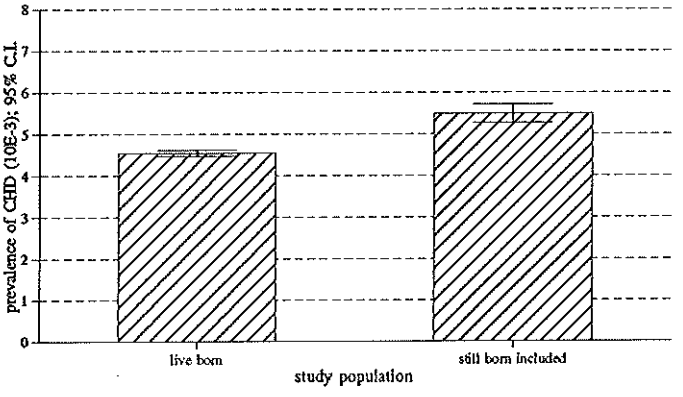



CHD = congenital heart disease; C.I. = confidence interval

*composition of the study population*

Subsequently, the composition of the study population may have influenced the prevalence reported. Stillbirths appear to have been included more or less arbitrary in several studies. The effect on the prevalence of congenital heart disease reported can be confirmed when the data are pooled according to the inclusion of non-live born products of conception (prevalence 0.550%; 95% C.I.: 0.528 - 0.572) versus liveborn only (prevalence 0.455%; 95% C.I.: 0.448 - 0.462). This is illustrated in figure 4.

Figure 4 Prevalence of congenital heart disease in relation to study population




CHD = congenital heart disease; C.I. = confidence interval

*definitions of congenital heart disease*

The definitions of congenital heart disease employed may also influence the results of the different studies. Regrettably, however, very little information about the exact definitions used is available.

*size of the study*

Another issue of design is the size of the study. The size of the populations investigated shows a wide range, from 1,817 to over a million births.

## DISCUSSION

The summary of the data available on the prevalence of congenital heart disease indicates that certain consistencies across the various studies are present. However, cautious interpretation of discrepancies in results reported is also warranted. It is very likely that differences in availability or access to diagnostic equipment or in attitudes to the use of autopsies exist and are further influenced by the era of study or the population studied.

For instance, in the United States the autopsy-rate increased from 5.4% to 11.9% in cardiac infants in approximately 10 years (4,8,30). This may have been one of the factors involved in the increase of prevalence of congenital heart disease (2% to almost 5%) noted over this period. Another, though less obvious illustration may be the degree of medical care provided for infants with chromosomal anomalies like Down syndrome. Culture and ever evolving ethical considerations within cultures may influence medical care and, as chromosomal anomalies are often associated with congenital heart disease, the reported prevalence may vary accordingly. Little quantitative data is available on these issues but qualitative assessment may help to understand the consequences of these sources of variability.

Contrary to qualitative argumentation on not strictly methodological issues mentioned above, the results of the inventory of the available data may provide information readily accessible for inference.

The era of case ascertainment may reflect the prevailing practice of medicine. Therefore, one may expect the prevalence reported to vary systematically over time. However, no specific trend, that is, either an increase or decrease in the prevalence of congenital heart disease over time, can be demonstrated in the reports reviewed. Other features of study design such as length of the period of follow up and the introduction of routine follow-up on all children may have surpassed the expected effects of evolving medical technology and societal values.

Length of postnatal follow up is shown to importantly influence the prevalence of congenital heart disease found in a particular population. A shorter period of (postnatal) follow-up will lead to the detection of fewer cases; especially subtle malformations that lack evident symptoms may only be recognised at later age.

Differences in methods of case finding or ascertainment also explain a major part of the variability of the prevalence. Janerich et al. have, similarly, proposed this to be a major reason why the prevalence of congenital defects differs widely (34). Other authors have also taken ascertainment into account when reviewing the prevalence of congenital heart disease (35,36). The completeness of ascertainment varies markedly across the various studies. The more comprehensive population based studies that apply routine examination to all infants, and additional referral if clinically indicated, report the highest prevalence,

whereas in hospital based studies, only using clinical and autopsy records, a lower prevalence is found. Likewise, a study that utilises a register designed especially to document congenital malformations will report a higher prevalence. In this respect, the results obtained by Bleuer et al., and Calgren et al., are illustrative (24,29). Other examples of the influence of case ascertainment or selection include two studies by Gerlis and Chinn et al. (5,33). They reported a remarkably high prevalence of congenital heart disease (> 10 per hundred) in autopsy series on spontaneous abortions or stillbirths. In general, as the number of sources and the quality of available data increases, the proportion of children with malformations detected also increases.

Awareness of (changes in) the diagnostic procedures applied may also reveal explanations for differences in reported results. As mentioned above, if all children are examined routinely within the first months of life a higher prevalence of malformations may be expected, especially if this involves the internal organs. Therefore, information on local practice of medicine appears to be essential. The effects practice and diagnostic procedures can have, may be illustrated by an "epidemic" of congenital heart disease that has been noted since 1970 by several authors (37-39). The increased numbers of cardiac malformations proved to be mainly mild cases, notably small ventricular septal defects. Probable explanations for the "increase" in prevalence include a raised awareness and referral to paediatric cardiologists and improved diagnostic procedures. The authors have attributed a major part of the increased prevalence of congenital heart disease to the introduction of ultrasound as a reliable diagnostic criterium. For instance, the Baltimore Washington Infant Study that has added diagnoses obtained by means of ultrasound as (non-invasive) inclusion criterium during the period of case ascertainment have noted an increase of prevalence of congenital heart disease (8). As is demonstrated in figure 3, this is not in accordance with our findings. It may well be that, prior to introduction of ultrasound, cases not considered serious were not submitted to invasive techniques like catheterization and, hence, were not ascertained in studies applying invasive methods for inclusion. Conversely, studies not applying the strict criteria of invasive diagnostic procedures (or echocardiography) probably already had accomplished a high level of ascertainment and, subsequently, a more accurate estimate or the prevalence. It appears that physical examination still is one of the most important screening tools for congenital

heart disease (40). Nevertheless, because the heart can be examined anatomically and functionally, ultrasound may have the advantage that the amount of detail of the diagnosis and assessment of its functional implications are improved. The prevalence figure, however, will not differ due to use of echocardiography alone. Especially, the more severe cases will be noted early in life anyhow and, subsequently, the matching prevalence is not altered by differences in practice nor by variation in length of follow up. Autopsy (records), which would seem to provide a very solid end-point diagnosis, must also be considered carefully and in relation to local circumstances. In many countries it is not customary to perform an autopsy and accordingly autopsy records possibly are not as reliable as they may seem. Moreover, as Hoffman et al. have pointed out, the extent of expertise of the prosector and of detail of the post mortem examinations may vary (19). In particular, spontaneous abortions and stillborn fetuses may not be submitted to an (extended) post-mortem examination and as premature death may well be related to a congenital anomaly (5,33,41,42), the prevalence of congenital heart disease may be (grossly) underestimated. Finally, not even the use of modern diagnostic techniques and all available data sources will render the complete picture of congenital heart disease. Russel et al. have postulated that even under optimal clinical observation of an infant with congenital heart disease, postmortem evaluation may show important undetected cardiac pathology (43).

As noted, composition or selection of the study-population also influences the prevalence reported. In view of the results obtained by Gerlis and Chinn, on average, one may expect an increased prevalence in the studies including stillbirths. Estimates of the prevalence of congenital heart disease in a study on spontaneous abortions almost reach 70% in the early fetus of $<$ 25 mm (5,33). Furthermore, Samanek et al. found a 2.1% prevalence of congenital heart disease in a large autopsy series which included stillbirths and infants that died from birth to the age of 15 years (44).

In addition to the difficulties mentioned so far, problems in comparing prevalence numbers emerge due to varying definitions and inclusion criteria for cases of congenital heart disease. Authors used to refer to the embryonic origin when defining congenital heart disease, gradually shifting to a stepwise analysis of defects, following blood flow through the heart. However, definitions and classification of congenital heart disease still

are a matter of debate (45). The diversity of definitions causes arbitrary inclusion or exclusion of, for example, bicuspid aortic valve or patent ductus arteriosus, leading to confusing results. Studies that have distinguished between major and minor defects have done so on a functional basis, e.g., causing death, physical handicaps or warranting surgery. This resulted in a more or less stable estimate of about 4 major cardiac malformations per thousand live births as was noted by Hoffman (36).

Recent hospital based Dutch data by Bruins and Temmerman corroborate with this figure (unpublished data).

A problem related to case definition follows from the measure of interest; the proportion of infants with a congenital defect born in a particular time period. Only at the moment of birth a cohort can be defined and at that particular point in time, or shortly thereafter, a neonate with a congenital malformation can be recognised as a case. Yet, in the literature on congenital defects one often encounters the use of "incidence", a measure of occurrence, of congenital malformations. Seemingly only a definition problem, as MacMahon and Pugh pointed out, the term "prevalence", or better still "prevalence at birth", should be used when referring to the above mentioned fraction (46). The actual incidence of congenital heart disease, the number of new cases that develops, can not be estimated. From the moment of conception onward, or even before if factors influencing the germ cells are taken into account, progression or induction of teratogenesis may occur, contributing to the actual incidence. However, because of early fetal loss many of these cases will never be born. Not being able to ascertain these cases precludes determination of the true occurrence rate. Furthermore, some malformations like small ventricular septal defects may heal or close spontaneously even before birth, again leading to underestimation of the occurrence of cardiac anomalies. It is important to realise that the incidence rate is a measure readily applicable in causal inference. Prevalence on the other hand is a measure of disease status and is a function of the occurrence of malformations, or incidence, and survival characteristics of the fetuses. Interrelating prevalence data, as if equivalent to incidence, directly to any conceivable risk factor may (strongly) underestimate the impact or teratogenic capacity of the risk factor depending on the ascertainment and survival until delivery of the affected fetuses.

The fact that many studies have reported on relatively small numbers resulting in unstable

estimates of proportions, i.e., wide confidence intervals, may also have influenced the reported figures. This statistical variability may also account for some of the differences in prevalence found.

Real differences among populations may provide yet another explanation. Populations may differ with respect to prevailing aetiologic factors of congenital heart disease. Correa-Villaseñor et al., reporting on a white versus black population difference in prevalence of congenital heart disease in the Baltimore Washington Infant Study, controlled for a number of socioeconomic (risk) factors like marital status, education, occupation, family income, number of family members, prenatal care and maternal age, possibly contributing to variability of prevalence estimates, and still could not explain all of the difference in prevalence (47).

Similarly, the natural history of some cardiovascular malformations may influence the results obtained. A small muscular ventricular septal defect or patent ductus arteriosus might close spontaneously early in life. This implies that, apart from all methodological variability, the natural history of several lesions will affect prevalence over time.

## CONCLUSIONS

Appraisal of the prevalence of congenital heart disease proves not to be unequivocal. Depending on a number of methodological issues, the population studied and the local practice of medicine, a wide range of prevalence may be obtained. However, despite the variability in case definition, the birth prevalence of major or severe congenital heart disease requiring acute medical attention has been reported with remarkable consistency. The prevalence of less severe cases, on the other hand, may need further research. The length of follow-up, case ascertainment, diagnostic procedures applied, population characteristics, number of participants and the case definition may all substantially influence the results.

It should be stressed, however, that if only a proportion of all cases of congenital heart disease can be ascertained, this does not imply that a particular study is not useful. If the search for cases is restricted to severe congenital heart disease, for example to assess the resources that have to be allocated, that may well be a worthwhile enterprise. Yet, one

must keep in mind that such a study has limited value when the aim is a description of the occurrence of congenital heart disease in a population, or if the prime interest is to study a causal relationship. Then complete ascertainment, including anomalies inducing cases of premature death, is a prerequisite.

A final remark can be made on the increasing numbers of congenital malformations being detected prenatally. Early detection of severe congenital heart disease will give parents the option to terminate pregnancy. Allan et al. have noted a drop in the number of newborn infants with hypoplastic left heart syndrome since the introduction of a prenatal screening program for congenital heart disease (48). Many parents chose termination of pregnancy after explanation of the possibilities and prognosis of this particular malformation. The use of ultrasound in obstetrics is widespread and the introduction of prenatal detection of cardiac anomalies by means of fetal echocardiography may alter the post-natal prevalence of congenital cardiac defects. In addition, the opportunity to detect severe malformations in utero has stimulated fetal care (49) and may result in reduced perinatal morbidity and mortality. However, the efficacy of routine fetal ultrasound screening for congenital heart disease in a low risk population has yet to be established. Future research focused on the feasibility of a fetal screening program for cardiac malformations may resolve the ongoing discussion on the utility of ultrasound in pregnancy. Furthermore, the impact of screening on the prevalence and the outcome of congenital heart disease could be evaluated.

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# CHAPTER 4

# CONGENITAL HEART DISEASE; EPIDEMIOLOGY, IMPACT AND FETAL IMPLICATIONS

## 4.1 INTRODUCTION

In recent decades numerous reports on congenital heart disease have appeared. Among these are epidemiologic studies and (national) health statistics to provide quantitative information regarding the impact of cardiovascular anomalies on public health. Furthermore, a great number of publications on various types of malformations is available. Even data on prenatally detected malformations have appeared.
It may, however, be difficult to link together this overwhelming body of information on the various aspects of cardiovascular anomalies. In the present review an effort has been made to comprehend some of the principal issues involved in congenital heart disease in order to provide a basis for further discussion and research.

## 4.2 EPIDEMIOLOGY

The prevalence of major congenital malformations has been estimated at about 3 per hundred live births (1,2). Of these, cardiovascular malformations constitute a significant proportion. The reported birth prevalence of congenital heart disease ranges from 2 to 12 per thousand (3,4) and increases have been suggested in recent years. The variability in reported numbers has been addressed by several authors and appears to be related to the design of a study (5,6). Similarly, the recent increase in numbers may be attributed to improved detection of minor cases, particularly ventricular septal defects (7,8), while in reality the occurrence has remained stable. Currently, a best estimate of the prevalence of congenital cardiovascular malformations would be 8 per thousand live births (9), thus a significant proportion of the total number of congenital malformations. In 1989 the birth rate in the Netherlands was 12.7 per thousand inhabitants (10). The total number of births reached 190,079 that year, implying some 5,700 children born with congenital defects of which about 1,500 can be expected to have congenital heart disease. Bruins and Temmerman performed a prospective hospital based study in the Netherlands in order to estimate the prevalence of congenital heart disease in the 1980 and 1985 birth cohorts and closely confirmed these expected numbers of cardiovascular malformations (11).
Cardiovascular malformations are not a single entity but can be classified according to a

large range of complicated diagnoses. Hoffman recently reviewed several series on congenital heart disease and although prevalence varies, the subdivision of cases according to diagnosis is reported with remarkable similarity (6). Ventricular septal defect constitutes the single largest group of about 30 % of all congenital heart disease, and is followed in decreasing order by patent arterial duct, atrial septal defect, pulmonary stenosis (each about 10 %), tetralogy of Fallot and coarctation of the aorta (each about 7%), aortic stenosis and transposition of the great arteries (about 5% each). These diagnoses account for approximately 85% of the cardiovascular malformations encountered in children (table 1). Note that the data from which this order has been derived are largely population based and may not reflect the proportions observed in a hospital setting.

Table 1 Prevalence (%) distribution of various types of cardiac malformations. Adapted from Hoffman (6).

| author | VSD | PDA | ASD | PS | ToF | CoA | AS | d-TGA | AVSD | HLH | HRH | TA | TAPVC | SV | DORV | Misc. | Total |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Carlgren Gothenburg | 27.1 | 9.5 | 4.3 | 3.8 | 4.1 | 9.8 | 5.4 | 6.0 | 3.0 | 0.8 | 2.4 | 1.4 | 0.8 | 0.0 | 0.0 | 21.7 | 396 |
| Rose et al. Toronto | 31.0 | 7.1 | 11.2 | 10.8 | 8.0 | 3.4 | 8.4 | 2.6 | - | 0.0 | 1.1 | 0.0 | 0.0 | 0.0 | 0.0 | 16.4 | 464 |
| Feldt et al. Minnesota | 34.6 | 10.6 | 7.3 | 5.0[1] | 5.0 | 5.6 | 6.1 | 7.8 | 4.5 | 4.5 | 3.4 | 0.0 | 2.8 | 0.0 | 0.0 | 2.8 | 179 |
| Mitchell et al. USA multicenter | 32.1[2] | 8.3 | 7.4 | 8.6 | 3.8 | 6.7[3] | 3.8 | 2.6 | 3.6 | 3.1 | 2.4 | 1.7 | 0.0 | 0.7 | 1.0 | 13.8 | 420 |
| Bound et al. Blackpool | 28.1 | 6.5 | 8.3 | 2.7 | 8.6 | 5.6 | 4.1 | 5.6 | 7.4 | 3.3 | 1.5 | 1.2 | 2.1 | 1.5 | 0.0 | 13.6 | 338 |
| Hoffman et al. California | 31.3 | 5.5 | 6.1 | 13.5 | 3.7 | 5.5 | 3.7 | 3.7 | 3.7 | 0.6 | 0.6 | 2.5 | 0.6 | 0.6 | 0.6 | 17.8 | 163 |
| Mészáros et al. Hungary | 20.9 | 11.9 | 10.4 | 10.4 | 4.5 | 6.0 | 11.0 | 4.5 | 4.5 | - | 1.5 | 4.5 | - | - | - | 9.0 | 43 |
| Laursen Denmark | 24.0 | 12.6 | 9.4[4] | 5.9 | 5.8 | 7.0 | 4.7 | 4.8 | 2.6 | 3.0 | 1.8 | 1.4 | 1.4 | 1.5 | 0.0 | 15.7 | 5249 |
| Dickinson et al. Liverpool | 32.5 | 11.9 | 5.9 | 7.6 | 5.9 | 6.3 | 5.1 | 5.0 | 2.4 | 2.8 | 2.5 | 1.1 | 0.8 | 1.7 | 0.0 | 8.0 | 884 |
| Ferencz et al. Baltimore-Washington | 26.3 | 2.6 | 7.5 | 7.0 | 9.2 | 6.8 | 3.3 | 5.0 | 8.6 | 5.7 | 3.2 | 1.5 | 1.7 | - | - | 11.6 | 1494 |
| Bruins et al. Netherlands | 32.3 | 5.8[5] | 5.6 | 7.7 | 6.0 | 4.3 | 6.3 | 4.3 | 4.4 | 1.5 | 1.0 | 0.9 | 0.9 | 1.5 | 1.1 | 15.7 | 2736 |

1 includes pulmonary atresia; 2 eleven with with pulmonary atresia; 3 seven with ASD or VSD; 4 includes ASD I; 5 excluding neonatal cases

Abbrevations: VSD ventricular septal defect; PDA patent ductus arteriosus; ASD atrial septal defect; PS pulmonary stenosis; ToF tetralogy of Fallot; CoA coarctation of aorta; AS aortic stenosis; d-TGA d-transposition of great arteries; AVSD atrioventricular septal defect; HLH hypoplastic left heart; HRH hypoplastic right heart; TAPVC total anomalous pulmonary venous connection; SV single ventricle; DORV double outlet right ventricle; Misc. miscellaneous

## 4.3 IMPACT

### 4.3.1 Mortality

One way to estimate the impact of congenital heart disease on the state of health of children is looking at mortality rates. A considerable decrease in both perinatal and infant mortality has been reported over the last decades. Perinatal mortality amounted to 34.2 per thousand births in 1950 and has declined to approximately 10 per thousand in 1984 (12). Infant mortality has shown a similar improvement, dropping from 29.8 to 9.6 per thousand live born and from 23.3 to 7.0 per thousand live born for male and female infants respectively. The proportion of infant mortality related to congenital malformations, however, has increased from 26% to 33% for male infants and from 31% to 36% for female infants from 1970 to 1990 (13) and may be explained by a declining overall mortality and a stable birth prevalence of congenital malformations, which thereby gain importance as a cause of morbidity and possibly mortality. The proportional contribution of cardiovascular anomalies to infant mortality, however, does not show a similar development. In contrast, the proportion of infants that have died due to congenital heart disease has remained more or less stable (perhaps slightly decreasing from 12.8 to 11.6% over the past two decades) (13). Accordingly, the contribution of congenital heart disease to infant mortality caused specifically by congenital malformations has declined from about 45% in 1970 to 34% in 1990. Paediatric cardiology and surgery with greatly improved diagnostic and therapeutic approaches in infancy have contributed to this course. Dutch data from Bruins and Temmerman confirm this evolution. Infant mortality as a result of structural cardiac malformations appears to have been approximately 9% between 1980 and 1985 (11).

Data on prenatal mortality either from spontaneous or induced abortions are still scarce. However, as Stein et al. pointed out that children born alive are a selection of the conceptions of which a sizable proportion has ended in miscarriage (14). As a result it can be anticipated that the incidence of fetal malformations is considerably higher than the prevalence at birth. The small number of studies on this issue have indeed reported a prevalence of cardiovascular malformations among spontaneous abortions and stillborn fetuses which exceeds the prevalence encountered at live birth by a factor 2 to 80 (15-17).

This extreme range may again be explained by methodological differences between the various studies. However, the overall impression of a substantially higher prevalence of fetal heart disease as compared to the birth prevalence remains evident. Furthermore, Allan et al. reported on the higher severity of cardiovascular malformations encountered prenatally by means of fetal echocardiography (18). She postulated that this could be explained by selection of patients referred for fetal evaluation or, alternatively, by selective fetal wastage in case of a more serious anomaly. After all, spontaneous abortion of severe cases would result in survival to term of comparatively mild cases or cases of congenital heart disease lacking major hemodynamic consequences prenatally.

Nevertheless, although mortality data suggest that the case fatality has decreased it remains beyond dispute that congenital heart disease still poses a major health problem in infancy. Furthermore, these numbers only provide a limited impression of the consequences of congenital heart disease. The various diagnoses are quite different with specific natural history and prognosis. Accordingly, morbidity, an other major aspect of congenital heart disease, should be discussed.

### 4.3.2 Clinical features

A substantial portion of congenital cardiac malformations has only a limited clinical consequence. For example, a small ventricular septal defect may not have hemodynamic consequences and has a tendency to close spontaneously in 30 to 40% of the cases (19). Conversely, 60% of the children with congenital heart disease do not require treatment and are presumed to have a normal life expectancy and quality of life (11). The remaining 40%, however, may suffer from a particular malformation on a short or long term basis and hence treatment should be provided. Surgical techniques and post operative care, including drug treatment, have evolved to such an extent that operative and early post operative mortality have reached levels beneath 5% for the majority of malformations even in the neonatal period (20). Furthermore, in recent years interventional paediatric cardiology has proven to provide a safe and effective alternative in the management of certain cardiovascular malformations (21).

Clearly, these summary figures do not apply readily to all malformations, some of which are very complicated and occasionally treated experimentally. The long term prognosis of

many of these problems, especially with respect to the more recently developed intervention techniques, has not yet been assessed. However, a proper understanding of the impact of congenital heart disease requires an appraisal of the life expectancy and late morbidity after treatment, preferably for each diagnosis separately.

*ventricular septal defects*

Not even ventricular septal defects, the largest single group of malformations, can be considered in its entirety because different forms of septal defects may have quite different natural histories and require different treatment regimens. Depending upon size and morphology of the defect, policies can be adapted. Spontaneous closure within the first five years of life in about 60% of the cases is characteristic for a small to medium sized muscular defect and hence can be managed medically in the majority of patients (22). In the Natural History Study about 70% of all patients with ventricular septal defects were initially managed medically of whom 30% subsequently required surgical intervention (23). Mortality among those managed medically reached 12.7%. Surgically managed patients have excellent short term survival of over 98% (22). However, long term survival is slightly lower (82.9%) than for those managed medically (23). Evaluation of the causes of death of patients with a history of congenital heart disease shows a marked association with the anomalies, e.g., in 65% of the patients managed medically to 90% of those managed surgically, sudden death (presumably arrhythmia), congestive heart failure, bacterial endocarditis or an unspecified cardiac cause is diagnosed. The majority of patients with a ventricular septal defect have a good prognosis with a 20 year survival of 87% and a New York Heart Association functional status of class 1 to 2, even for those who underwent surgery (23,24). Probably, these long term results will improve further due to recent developments in diagnostic and surgical techniques

*atrio-ventricular septal defect*

A more complicated variant of ventricular septal defect, the atrio-ventricular septal defect, which is often found in association with Down syndrome, combines multiple anomalies. This malformation is composed of several entities: a low primary atrial septal defect, one common atrio-ventricular valve and a ventricular septal defect. The disrupted internal

anatomy of the heart then causes several other structures to be displaced. The ostium of the aorta shifts ventrally and the atrio-ventricular conduction system moves dorsally. Moreover, atrio-ventricular septal defects may occur as a complete variant, where both the atrial septal defect and the ventricular septal defect are of importance, or as an incomplete variant presenting with an atrial septal defect only. The natural history and hence the treatment varies accordingly. The complete variant of atrio-ventricular septal defect may cause massive left to right shunting and atrio-ventricular regurgitation of blood, as a result of which these patients may develop progressive pulmonary vascular obstructive disease and heart failure and as subsequently often succumb before the age of 5 years. The extreme variants of atrio-ventricular septal defects have an even worse perspective with severe cardiac failure in early infancy resulting in death if surgery can not be performed. The partial variant has a far less dramatic course provided that atrio-ventricular insufficiency is limited. In view of the poor prognosis, surgical management has a relatively favourable outcome in complete atrio-ventricular septal defects. Infant mortality reaches 15% and half of the patients develop mitral insufficiency, which may require treatment at a later stage. The results of cases with incomplete atrio-ventricular septal defects are more favourable with only a 2% infant mortality. Dutch data from 1980 and 1985 on 130 patients, complete and incomplete atrio-ventricular septal defects combined, of whom 56 were operated upon in the first year, confirm the seriousness of this type of cardiovascular malformation with an infant mortality of 23% in the surgical group (11)

*patent ductus arteriosus*

The patent ductus arteriosus may close spontaneously as part of normal development in neonates born pre-term. Spontaneous closure has also been reported at later age. Defective wall constitution, however, precludes spontaneous closure. Bruins & Temmerman reported a spontaneous closure rate of about 15% in the post neonatal period and, furthermore, reported nil operative mortality in 109 patients (11). Currently, interventional cardiology also offers a solution, e.g., trans-catheter umbrella closure with very promising results and improved post procedure recovery and morbidity, as compared to surgical treatment (25). Patent ductus arteriosus can be treated safely and effectively without major complications.

*atrial septal defect*

Atrial septal defects can be categorised according to the size and morphology of the lesion too. Yet, compared to ventricular septal defects spontaneous closure is far less common. Bruins & Temmerman reported this to occur in 6% of 152 cases (11). If not treated, patients may not have any complaints until adult age despite sizable shunting. However, by then irreversible changes of the pulmonary arteries and myocardium as well as dysrhythmia may have occurred, resulting in an unfavourable prognosis. Accordingly, surgical intervention is imperative at a younger age and has excellent results with a short term mortality of less than 1% (11,23). Of the surgically treated patients some suffer from unfavourable consequences of surgery such as dysrhythmia (±5%) or mitral valve prolapse (±37%) and may require additional treatment (27-29). Interventional cardiology may further reduce these sequelae if umbrella closure can be achieved. Overall, patients with atrial septal defects have a very good prognosis.

*pulmonary stenosis*

Pulmonary stenosis is increasingly treated by means of balloon dilatation as an alternative for surgical intervention after its introduction by Kan in 1982 (30). Dutch data confirm the success of this mode of therapy with outstanding short and longer term prognosis (31). If performed on children over six months of age the pressure gradient over the pulmonary valve was shown to decrease markedly in all cases. Long term adverse outcomes were mainly restricted to mild pulmonary regurgitation which is well tolerated. Severe or complicated cases of pulmonary stenosis requiring treatment under six months of age may be better off when managed surgically (32). Recently Constance reported on the Natural History Study II results of surgically treated patients (23). These patients also appear to do very well with a 25 year survival rate of 95%, comparable to the general population. Of the survivors 97% were in New York Heart association class I condition. Bruins and Temmerman also reported excellent results observing no mortality in 210 patients of which 24 were managed surgically within the first year of life (11). Morbid events appear to be rare irrespective of treatment when properly chosen. Patients with pulmonary stenosis may expect a normal life expectancy, excluding procedure related mortality (23).

*tetralogy of Fallot*

Classical description of Fallot's tetralogy , 'la maladie bleue', mentions a ventricular septal defect, a to the right deviated aorta, infundibular stenosis of the pulmonary artery and consequently right ventricular hypertrophy. Currently, this complex anomaly is regarded as secondary to a mal-alignment, ventrally and to the right, of the outlet or infundibular part of the ventricular septum. Subsequently, a ventricular septal defect subsists, the aorta is deviated to the right, over-riding the ventricular septal defect, and the right ventricular outflow tract is narrowed. Tetralogy of Fallot has many variants determining the clinical features of this syndrome of cardiovascular malformations. Treatment is invariably surgical but the timing of operation is determined by the obstruction of the right ventricular outflow tract, the type of pulmonary stenosis, the size and development of the pulmonary arteries and finally the clinical status of the patient (33). In particular a cyanotic spell which is a life threatening complication of tetralogy of Fallot demands acute intervention. Treatment used to consist of two-stage surgery; early palliation by means of a shunt and correction at later age. However, early corrective surgery has proven at least equally effective and this therapy is now adopted with less than 5% early operative mortality and subsequent 8-year survival of 95% resulting in a good clinical condition for a majority of 85% (34). Data from Bruins and Temmerman on 165 patients of whom 109 were operated before their first birthday and subsequently experiencing a 85% first year survival support these figures (11).

A subgroup of 5 to 10% of the post operative patients have a residual ventricular septal defect which is usually well tolerated. However, approximately 1 in 10 may require re-operation because of hemodynamic consequences or a remaining pressure gradient in the right ventricular outflow tract (34). Another problem that is frequently encountered after surgical correction is pulmonary valve insufficiency (35). This insufficiency is often well tolerated, although some patients may require subsequent valve replacement. Despite these relatively favourable outcomes the right ventricular function has been shown to be impaired especially in children operated on at later age (36). Perhaps the currently adopted policy of corrective surgery before the age of two years will avert this problem. A commonly encountered problem in patients operated for congenital heart disease is the occurrence of rhythm and conduction anomalies. In approximately 80% of the patients

operated for tetralogy of Fallot a disorder of conduction is present and, furthermore, up to 45% show ventricular extra systole on 24-hour ambulatory ECG monitoring (36). This is a serious problem because despite an anatomically adequate surgical result sudden death occurs in 3 to 4% of the cases sometimes decades after operation. Even after corrected tetralogy of Fallot a patient will always require regular follow-up.

*coarctation of the aorta*

Coarctation of the aorta is classified according to the location of the constriction relative to the arterial duct into three categories; pre-ductal, juxta-ductal or post-ductal. It can be present in isolation or in combination with other cardiovascular malformations complicating diagnosis and treatment. However, coarctation is usually considered the most serious anomaly predominantly determining the prognosis (3). Coarctation of the aorta may present either shortly after birth with severe cardiac failure or may be detected at a later age on routine physical examination. Eventually all cases require an intervention because of complications occurring with sustained hypertension. Optimal timing of operation is still a matter of debate, although, there is a tendency toward correction at younger age (37). Interventional cardiology may offer a solution for selected cases and reduce morbidity and mortality (38). In spite of this coarctation of the aorta must be considered a serious anomaly with high infant mortality rates of up to 50% in the serious and complicated cases (3) and an overall infant mortality of at least 13% (3,11). After surgery a proportion of the patients may maintain or develop hypertension usually caused by residual-stenosis or re-stenosis and require additional treatment or medication (39). In addition, an infrequent but grave complication of the surgical procedure is spinal cord injury and subsequent paraplegia. Only a minority of patients free of stenosis, hypertension or additional cardiac malformations can be expected to live normal lives.

*aortic stenosis*

Aortic stenosis can also be classified according to the location of the lesion; in this instance relative to the aortic valves, i.e. supra-valvular, valvular or sub-valvular. Furthermore, aortic stenosis may occur in combination with other cardiovascular anomalies. Each location and combination of malformations calls for a separate approach.

Supra-valvular stenosis occurs rarely and again sub-types are distinguished. With this type of malformation the coronary arteries, which insert proximal to the stenosis, are exposed to a high blood pressure. Early sclerosis may arise and has to be dealt with accordingly. Furthermore, genetic counselling is warranted because autosomal dominant inheritance may be involved. Final surgical correction is indicated if there is a pressure gradient of over 50 to 70 mm Hg (40).

Valvular aortic stenosis is by far the most frequent variant. Patients often remain free of complaints unless a very serious stenosis exists. These cases may already present in the neonatal period and have a poor prognosis in particular if the myocardium has been affected. Less severe cases are generally discovered at a later age because of the presence of a systolic murmur and sometimes complicated by impaired exercise tolerance or even angina pectoris and syncope. Treatment is indicated if the patient presents with physical symptoms, ECG anomalies, a resting peak systolic pressure gradient of $>$ 50 mm Hg over the stenotic valve, an abnormal exercise ECG or an enlarged heart on the chest X-ray (41). Management used to be surgical with low risk and good results in the first decade or intermediate term. However, balloon dilatation has also proven valuable as a therapy for valvular aortic stenosis and may postpone surgical intervention (41). Valvotomy and balloon dilatation should be deemed palliative procedures requiring regular check-up. Valvular aortic stenosis can be considered an evolving process in need of continuous re-appraisal because the valves may become sclerotic, stenotic again or regurgitation may develop, demanding valve replacement or repeat valvotomy in 15 to 40% of the cases (23,40). Recently published figures on the long term results of management of patients with aortic stenosis show a 25 year survival of 92.4% for patients with a gradient $<$50 mm Hg at entry, whereas those with a pressure gradient of $>$50 mm Hg have a 81% survival (23). Both values are considerably below normal life expectancy. Worth mentioning is the fact that over half the cardiac related fatalities were sudden and unexpected, supposedly related to arrhythmia. A further fact of concern is the clinical status of the patient involved. A proportion of 7.7% did not reach NYHA class I. Moreover, only about half of the patients were judged to have an excellent to good status (23).

In about 8 to 10% of the cases of aortic stenosis the constriction is located sub-valvular

and is considered an acquired progressive disorder relatively often coinciding with other anomalies (42,43). Therapy is surgical and appears to have a good prognosis if treated timely. However, recently de Vries stressed the frequent post-operative morbidity and recurrence (44). Furthermore, it has not been unequivocally demonstrated that early surgery is the preferred strategy. Nevertheless, once the final stage of tunnel-stenosis is reached operation will be difficult and carry a considerable risk (45-49). Careful and frequent evaluation appears to be essential.

*transposition of the great arteries*

Transposition of the great arteries usually means that the aorta takes a position to the right (dextral) and ventral to the pulmonary artery resulting in a ventriculo-arterial discordance. This anomaly may be encountered as a single malformation or in combination with other cardiovascular anomalies complicating the clinical course. Just over half of the cases occur isolated or in combination with minor anomalies. About 30% has a hemodynamically relevant ventricular septal defect, a further 10% has left ventricular outflow tract obstruction and finally another 10% has a combination of these malformations (50).

Before the introduction of modern medical and surgical procedures the majority of infants died before their first birthday because of extreme hypoxia. Currently, however, the use of prostaglandin $E_1$, preventing closure of the arterial duct and subsequently allowing mixture of oxygenated and de-oxygenated blood, balloon septostomy, also permitting shunting and mixture, and corrective surgical procedures are applied which have greatly enhanced the prognosis resulting in 20 year survival up to 80% (51). Fyler presented data on dextro-transposition of the great arteries in the 70s and reported an infant mortality of 39% (3). More recent Dutch data from 1985 data illustrate the advances in treatment and show an infant mortality of the operated patients of 15% (11). The prevailing operative procedure applied used to be a physiologic solution according to Mustard (52). Early results were very encouraging with operative mortality of less than 5%. However, several late complications such as: obstruction of cardiac inflow at the orifice of the vena cava inferior and superior causing high venous pressures, obstruction at the orifices of the pulmonary veins with subsequent pulmonary hypertension and finally leakage and shunting through the sutures of the conduit between the caval veins and the mitral valves, may

occur. Furthermore, right ventricular dysfunction may evolve because in the long run the right ventricle may not be able to meet the demands of the systemic circulation. In addition, though usually this is well tolerated, the left ventricular out-flow tract may become obstructed. Finally, dysrhythmia appears quite often in patients operated on, which may end in sudden death in 5 to 10% sometimes years after apparently successful surgery (53). Obviously, this group of patients is in need of a thorough follow-up. During the last decade an alternative for the physiologic correction has increasingly been applied; the anatomical correction or arterial switch procedure. The short and mid-term results of this approach are good. Long-term results are not available at the moment, yet seem quite encouraging (54). Some sequelae that have been described are stenosis of the pulmonary artery at the site of the anastomosis arising in about 10% and minor aortic insufficiency in 5 to 15%. A major advantage is that arrhythmia can probably be avoided. Late mortality has been estimated to be less than 5%. A remaining point of concern is the development of the coronary arteries which first originated from the functional pulmonary artery, the anatomical aorta. During the surgical procedure they are reimplanted in the "neo-aorta". Future problems may occur due to this extensive handling. Thus, these patients will still require long term follow-up.

*hypoplastic left heart (syndrome)*

Hypoplastic left heart syndrome is a disorder consisting of several cardiac anomalies: i.e. critical stenosis or atresia of the aortic valve and a rudimentary or absent left ventricle, mitral valve and ascending aorta (55,56). Circulation is dependent on a patent arterial duct which may explain why newborns with hypoplastic left heart syndrome do reasonably well at first but then show progressive deterioration when pulmonary vascular resistance decreases and the arterial ductus closes. If not treated shortly after birth this anomaly almost invariably follows a fatal course within the first weeks post partum. The use of prostaglandin $E_1$ to maintain duct patency and additional medical treatment including mechanical ventilation allows time to establish the diagnosis and draw up a treatment strategy. Once the diagnosis of a hypoplastic left heart is established, three options are available to the parents and physician facing this problem (56). Abstinence in combination with supportive care is a justifiable option especially given the uncertain results of the

current options. Alternatively, when available, a donor transplant may be offered. However, immune response and subsequent graft rejection has not yet been resolved completely. Furthermore, long-term prognosis has not yet been established since this procedure was only started in the mid 1980s. The mid-term prognosis of those operated appears encouraging with a 3 year survival rate of over 80% (55). The third alternative, a two-staged palliative reconstruction, was first reported by Norwood in 1981 (57). Continuing efforts to improve this technique have lead to a 40 to 60% survival of the first stage. Subsequently, these patients are candidates for a stage two modified Fontan procedure. This procedure again has an inherant mortality, resulting in a 25 to 30% overall survival beyond the age of 2 years. A switch from the Norwood procedure to the transplant option may improve these overall results slightly. However, the initial advantage of less aggressive neonatal immune response may be lost. The clinical status of post-operative patients is relatively good. The exercise tolerance of transplant survivors appears to approach normal values, yet, immuno-suppression will always be required. Survivors of the second stage of the Norwood procedure may never reach a normal exercise tolerance, although, the majority will be able to function according to NYHA class I or II without medication (58).

*hypoplastic right heart*

Hypoplastic right heart may be considered a consequence of tricuspid atresia which prevents blood flow from the right atrium into the right ventricle. Subsequently, the right ventricle remains underdeveloped. A co-existing ventricular septal defect may allow some flow through the right ventricle and the pulmonary artery which may otherwise also remain underdeveloped. Extra-cardiac anatomical variation in particular a transposed position of the aorta and pulmonary artery may finally complete this type of malformation. The symptoms and prognosis are to a large extent determined by the magnitude of the pulmonary blood flow. Progressive central cyanosis, sometimes only appearing after several years, as a result of spontaneous closure of a ventricular septal defect, a patent arterial duct closing or if pulmonary hypertension evolves, is the major symptom. In addition, hypoxic spells may occur as a sign of critically low pulmonary blood flow.

Without reservation tricuspid atresia, or hypoplastic right heart, can be considered a

serious congenital anomaly. It has a 65 to 70% infant mortality and if not treated only 10% survives to reach the age of 10 years. Fontan has introduced a physiologic correction for this group of anomalies over two decades ago. Subsequent adaptation has resulted in improved results and currently operative mortality is <5% under optimal conditions (59). Of the survivors > 75% do well with a NYHA class I functional status and no additional medication. However, cautious interpretation is warranted because late complications cause a 10 to 15% mortality long after surgery.

## 4.4 FETAL CARDIAC STATE

The anomalies discussed previously constitute the majority of cardiovascular malformations encountered in live born, and have all been reviewed from a postnatal perspective. However, the fetal circulation is profoundly different from the postnatal circulation. Accordingly, the abnormalities described may have different consequences for fetal well-being. Therefore, the nature of the fetal circulation may need to be emphasised. Applying the sequential approach, oxygenated blood from the placenta, through the venous duct, enters the right atrium through the inferior caval vein, mixes with de-oxygenated blood from the lower half of the body, then is preferentially passed through the foramen ovale into the left atrium. From there flow will be guided into the left ventricle and, subsequently, into the ascending aorta. De-oxygenated blood from the superior vena cava enters the right atrium, flows into the right ventricle, which pumps into the pulmonary artery. Prenatally, pulmonary flow is negligible, thus the blood-flow from the pulmonary artery continues through the ductus arteriosus into the descending aorta (60). Specific features of the fetal circulation, the foramen ovale and the (patent) ductus arteriosus allow preferential shunting of oxygenated blood. As a consequence the left and right heart operate in parallel prenatally, hence, at identical after-load and pressure, rather than sequentially, that is at different after-loads, postnatally.

Furthermore, the proportional distribution of cardiac anomalies above is derived from postnatal epidemiologic studies on the prevalence of congenital heart disease. Prenatally this order may be entirely different because the live-born population can be perceived as a selection originating from a much larger 'population' of conceptions many of which ended

in miscarriage prematurely, possibly related to congenital (cardiac) anomalies. Yet, to indicate what impact the majority of postnatally encountered anomalies may have prenatally, and to clarify what current fetal medicine may have to offer, an identical hierarchical order will be maintained.

*ventricular septal defect*

As right and left ventricles operate at an equal after-load prenatally, there is no pressure gradient between the ventricles. Accordingly, important shunting will not occur and as a result a ventricular septal defect has no hemodynamic importance in fetal life. Possibilities for prenatal diagnosis are restricted because a considerable proportion of the malformations are too small for the resolution of currently available ultrasound scanners. Merely the large defects may be recognised by means of a fetal four chamber view. Furthermore, the lack of shunting eliminates recognition by means of Doppler techniques. Finally, prenatal detection of this type of anomaly is not likely to alter postnatal opportunities and options for treatment because of the usually limited (hemodynamic) consequences in the short term. The noted relation with other congenital anomalies and chromosomal defects would, however, make prenatal detection desirable.

*atrioventricular septal defect*

The atrio-ventricular septal defect is a more serious defect postnatally, yet again, this anomaly does not have a detrimental effect on the fetus. As part of normal development blood from the inferior vena cava is shunted through the foramen ovale, which is difficult to distinguish from an atrial septal defect. At ventricular level significant shunting does not occur as the left and right ventricle operate at equal after-load. Therefore, Doppler ultrasound does not offer a solution for the detection of this anomaly. However, the anatomy of the fetal heart, in particular the four chamber view, as visualised by ultrasound will be affected and renders this malformation detectable prenatally by means of 2-D ultrasound. This would be desirable as atrio-ventricular septal defects are often related to chromosomal anomalies, in particular Down's syndrome. Prenatal recognition of this type of anomaly is an indication for fetal karyotyping and may subsequently determine adjustment of obstetrical management if a chromosomal defect is detected. Apart from

patients with severe atrio-ventricular valve regurgitation, which may already present with heart failure prenatally, postnatal treatment and prognosis will not be affected. Acute deterioration of the neonate with atrio-ventricular septal defect is unlikely.

*patent ductus arteriosus*

A patent ductus arteriosus, a normal structure of the fetal circulation, by definition can not be considered an anomaly prenatally. This fetal vascular structure can, however, be identified prenatally in extended 2-D echocardiography of the right heart connections and the outlet of the fetal heart. Flow through the ductus arteriosus should also be demonstrable during Doppler ultrasound studies.

*atrial septal defect*

The foramen ovale, if visualised during fetal echocardiography can rarely be distinguished from a pathological atrial septal defect. Furthermore, a functional distinction between atrial septal defects and the foramen ovale is difficult. Accordingly, anatomical deformations and hemodynamic consequences will be limited to accompanying malformations which may be present. Still, though not affecting fetal well being, large septum primum defects may be detectable because of an altered four chamber view.

*pulmonary stenosis*

Stenosis of the pulmonary valves hampers blood flow through the pulmonary artery. This poses a threat to postnatal life since pulmonary circulation is needed for the oxygenation of blood. In contrast, prenatal oxygenation occurs via the placenta, hence, fetal life will not be in danger. The normal development of the fetal heart, however, may be impeded. Hemodynamic complications with markedly increased outflow resistance of the right ventricle may bring about changes in the right ventricle such as hypertrophy. The main, left and right pulmonary arteries may remain relatively underdeveloped as a result of diminished flow. Opportunities for antenatal detection of this type of anomaly depend on the above mentioned secondary changes. Therefore, it can be anticipated that only severe cases, manifesting with an altered four chamber view and right heart connections, are detectable by means of 2-D ultrasound. This also applies to Doppler ultrasound, which

may show increased flow velocity in the main pulmonary artery and diminished flow through the ductus arteriosus. The prognostic advantage of prenatal detection will depend on severity of the stenosis. If the pulmonary circulation is duct dependent prenatal diagnosis and subsequent optimal postnatal care may affect the prognosis.

*tetralogy of Fallot*

Fallot's tetralogy, embryologically emanating from a mal-alignment ventricular septal defect, with postnatal persistence of right ventricular hypertrophy as a consequence of right ventricular outflow tract obstruction, can be reviewed accordingly. Again, the specific characteristics of the fetal circulation with physiological right to left shunting and identical after-load, prevent adverse effects on the developing fetus. Prenatal detection is dependent on recognition of the three primary defects. As mentioned above, only a large ventricular septal defect can be detected during 2-D scanning. The dextro-deviation of the aorta may be noticed during 2-D scanning if the left heart connections and outlet are imaged. Finally, pulmonary stenosis may only be detected on right heart connections and outlet images. Doppler techniques may provide additional information since prenatal flow patterns may be disturbed as well. The expected gain, if the anomaly is detected prenatally, may be limited to those cases with severe obstruction of the right ventricular outflow tract and hypoplasia of the pulmonary arteries. Only this category is subject to immediate neonatal problems due to restricted pulmonary circulation and should therefore preferably be dealt with promptly after birth.

*coarctation of the aorta*

Constriction of the aorta may evolve with closing of the ductus arteriosus, and accordingly develop postnatally. However, cases that occur prenatally will not have major fetal hemodynamic consequences or influence fetal well-being. The delivery of adequate blood flow through the upper part of the body is not hampered and flow through the ductus arteriosus secures supply to the lower half of the body. As a result prenatal detection of coarctation by means of 2-D ultrasound usually depends on ultrasonographic visualisation of the outlet, or more specific, the aortic arch with branching arteries and the ductus arteriosus. Additional Doppler ultrasound may theoretically reflect increased flow velocity

or altered flow patterns at the site of constriction but this has not been demonstrated. The impact of prenatal recognition of coarctation of the aorta may be limited to severe cases because, due to ductal closure, these may deteriorate soon after birth.

*aortic stenosis*

Aortic stenosis has a limited impact on prenatal life; even severe stenosis appears to be well tolerated by the fetus, because a diminished left heart output may be compensated by increased right heart output and subsequent increased shunting through the ductus arteriosus. In the majority of cases stenosis of the aortic valves will present some time after birth with relatively mild symptoms. Very severe outflow obstruction may, however, cause problems prenatally if left ventricular myocardial damage occurs. Difficult 2-D ultrasonographic detection of this type of anomaly can be anticipated and obviously depends on imaging the left heart connections, more specifically the aortic valve. Secondary myocardial changes and left ventricular dilatation may lead to the diagnosis in severe cases. Altered flow may be observed with Doppler techniques. As mentioned above, the natural history is generally mild and as a consequence the potential profit of prenatal detection is confined to the severe cases.

*transposition of the great arteries*

The nature of this type of anomaly assures adequate blood flow to all fetal parts and as left and right ventricles operate at equal after-load the right ventricular function will not be affected prenatally. Accordingly, heart failure will not evolve prenatally. Antenatal diagnosis is limited to outlet images of the great arteries. A neonate with transposition may benefit from prenatal detection because subsequent to the transition of the fetal circulation to the postnatal circulation severe hypoxia may develop. However, the ductus arteriosus does not usually close abruptly after delivery and current prostaglandin treatment will prevent deterioration of the compromised neonate.

*hypoplastic left heart (syndrome)*

Hypoplasia of the left ventricle implies that the left heart is (functionally) absent. However, the right ventricle is capable of supplying the fetal circulation with sufficient

blood flow shunted through the ductus arteriosus. Hence, only after birth with diminishing ductal flow life becomes dependent on both ventricles functioning sequentially and will be threatened. It is clear that the anatomy of the fetal heart is very much affected and this can be demonstrated by means of 2-D echocardiography. Because of the circulatory evolution (the systemic circulation becomes dependent on the left ventricular function with closure of the arterial duct) which commences after birth prenatal detection would be important to be able to offer optimal care shortly after delivery. Furthermore, taking into account the still serious prognosis for these cases of congenital heart disease, the parents may strongly favour termination of pregnancy.

*tricuspid atresia/hypoplastic right heart*

From a fetal circulatory point of view, hypoplasia of the right ventricle results in a situation comparable to that of hypoplasia of the left ventricle. It has no impact on fetal well being. Prenatal detection is feasible by means of 2-D ultrasound since the anatomical features of the heart are completely distorted. Whereas, in this condition a normally developed pulmonary artery is essential during postnatal life, this is not the case prenatally. Antenatal ultrasonographic evaluation of the peripheral pulmonary arteries may be difficult because flow is limited prenatally and can only be visualised in the right heart connections and outlet images. As progressive deterioration will occur postnatally with diminishing shunting through the ductus arteriosus, advantages of prenatal detection are particularly related to the assessment of pulmonary arterial connections. In case the outlook is grim termination of pregnancy may be an option.

*univentricular heart*

A univentricular heart, similar to hypoplastic right and left heart, has a limited impact on fetal well being prenatally. During routine ultrasound evaluation the fetal four chamber view should disclose the absence or severe hypoplasia of one ventricle. In fact, univentricular heart largely is a general diagnosis, often occurring in combination with other anomalies such as double inlet left ventricle or certain types of double outlet right ventricle. Most cases of univentricular heart are part of complex malformations that invariably predict a complicated postnatal course. In particular the volume of pulmonary

blood flow will determine the prognosis. Accordingly, assessing the pulmonary vascular dimensions is of prime importance after birth.

## 4.5 GENERAL COMMENTS

Papers on the actual occurrence of congenital heart disease are scarce. A cohort study to assess the frequency of occurrence of cardiovascular malformations should ideally prospectively gather follow-up data on each conception, which is a demanding task. Currently, only limited retrospective data are available from some attempts that have been made to estimate the rate of anomaly related abortions. It appears that even the birth prevalence of congenital heart disease has not yet been accurately established, although a reasonable estimate is available especially on the relative proportions of the various sub-types of cardiac malformations. With this limitation of the data in mind and the treatment options presently available for neonates or infants with congenital heart disease, which have resulted in a substantially improved prognosis with less than 10% overall mortality, one might conclude that cardiovascular malformations no longer have a major impact on children's health(care) in general. This, however, is not justified as the efforts and resources these patients take are tremendous. Prenatal detection has been proposed as a (partial) solution of the problem of congenital anomalies. Table 2 summarises the information on prevalence and mortality presented. Additionally, table 2 gives an interpretation of the potential of an ultrasound screening programme for congenital heart disease as encountered in a live-born population.

Table 2 Summary-table of the prevalence, impact, detectability and expected effect of prenatal detection on post-natal prognosis.

| type of anomaly | prevalence (%); of all CHD | mortality (%) | prenatal detectability by means of 4CV | prognostic advantage of prenatal detection |
|---|---|---|---|---|
| ventricular septal defect | 30 | < 5 | - (±) | - |
| atrio-venticular septal defect | 5 | ≈ 25 | + (±) | - |
| patent ductus arteriosus | 10 | ↓↓ | - | - |
| atrial septal defect | 10 | < 5 | - (±) | - |
| pulmonary stenosis | 10 | ↓ | - | ± |
| tetralogy of Fallot | 7 | < 10 | - (±) | - (±) |
| coarctation of aorta | 7 | ≈ 15 | - | ± |
| aortic stenosis | 5 | ≈ 10 | - | - |
| transposition of great arteries | 5 | ≈ 15 | - | - |
| hypoplastic left heart | 2 | ≈ 70 | + | ± |
| hypoplastic right heart | 2 | ≈ 70 | + | ± |

CHD = congenital heart disease; estimated birth-prevalence: 8 per thousand live-born.
4CV = four chamber view; suggested ultrasound technique of prenatal screening for congenital heart disesase.
- = detection not possible or no prognostic effect; ± = detectability and effect depending on size and location of (anatomical) defect; + = detection possible or positive prognostic effect; a minority of the cases, between brackets, may be detectable or have a prognostic advantage of prenatal detection, again depending on size and location of the anomaly.

Many of the cardiovascular anomalies presenting in a newborn population have a limited impact on prenatal survival. This implies that the yield in prognosis for the subgroup of fetuses that would have survived to term may not improve significantly in a society that can provide immediate high level paediatric care to all critically ill neonates. A numerically small proportion may benefit from prenatal detection especially if prenatal treatment becomes available. We must keep in mind that indeed the live born are a selection of the cases present at 20 weeks gestation, and may well be less severely affected. Currently, very little is known about the prenatal natural history of congenital

heart disease. It may be that prenatal detection of cardiovascular anomalies in the second trimester has a potential yield for the subgroup of affected fetuses that would otherwise have aborted spontaneously. Future research on this specific group of cases of congenital heart disease should disentangle the natural history and possibilities for treatment. The gain could be sizeable as data on incidence and causal mechanisms may be directly interrelated. Furthermore, the impact of cardiac anomalies on fetal survival could also be established with greater accuracy.

Despite the fact that prenatal detection may not have the benefit one might intuitively expect, the association of cardiovascular anomalies with other congenital malformations and chromosomal anomalies may indicate the need for prenatal detection indicated. The presence of congenital heart disease in the fetus is a risk-factor that should engender to more extensive fetal examination. Furthermore, one should bear in mind that prenatal detection of severe congenital malformations may dissuade obstetricians and women in labour from interventions like a Caesarian section on account of fetal distress. Thus, possible maternal risks of such a procedure may be averted. Finally, it appears that exclusion of fetal anomalies by means of an non-invasive screening test is highly appreciated by future parents. After all, in Western societies the majority of expectant women choose to have a prenatal ultrasound.

The issue of a screening test touches upon yet another crucial point. Even well-trained optimally equipped sonographers can attain limited returns as a substantial proportion of the malformations encountered may just not be detectable with the current ultrasound machines and techniques. Therefore, we feel that before a screening test for prenatal detection of congenital heart disease is implemented, the efficacy of such a strategy should be evaluated.

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# CHAPTER 5

# PRENATAL DIAGNOSIS OF CONGENITAL HEART DISEASE; PROSPECTS AND PROBLEMS

## INTRODUCTION

Over the last decades diagnostic ultrasound examination of the human fetus has evolved from a research tool into a valuable clinical diagnostic test. With improvement of ultrasound equipment its use has gradually shifted from mere evaluation of gestational age, position and number of fetuses and placenta location to more formal and systematic screening for congenital anomalies. Among those, congenital heart disease, with a relatively high prevalence of about 8 per thousand live births (1), has proven to be accessible for prenatal detection in many cases (2-11).

The aetiology of congenital heart disease to a large extent still is unknown. Approximately 90 % of the cases are of multifactorial origin, e.g., result from an interaction between genetic constitution and environmental influences without further aetiologic specification (12). Accordingly, the majority of affected infants is born to mothers without previously known risk factors for bearing children with congenital heart disease. This implies that most of the severe cases will become apparent at or soon after birth unless detected prenatally. A systematic prenatal screening procedure for congenital malformations of the heart, made available to all pregnant women may accelerate the diagnosis to a point in time which allows adjustment of obstetrical management (13,14). Generally, it is assumed that this in turn could have beneficial effects for the neonate and the parent(s). The timing, location and the mode of delivery can be determined to grant the neonate optimal chances for survival (10,15,16). The strong association with chromosomal defects and non-cardiac malformations implies that karyotyping and extended structural ultrasound examination of the fetus should be performed after detection of an anomaly (12,17-19). Subsequently, genetic counselling can be offered to the parents to inform them of the risk they carry for having affected offspring in the future. In case of fetal tachycardia, possibly associated with fetal hydrops, subsequent transplacental drug treatment may be offered to try and improve fetal condition (20-22). The recent development of fetal medicine has created a new era of possibilities. Furthermore, detecting a non-viable fetus early in pregnancy offers the option of termination of pregnancy. Eventually, reassuring the future parents after exclusion of (severe) fetal anomalies may be perceived as the greatest value of screening.

Many reports have appeared on the efficacy of ultrasound screening for congenital heart disease in obstetrics (23-32). However, most of the results available are obtained from teaching hospitals or tertiary referral institutions with above average expertise and interest in the subject. Additionally, and perhaps more important, the patients involved may be a selection of high-risk cases. Without due consideration the findings of these experts can not be extrapolated to a hypothetical yield that a screening programme may have if applied routinely to all pregnant women or low risk pregnancies. The purpose of this paper is to review the results of screening programs as presently available and to arrive at some conclusions and recommendations for further study.

## APPROACH

### *Papers*

Papers and books on ultrasound screening in obstetrics published before 1993 were selected using several sources of information. Computer based literature reference systems Medline and Current Contents have been applied in order to check for reports published from 1980 and onward. A lateral reference search mainly aiming at the period before 1980 completed the survey. This rendered a considerable list of reports on ultrasound employed to detect congenital heart disease prenatally. Ultimately a limited number of reports (table 1) appeared to be relevant to this review, comprising information published on prenatal screening programs for congenital cardiovascular malformations by means of ultrasound.

Table 1 Prenatal ultrasound screening programs for congenital heart disease as reported from 1986 to 1993.

| author | years of study | hospital type | gestational age range | diagnostic procedures prenatal | postnatal | follow up duration | study design | method of ascertainment | study population | number of fetuses | total number of cases | yield ($10^{-3}$) | sensitivity ($10^{-2}$) [a] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Allan et al.[24] | 80 - 85 | general | ≥ 16 | 4CV | clinical evaluation | not specified | prospective | follow up of cases only | low and high risk | unknown | 89 | unknown | 45 [b] |
| Hegge et al.[26] | 81 -86 | teaching | 15 - 27 | 4CV (≥ 1) | clinical evaluation and autopsy records | not specified | retrospective | follow up of cases only | low and high risk | 6700 | 26 | 3.9 | 48.5 |
| Fermont et al.[27] | 82 - 84 | general | 14 - 41 | 4CV (≥ 1) | clinical evaluation including echocardiography | neonatal period | prospective | follow up of cases only | low risk | 28000 | 39 | 1.4 | 17.4 |
| Rustico et al.[29] | 86 - 87 | teaching | 23 (average) | two dimensional echocardiography (≥ 1) | routine examination, clinical and autopsy records | 2 - 3 months post partum | prospective | follow up of all children | low risk | 1841 | 18 | 9.8 | 38.9 [c] |
| Vergani et al.[32] | 87 - 89 | teaching | 18 -20 | 4CV (≥ 1) | clinical evaluation and autopsy records | 1 week post partum | prospective | follow up of all children | low and high risk | 5336 | 32 | 6 | 60.8 |
| Bromley et al.[25] | 87 - 90 | teaching | ≥ 18 | 4CV (fetal echocardiography) [d] (≥ 1) | clinical and autopsy records | not specified | retrospective | follow up of cases only | low and high risk | unknown | 69 | unknown | 60.9 (82.6) [b,d] |
| Tegnander et al.[31] | 88 - 90 | teaching | 18 | 4CV (once) | echocardiography clinical and autopsy records | 1 - 3 years | prospective | follow up of cases only | non selected | 7182 | 43 [e] | 6 | 7.0 |
| Achiron et al.[23] | 88 - 90 | teaching | 18 - 24 | 4CV (fetal echocardiography) [d] | routine examination, echocardiography and autopsy records | neonatal period | prospective | follow up of all children | low risk | 5400 [f] | 23 | 4.3 | 25.5 (41.7) [d,f] |
| Sharland et al.[30] | 88 - 90 | general | not specified | 4CV (≥ 1) | clinical evaluation | not specified | prospective | follow up of cases only | low and high risk | 23861 | 69 | 2.9 | 27.7 |

4CV: Four Chamber View. Plane of the ultrasound examination used in all screening procedures. Number of ultrasound examinations applied in order to achieve a 4CV; between brackets if specified.

a: Unless specified calculated with an assumed prevalence of congenital heart disease of 8 per 1000 live births.

b: Population-base unknown; calculation according to reported number of cases.

c: Calculation according to reported prevalence of 9,8 per 1000 births.

d: Extended prenatal echocardiography; including short axis,long axis inflow and outflow tracts.

e: Calculation according to the reported prevalence of 6 per 1000 live births.

f: Ignoring the reported lost to follow up of 53 fetuses; subsequent calculations accordingly.

*Analysis*

The birth prevalence of congenital malformations is defined as the number of cases divided by the number of births and is usually expressed per thousand live births. The prevalence figures of congenital heart disease reported have been shown to vary over a wide range related to various issues of study design (33,34). Because a similar problem may have occurred in the studies reviewed, only the original study size and number of cases detected have been summarised. Subsequently, direct calculation of various measures of occurrence is possible from the quantitative information in most of the reports. For instance, the yield of cases, or proportion of infants affected by congenital heart disease, is calculated by dividing the actual number of malformations detected prenatally and/or postnatally by the number of fetuses screened. Also, the sensitivity of the diagnostic procedure, defined as the proportion of cases detected, calculated as a fraction of the total number of cases detected, can be estimated. However, as mentioned above, differences in study design across the various studies may have resulted in incomparable yields of congenital heart disease which in turn may have biased the sensitivities originally reported. Accordingly, an attempt was made to correct for this source of bias. It appeared that the yield of cases varied markedly and was not in accordance with what may currently be a best estimate of the prevalence of cardiovascular malformations, namely 8 per thousand live births (1). Dividing the number of malformations detected prenatally by the number of malformations that may be expected in the screened population, assuming a conservative estimate of prevalence of congenital heart disease of 8 per thousand live births (1), renders a corrected sensitivity. To help illustrate the corrected figures table 2 displays the possible outcomes of a digotomous (screening) test and is referred to in the following formulas.

Table 2 2 x 2 table of possible outcomes of a (diagnostic) screening test.

| | | congenital heart disease | | |
|---|---|---|---|---|
| | | present | absent | |
| screening test | positive | A | B | A + B |
| | negative | C | D | C + D |
| | | A + C | B + D | A + B + C + D = T |

A = number of true positive test results; B = number of false positive test results; C = number of false negative test results; D = number of true negative test results; T = total number of fetuses screened.

The yield of congenital heart disease is calculated by *(A + C)/T*; *A* being the number of cases detected before birth, *C* being the number of cases detected only after birth and *T* being the total number of cases screened. Normally one would calculate the sensitivity by *A/(A + C)*. However, as mentioned above comparing the different studies regarding this test characteristic demands a common denominator. Replacing *A + C* by a fixed number of cases of congenital heart disease that can be expected under the assumption of a common prevalence corrects for the apparent variability of the sensitivity due to ascertainment methods. The number is calculated by taking the product of the total number of fetuses in the study and 0.008 (the above mentioned best estimate of prevalence of congenital heart disease). Thus, the sensitivities presented in table 1 are estimated by *A/(T*0.008)*.

## FINDINGS

Diagnostic ultrasound has been introduced only a few decades ago and the routine use of this technique in obstetrics has been proposed even more recently. Reports on the potential of fetal echocardiography as a screening test for congenital malformations have been appearing since about 10 years (2). In general, these communications originate from teaching hospitals or other specialised centres. In the discussion of their work the authors frequently speculate on the favourable effects that routine application of ultrasound may have on the outcome of pregnancy. Very few papers, however, have been published from actual studies designed to quantitatively evaluate the efficacy of ultrasound as a routine

screening procedure for congenital heart disease. From an extensive list of articles and abstracts on prenatal ultrasonographic detection of congenital malformations, only nine reports focus on screening for congenital heart disease. If reported in the publications, information on hospital type, gestational age range, prenatal and postnatal diagnostic procedures applied, duration of postnatal follow up, study design, method of case ascertainment, characteristics of the expectant women or rather the pregnancies constituting the study population, the number of fetuses screened and the number of cases detected either prenatally and/or postnatally was extracted. These main design properties and results are summarised in table 1. Regrettably, definitions of congenital heart disease applied are not provided by any of the authors and therefore can not be evaluated.

Possible consequences of differences in design across studies for the comparability of the results can be inferred by partitioning of the studies reviewed according to methodological characteristics.

As is shown in figures 1 and 2 respectively, categorisation according to the type of hospital where the prenatal ultrasound examination was carried out indicates that the overall yield of cases detected is higher and a larger proportion of malformations is detected prenatally (sensitivity) in teaching hospitals. The study by Tegnander et al. (31) appears to be an exeption.

Figure 1 Yield of congenital heart disease according to type of hospital

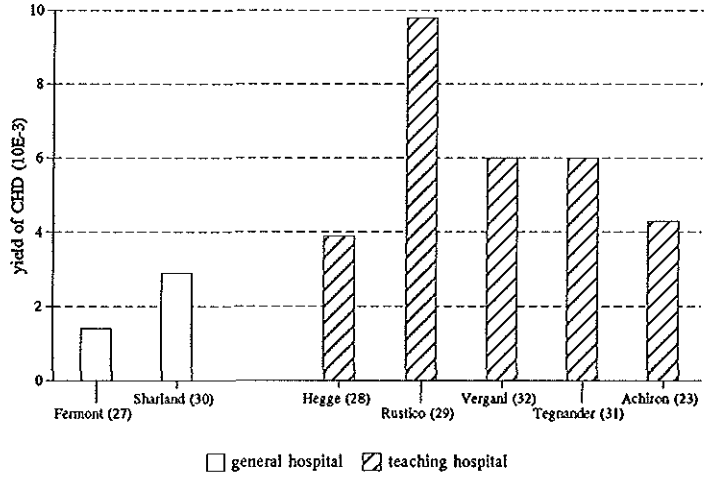
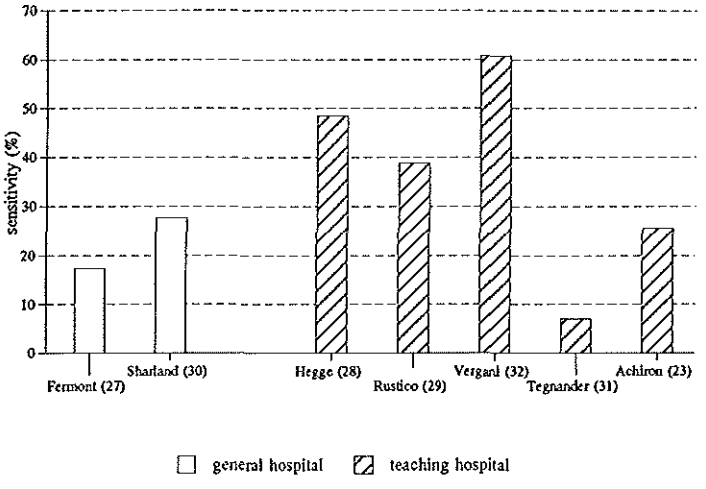


Figure 2 Sensitivity of fetal echocardiography according to type of hospital

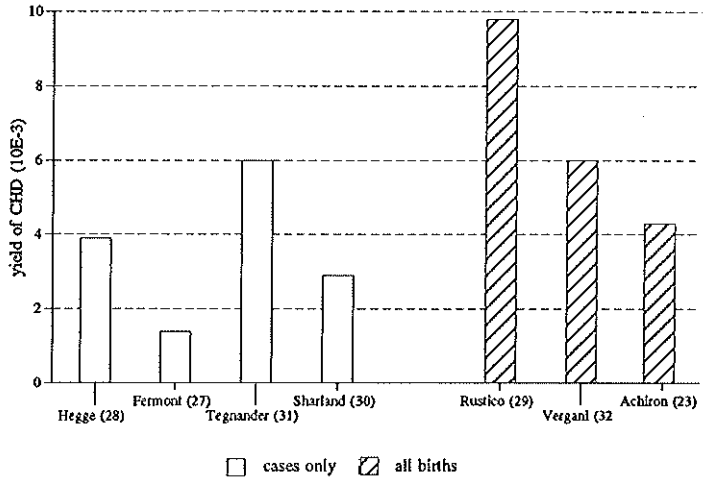



The gestational age at which the ultrasound examinations were performed appears to be within a range considered adequate for visualisation of the fetal four chamber view.

Similar to case definition, the diagnostic procedures applied have not been described in detail. However, with repeated fetal scans and extended examination better detection is obtained.

Also, the completeness of follow-up should be considered. In fact, several issues influence the results in this respect. Duration of follow-up and study design, either retrospective or prospective, and case ascertainment are in question. However, as duration of follow-up again is not specified sufficiently it is difficult to evaluate the data in this regard. Separating data according to either retrospective or prospective demonstrates a relatively high sensitivity in retrospective studies. Figure 3 gives the yield of congenital heart disease according to the ascertainment of follow-up.

Figure 3 Yield of congenital heart disease according to ascertainment of follow-up




With routine postnatal examination of all infants, irrespective of symptoms of congenital heart disease, higher numbers of cases are detected.

Finally, the populations studied consist of low risk or low and high risk pregnancies. The yield of cardiovascular malformations does not appear to vary systematically with either population type. However, on average the sensitivity calculated in the low risk pregnancies is beneath that attained in the mixed groups.

## DISCUSSION

Apparent from table 1 is the variability in the proportion of cases of congenital heart disease found in the populations studied. The column "yield", with a range of 1.4 to 9.8 per thousand births, reflects this spread. It is unlikely that this represents a real difference in occurrence of congenital heart disease across the various populations studied. For instance, case definition, though none of the authors has specified the definition and classification of congenital heart disease applied, may have influenced the yield. The inclusion or exclusion of several cases of minor defects like small ventricular septal defects, especially if the study is of small size, could have had a substantial impact. Despite difficulties of interpretation arising from possible differences in case definition, other methodological issues have to be addressed. Several methodological differences have

been shown to be associated with the number of cases of congenital malformations detected and therefore the comparability of results.

Figure 1 clearly shows that studies conducted in teaching hospitals have reported a larger proportion of children with congenital cardiovascular malformations. This may represent the underlying ability to recognise congenital heart disease in the study population with the appropriate diagnostic procedures. Moreover, with the exeption of the study by Tegnander et al. (31), it is apparent in figure 2 that the sensitivity achieved, or the ability to detect congenital heart disease prenatally by means of ultrasound, is also considerably higher in these reference centres. It is quite possible that the limited amount of time and personnel available per ultrasound scan and the less specialised skills of the ultrasonographers in general hospitals have implications for the feasibility and effectiveness of routine ultrasound screening for congenital heart disease. It is unlikely that inclusion or exclusion of high risk pregnancies has distorted this observation because both teaching and general hospitals have equally included high risk cases.

The gestational age at which fetal ultrasound evaluation is performed has been shown to affect the accuracy of the diagnostic procedure (2,7,11). Currently available ultrasound equipment allows trans-abdominal recognition of fetal structures from a gestational age of about sixteen weeks onward. This minimal duration of pregnancy for visualisation of congenital heart defects appears to have been met by all studies.

The diagnostic procedures applied prenatally may also influence the results. No uniform procedure has been defined so far, again complicating comparability. Tegnander et al. reported on a single four chamber view evaluation in a non-selected population, whereas Rustico et al. mention the use of two dimensional echocardiography without further specification, offered at least once in a mixed low and high risk population (29,31). Often the scanning time, the staff and the resources available for each individual pregnancy limit the possibilities for detailed or repeat scans. The situation described by Tegnander (31), one single four chamber view incorporated in a structural ultrasound examination in the second trimester, seems to best reflect a realistic screening procedure applicable in current practice.

The way which postnatal diagnosis is accomplished is not exactly specified in any of the reports, but has also been shown to influence the yield of congenital heart disease (33,34).

A standardised protocol including routine examination of all products of conception is preferable.

This has implications for the necessary duration of postnatal follow up. Serious congenital malformations will be detected soon after birth. However, less severe defects possibly causing fewer and less obvious symptoms may only be detected at a later age unless physical examination with history taking is offered routinely to all children. This way, for example, an otherwise unnoticed murmur will also be evaluated, establishing a final diagnosis. A follow up period of sufficient length, probably (at least) six months post partum, seems necessary (35) . By then the majority of the cases of congenital heart disease will have been detected.

The directionality of time in the way data are gathered may bias the results. It is generally understood that prospective data collection, as opposed to retrospective data collection, is to be preferred. Bromley et al. (25) and Hegge et al. (28) have evaluated the performance of prenatal ultrasound using estimates of prevalence based on postnatally recognised cardiovascular malformations. The accuracy of this procedure greatly depends on the completeness of case ascertainment; incomplete ascertainment may bias the results considerably. Cases suspected prenatally will have had a full work up and are not likely to be missed postnatally. However, perhaps apart from possible prenatal spontaneous closure of a ventricular septal defect, a case of congenital heart disease not detected or present postnatally, may well not have been detected prenatally either. Therefore, and not surprisingly the calculated sensitivities of the two retrospective studies are relatively high, e.g., 48.5 % and 60.9 % respectively, and may overestimate the actual situation.

The same potential flaw in study design exists in prospective studies if not all cases of congenital heart disease are recognised and monitored postnatally. A thorough evaluation of a screening procedure demands full ascertainment of all cases. Thus, as mentioned above, routine follow up of all children, with history taking, physical examination and further evaluation if warranted is a prerequisite.

The fact that the type of population studied did not appear to have affected the yield of cases does not mean this is not an important issue. The inclusion of high risk pregnancies in the studies presented may still have subverted the results. High risk pregnancies may represent a subgroup with a higher prevalence of congenital malformations, possibly

showing a greater number and more severe symptoms. This, in turn, provides an explanation for a larger proportion of cases of congenital heart disease being recognised prenatally in the mixed population type study. Moreover, the sensitivities reported in this review are calculated according to a rather conservative assumption of 8 per thousand live births. As the prevalence of congenital heart disease may in reality be higher in the high risk group, the sensitivities calculated would decrease proportionally.

## CONCLUSIONS

Most of the available reports on screening for congenital heart disease by means of ultrasound, more specifically the four chamber view, appear to suffer from one or multiple flaws in study design which may have contributed to an overestimation of the efficacy of routine fetal echocardiography. As mentioned previously, it would seem that the study by Tegnander et al. reflects a realistic screening situation (31). The sensitivity calculated from their data with an assumed prevalence of 0.008 is very low: 7.0 %, and has yet to be confirmed. Other studies, not aiming at evaluation of fetal echocardiography in particular, but rather for fetal ultrasound in general have reported similar results (16,36-39). These results are in marked contrast with early reports suggesting sensitivities as high as 85 to 95 %, which are likely to have produced all too optimistic views (24,26).
Future research, evaluating the efficacy of a screening procedure should evaluate the test prospectively in a representative (low risk/non-selected) population and clinical setting. Remaining issues to be taken into account are meticulous case definition and case ascertainment after a sufficiently long period of follow up. Finally, the study has to be of adequate size to allow for statistical variability.
Evaluating an antenatal screening test for congenital heart disease by means of an ultrasonographically obtained fetal four chamber view in a low risk population, as performed in a general hospital once at about 20 weeks gestational age, with routine (postnatal) follow up of all pregnancies may contribute to the ongoing international discussion on the recommendation of fetal anomaly screening.

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# CHAPTER 6

# EVALUATION OF ROUTINE FETAL ULTRASOUND SCREENING FOR CONGENITAL HEART DISEASE IN NORMAL PREGNANCY; A PROSPECTIVE STUDY IN THE NETHERLANDS

## INTRODUCTION

Congenital heart disease accounts for a large proportion of congenital malformations. The estimated birth prevalence of congenital malformations appears to be within the range of 20 to 30 per thousand live births (1,2). Cardiovascular anomalies occur in at least 8 per thousand live births (3), of which approximately half are of little hemodynamic consequence or can relatively easily be corrected (4,5). Yet, cardiovascular malformations still constitute a major health problem responsible for over a third of congenital anomaly related infant mortality (6). Furthermore, as congenital defects may be associated with abortions the prevalence is likely to be even higher prenatally. However, limited data are available because of difficulties in gathering data on anomalies present prenatally. The prenatal prevalence of congenital heart disease appears to range from 12 to 154 per thousand, depending on gestational age and study design (7).

Over the last decade several authors have reported on the potential of a routine fetal four chamber view evaluation at approximately 20 weeks gestational age for antenatal detection of congenital heart disease (8-17). A normal four chamber view is supposed to exclude the majority of serious malformations. The prospect of a safe and simple screening test for this important neonatal health problem has led to incorporating the four chamber view into fetal ultrasound in the Netherlands (18). The capability of predicting congenital heart disease may have obvious benefits for fetus and future parents. If an anomaly is detected, obstetric policy, especially regarding time and mode of delivery, could be adapted. Subsequently, considering the strong relation of congenital heart disease with chromosomal anomalies, fetal karyotyping could be performed combined with genetic counselling (19-21). Finally, upon excluding anomalies, reassuring the prospective parents may have significant value.

Currently, the majority of expectant women, to a certain extent routinely, receive fetal ultrasound examination for exclusion of congenital anomalies in the Netherlands. In the event of suspected fetal or pregnancy pathology extensive structural ultrasound examination is requested. The ultrasound unit of the Department of Gynaecology and Obstetrics of Dijkzigt University Hospital, Erasmus University Medical School Rotterdam serves the Rotterdam metropolitan area as a referral centre.

At present, a formal evaluation of the fetal four chamber view incorporated into a single routine fetal ultrasound scan at about 20 weeks gestational age, as a screening test for congenital heart disease, has not yet been performed. The relevance of the submitted work ensues from this lack of evidence of the efficacy of the proposed screening test. The present report conveys the design and conduct of a clinical evaluation of routine ultrasound examination as a prenatal screening test for congenital heart disease.

## METHODS

### *Population*

To establish the test characteristics of the fetal four chamber view to screen congenital heart disease, a prospective cohort study enroling pregnant women between 16 and 24 weeks gestation without known risk factors for (re)occurrence of congenital heart disease (table 1) was designed.

Table 1 Risk factors for the occurrence of congenital heart disease in the offspring currently viewed as indication for (non routine) structural ultrasound screening.

| fetal anomalies | maternal anomalies | | familial anomalies |
|---|---|---|---|
| intra-uterine growth retardation | congenital heart disease | | congenital heart disease |
| arrythmia | diabetes mellitus | | genetic syndromes |
| aneuploid | collagen diseases | | |
| polyhydramnion | phenyl ketonuria | | |
| oligohydramnion | rubella | | |
| non-cardiac anomalies (including abnormal karyotype) | teratogens: | alcohol<br>amphetamines<br>anticonvulsants<br>lithium<br>morphomimetics<br>retinoic acid | |

Cardiac anomalies were defined analogous to the ICD IX, according to the major characteristics (22). The time allocated to intake was initially fixed at 18 months. The duration of individual postnatal follow-up was set at six months. At that age all significant

heart disease is likely to have been identified (23). To estimate the number of participants needed for the study, first a conservative estimate of the prevalence of congenital heart disease of 6 per thousand live born was assumed. Second, a literature survey of reports on fetal four chamber view evaluation suggested a sensitivity of 85% and a specificity of 99%. Presupposing a 95% confidence interval of plus or minus 10% for the sensitivity a minimal number of 49 cases needed was calculated. The lower margin of the size of the population of screened fetuses required to realise 49 cases was subsequently estimated to be at approximately 8000. Accordingly, the aim was to recruit 10,000 participants. Accomplishment of recruitment of such a number of respondents implied collaboration with a number of referring hospitals in the vicinity. Hence, the staff of peripheral hospitals were invited to collaborate, providing their personnel was experienced in the evaluation of the fetal four chamber view and a sufficient number of fetal ultrasound examinations were performed per year. Initially nine centres were invited. According to the annual reports of these centres sufficient numbers of pregnancies were scanned to establish a cohort of 10,000 pregnant women within 18 months, thus, averaging a weekly screening rate of 130 pregnant women. Simultaneously, a procedure to ascertain the follow-up of the participating women and their offspring was designed.

*Postnatal data collection*

In the Netherlands, Child Health Clinics, under the responsibility of the Community Health Services, provide health care to all infants at regular intervals. The parents are counselled from one month postnatally onward and the infants undergo a standardised physical examination routinely. This provides an excellent opportunity to determine postnatal cardiac status. Consequently, local Health Services were also invited to collaborate. Furthermore, as the investigators represent the regional tertiary care centres, complementary medical information would be readily accessible. In cooperation with the staff of the participating hospitals and representatives of regional Community Health Services a set of forms for completion was conceived, including written explanation for the pregnant women and attending physicians of the Child Health Clinics (appendix A to E). After consulting the staff of the referring hospitals it appeared that completion of extensive forms would hamper clinical practice at the ultrasound units and hence the

intake of participants. Therefore, in a pilot phase this particular section of the study was evaluated and the forms adapted accordingly. The following procedure was adopted: upon identification at a local ultrasound unit as a potential candidate the expectant woman was asked to participate. Subsequently, an oral consent for the utilisation of selected medical data was obtained. Next, the participant's particulars, the name of the attending general practitioner, the date of the examination, the last menstrual period, the gestational age, the referring obstetrician, reason for referral and the results of the ultrasound evaluation were reported on a numbered form for completion (appendix A), also mentioning whether subsequent referral for a tertiary extended structural examination was requested. At the end of the ultrasound session the participating woman was handed an envelope containing: 1) a written explanation for the respondent (appendix B), 2) a second envelope to be handed to the physician attending to the infant (at the local Child Health Clinic) during the first visit. This second envelope contained: 3) a written explanation for the attending physician (appendix C) and 4) a set of forms modelled like business reply-cards (appendix D and E) with identification numbers identical to those on the form with ultrasound data. The first reply-card notifying continued follow-up, date of examination, birth date, gender and initial history and/or physical examination of the neonate (appendix D), was to be returned immediately after identification as a participant by the physician examining the child. The second reply-card reporting again date of examination, birth date and final health status (appendix E), was to be returned at six months of age. The main objective of the method described above was that the work load would not markedly obstruct daily clinical routine at the ultrasound units nor at the Child Health Clinics, yet would yield the necessary information. The Child Health Clinics operate in such a way that when a health problem is suspected the infant will be referred for further examination. Therefore, all diagnoses could be verified by attending paediatricians, paediatric cardiologists or pathologists.

*Validation of recruitment*

As it was realised that selection of pregnancies with regard to the suspicion of pathology could jeopardize the validity of this research project a separate validation study was planned. At each cooperating ultrasound unit the records of 100 subsequent obstetrical

ultrasound evaluations were arbitrarily drawn. These were to be compared to the ultrasound records in our possession with respect to gestational age, referring obstetrician, reason for referral and finally appearance of anomalies. After matching for gestational age and reason for referral, a similar distribution among the validation-sample and the records of the research data-base regarding the referring obstetrician and occurrence of anomalies would exclude significant selection. Furthermore, Dijkzigt University Hospital is the only tertiary referral centre for extended fetal echocardiography in the greater Rotterdam area. Therefore, all pregnancies referred with a suspected anomaly of the fetal four chamber view could be traced. Subsequently, it could be verified whether the pregnant woman would have qualified as a candidate. If referral of potential respondents outside the research protocol would appear to be limited this would further assure the validity of the study.

*Data handling*

A final logistic problem to be solved was the handling and storage of the data. Periodical personal visitation of the participating hospitals and the ultrasound units permitted data-collection and completion if required. Furthermore, accompanied by "news-letters" stating the latest results and developments, direct feedback and coaching of the ultrasonographers was secured. The anticipated magnitude of the data-set required the development of a computer data-base with automated sub-directories to store the particulars of respondents and general practitioners, ultrasound data and follow-up data. This was realised using the INGRES relational database software (24). Moreover, the completion of follow-up data could to a large extent be ascertained automatically. Measures were taken to limit "loss to follow-up" to a minimum. In absence of follow-up data six months after the calculated term date the general practitioner of the participant was to be approached to try and acquire the missing data.

## RESULTS

*Recruitment*

Initially 9 centres for routine fetal ultrasound, including 2 staffed by personnel of

University Hospital Rotterdam - Dijkzigt, were invited and agreed to collaborate. Depending on local circumstances the scans were performed either by residents in gynaecology, gynaecologists, midwives or ultrasound technicians, all trained to evaluate the fetal four chamber view. From February 1991 onward the sets of data-forms were distributed among the participating ultrasound units and intake started. However, it appeared that the influx of screened pregnancies reached just half the required number. The initial failure to enrol 130 respondents weekly was evaluated during regular visits to the ultrasound units. Overestimation by the physicians in charge of the ultrasound units of the number of pregnancies screened at the required gestational age and tight time schedules of the consulting hours appeared to be the major causes. Another problem that became apparent was that a substantial proportion of the women were of foreign origin. The language barrier in these cases may sometimes have prevented participation as it was particularly difficult to obtain consent for participation. Consequently, a further 7 centres were invited to collaborate, resulting in a total of 15 cooperating ultrasound units (appendix F). Due to the protracted follow-up completion of individual data sets lagged behind the intake by approximately one year. Moreover, the implementation of the follow-up procedure did not evolve as intended. Despite the willingness of the Community Health Services to cooperate parents often failed to identify themselves as participants. Only in 60% of the cases was follow-up obtained by means of the business reply-cards. Hence, consultation of the general practitioner was impelled in a much larger number of cases than anticipated. Periodically, the data base was checked for participants of whom follow-up data was due on the basis of the expected date of delivery plus six months to allow for sufficient follow-up time. Next, standardised letters were generated by computer and addressed to the attending general practitioner asking for the required follow-up data. If after a month no reply had been received a telephone inquiry was attempted. Upon change of physician the one currently attending was approached. In case still no follow-up could be obtained, firstly, the current address was obtained via the Municipal Registries, and secondly, the gynaecologist supervising the participating ultrasound unit was asked to send a form, attempting to obtain informed consent along with the address of the attending physician. Using this set of measures, follow-up could be obtained in most cases (>81%).

*Validation*

Possible bias due to selection of pregnancies was a point of major concern particularly as only a proportion of the eligible women was enrolled. It has, however, been reassuring to note that only one patient not participating in the study, yet qualifying according to the study protocol, was referred from a participating ultrasound unit because of suspected fetal heart disease. Furthermore, the results of the validation study showed that with respect to the proportion of pregnancies which were referred with suspected fetal pathology there was no difference between the study population and the random validation sub-sample (table 2). The proportions of referring obstetricians, though, did differ to a certain extent.

Table 2 Comparison of characteristics of mothers enroled in the main study and a random sample of obstetric ultrasound evaluations.

| | | study participants % (n = 6922) | | random sample % (n = 1500) |
|---|---|---|---|---|
| gestation (weeks) | < 16 | 1.5 | | 38.7 |
| | 16 - 24 | 96.1 | | 33.8 |
| | > 24 | 2.3 | | 27.5 |
| indication of ultrasound | routine | 70.8 | | 58.6 |
| | pregnancy duration? | 18.7 | | 6.7 |
| | miscellaneous | 10.3 | | 34.7 |
| referring obstetrician | midwife | 58.7 | | 54.2 |
| | general practitioner | 6.8 | | 23.9 |
| | consultant | 34.3 | | 21.9 |
| result of ultrasound | normal | 99.6 | 92.6 + [3]7.30 | 97.4 |
| | abnormal | [1]0.4 | [2]0.1 | 2.6 |

1 = other congenital anomalies; 2 = congenital heart disease; 3 = indeterminate ultrasound result; no further action, therefore regarded normal

## DISCUSSION

In a prospective cohort study to evaluate the fetal four chamber view as a screening test for congenital cardiac malformations, ascertainment of all cases arising from the study population is important. Problems in obtaining follow-up data on all cases of the anomaly

or disease of interest in the population or study sample should be minimal. If an (experimental) diagnostic test is being evaluated, it is likely that all suspicious findings will undergo rigorous follow-up, including additional diagnostic testing. However, those cases that have not been detected by the test may remain undetected unless the complete study population is routinely submitted to a second ("gold standard") examination. If the remainder of the cohort only has incomplete follow-up, selective under-ascertainment of false negative experimental tests may result, thus, overestimating the actual test performance. This is a problem that pertains to many studies conducted thusfar. A further point of concern in the evaluation of a diagnostic test may be the setting in which the experiment is conducted. If performed in a teaching/referral centre the expertise present and special interest may create an optimal, though perhaps not realistic situation. Preferably, a reflection of prevailing clinical practice should be adopted to establish the efficacy of the procedure and guidelines of practice.

Theoretically the design of this study might have enabled straightforward determination of the test characteristics, however, several complications arose during the conduct of the project. The numbers of eligible pregnant women did fall behind the prognosis and, furthermore, the compliance of some of the ultrasound units did not reach the required level. To overcome the prospect of too small numbers two solutions were employed. More ultrasound units were involved and the intake period was extended. A third concern was the rather low compliance of participants with the follow-up scheme. A far higher proportion of complete compliance was anticipated assuming that future mothers would almost invariably be exceedingly motivated to comply with the protocol of a project concerning prenatal detection of congenital anomalies. A great deal of effort had to be put into obtaining the follow-up data on the screened fetuses. A pilot study evaluating the contrived design completely might have revealed the above issues. These could subsequently have been dealt with in the design phase, yet would have added further to the complexity and cost of the project.

Regarding the validity of the data it appears that selection of participants at intake, according to anomalies suspected, has not occurred. The over-representation of pregnancies under consultant care may well be explained by the fact that referral for ultrasound evaluation between 16 and 24 weeks gestational age already had become an

established procedure with gynaecologists, whereas midwives and general practitioners may still have tended to refer either at earlier stages or later in pregnancy.
The unique cooperation which was achieved with Community Health Services in the Netherlands deserves further attention. From infancy until school age, all children have regular medical examinations. Recently, a standardised protocol and medical record has been adopted by all local Health Services. Potentially, this provides a valuable source of information for future research on a wide variety of issues.

In conclusion, diagnostic (screening) tests should be evaluated prospectively in a realistic clinical setting. However, study design and conduct may need careful consideration and pilot evaluation to avoid extensive adjustment of study-procedures and delay.

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# CHAPTER 7

# EFFICACY OF ROUTINE FETAL ULTRASOUND SCREENING FOR CONGENITAL HEART DISEASE IN NORMAL PREGNANCY

## INTRODUCTION

Congenital heart disease constitutes an important proportion of all major congenital malformations, which are present in 2 to 3 % of neonates (1,2). The estimated birth prevalence of cardiac malformations is 8 per 1,000 (3). Approximately half of the cases of congenital heart disease have only minor consequences or can relatively easy be corrected surgically. Yet, 35 % of infant deaths due to congenital malformations is related to cardiovascular anomalies (4,5). Hence, congenital heart disease still is an important issue in infant health. In addition cardiovascular anomalies are strongly associated with other anomalies or chromosomal aberrations (6,7,8).

The etiology of congenital malformations of the cardiovascular system is largely unknown (7,9,10), and primary prevention is not yet possible. Therefore, prenatal detection and subsequent adjustment of the obstetric policy, or termination of pregnancy in case a fatal anomaly is detected, are the main options available. Ultrasound visualisation and interpretation of the fetal four chamber view at 16 to 24 weeks gestational age has been advocated as an efficient and accurate screening test for prenatal detection of the majority of severe cardiac malformations (11,12). Accordingly, assessment of the four chamber view has been incorporated into routine fetal ultrasound in many countries including the Netherlands (13). In spite of its popularity, a formal evaluation of fetal echocardiography by means of the fetal four chamber view in a low risk population at a gestational age of about 20 weeks has not been performed.

The efficacy of routine fetal echocardiography has not been proven beyond doubt and this encouraged us to establish the performance of the test in normal pregnancies.

## SUBJECTS AND METHODS

### *source population*

Pregnant women referred for routine fetal ultrasound were invited to participate in the study by the sonographers, e.g., ultrasound technicians, midwives or physicians, when fulfilling the eligibility criteria. Together 15 referring ultrasound units in the Rotterdam metropolitan area participated. All participating women reside in the South-Western part

of the Netherlands. From March 1991 until January 1993 6,922 fetuses were scanned and included in the study. Mean maternal age was 28.9 years (SD 4.6; range 14 to 47).

*eligibility criteria*

Women were considered eligible if scheduled for routine fetal ultrasound between 16 and 24 weeks of pregnancy. Determination of gestational age or growth discrepancy, reassurance because of a preceding miscarriage, lack of fetal movements, inability to detect fetal heartbeats and some miscellaneous reasons were also considered a routine examination. All women with known risk factors for congenital heart disease in their offspring, e.g. a previous child, their partner or themselves affected with congenital heart disease, maternal juvenile diabetes, maternal lupus erythematosus, maternal phenyl ketonuria, maternal rubella and maternal drug or teratogen exposure, for example use of anti-convulsants, retinoid acid or morphomimetics, were excluded as these characteristics currently constitute an acknowledged indication for additional fetal echocardiography.

*personnel and appliances*

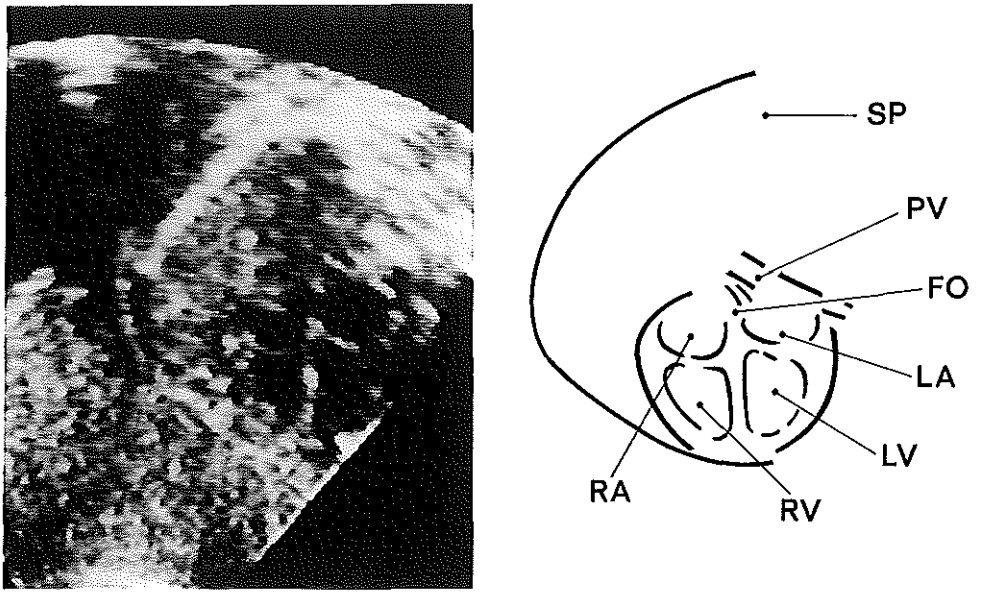
In each of the participating ultrasound centres the majority of examinations was performed by specific experienced personnel. Accordingly, of 6,922 examinations 3,747 (54%) were performed by technicians, 776 (11%) by midwives, 1,391 (20%) by trainees in obstetrics and gynaecology and 1,008 (15%) by consultants. The majority of sonographers involved in the study had ample background in fetal ultrasound examination and, in addition, all had taken a brief intensive ultrasound training course on the evaluation of the fetal four chamber view preceding participation. During the study the ultrasound units were frequently visited. Also, the sonographers were counselled by the project supervisor and were informed about the study progress without disclosure of the findings. Various brands and types of ultrasound equipment, all state of the art 2-dimensional appliances, were used in the participating ultrasound units depending on local preference.

*data handling*

All ultrasound examinations of the fetal four chamber view were evaluated and coded as

normal, abnormal or impossible to assess, according to standard criteria. The fetal heart should be located in the middle of the thorax, occupy approximately 1/3 of the thorax, display atria of equal size, ventricles of equal size, an intact ventricular septum, a foramen ovale flap demonstrated in the left atrium and have off-set atrio-ventricular valves, that is, a more apical insertion of the tricuspid valve and possible visualisation of a 'moderator band' in the right ventricle (11,12) (fig 1).

Figure 1 Normal fetal four chamber view




SP = spine, PV = pulmonary veins, FO = foramen ovale, LA = left atrium, LV = left ventricle, RV = right ventricle, RA = right atrium

In addition, data on gestational age as determined by biometry, a code for the category of referring obstetrician (midwife, general practitioner or gynaecologist), the indication for an ultrasound scan (routine, determination of gestational age or other), suspected presence of other congenital malformation(s) and whether or not the pregnant woman was subsequently referred for extended fetal ultrasound examination, were registered.

Follow-up data on all women and their children were collected until six months postnatally. In collaboration with local Child Health Clinics, which offer a physical examination of the infants and an interview of the parents routinely, the required data (date of birth, sex and presence of congenital anomalies) were obtained for most women. If necessary, the woman's general practitioner was consulted. In case an anomaly was suspected, hospital records, findings on additional ultrasound examination and autopsy records were read over and coded.

*data analysis*

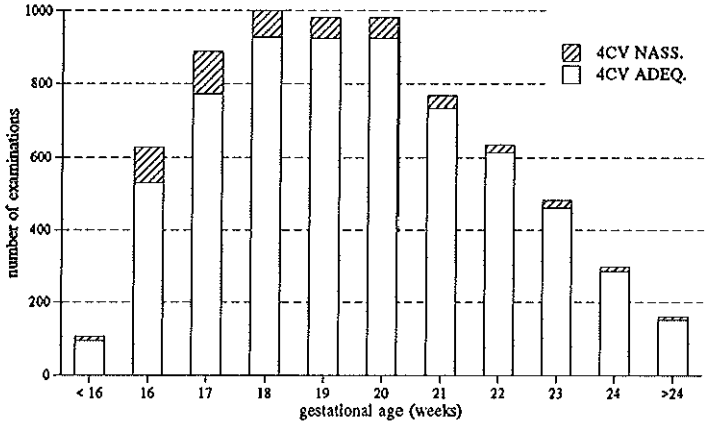
By comparing the prenatal diagnosis (presence or absence of anomalies) to the postnatal diagnosis, the latter being taken as a gold standard, all ultrasound examinations were categorised as true positive in case a suspected anomaly was confirmed, false positive in case a suspected anomaly could not be confirmed, false negative in case an anomaly was missed by ultrasound examination or true negative in case no anomalies were present. As no consequences are attached to an indeterminable four chamber view the cases involved were considered to be normal. The data were subdivided according to presence of congenital heart disease and non-cardiac congenital anomalies. In addition, all anomalies were categorised as major (definitely considered detectable prenatally), minor (possibility of prenatal detection is debatable) or undetectable (excluded from analysis). The last category consists of anomalies like patent ductus arteriosus, sometimes occurring in combination with secundum type atrial septal defect, cryptorchism and syndactyly. As there is general consensus that these anomalies may be considered part of normal fetal development or can not be recognised on prenatal ultrasound examination these cases were subsequently omitted from analysis (14). The sensitivity, the specificity, the predictive value positive and the predictive value negative were calculated with corresponding exact 95 % binomial confidence intervals (15). In addition, the prevalence of congenital malformations (the proportion of infants affected) was calculated.

## RESULTS

### *subjects and ultrasound examinations*

Of the total of 6,922 fetuses screened 6,571 (95%) underwent a routine ultrasound examination between 16 and 24 weeks gestational age. Figure 2 shows the distribution of the duration of pregnancy at which the ultrasound examinations were performed. In 501 (7.2 %) fetuses an adequate four chamber view could not be obtained. Figure 2 also demonstrates how visualisation of the four chamber view related to gestational age.

Figure 2 Distribution of gestational age at the time of ultasound examination with proportional display of adequate four chamber view evaluations




Legend: 4CV = four chamber view; NASS. = not assessable; ADEQ. = adequate

Follow-up until six months post partum has been completed for 5,660 fetuses (81.8%). Of these, 119 appeared to have been included despite known risk factors for congenital heart disease and 222 were screened outside the 16 to 24 weeks gestational age range. Consequently, the analysis presented pertains to 5,319 routine fetal ultrasound examinations in the gestational age range of 16 to 24 weeks (mean 19 weeks and 5 days;

SD 2 weeks and one day), with complete information available on the outcome of pregnancy until 6 months post partum.

*outcome of ultrasound*

Of all women screened prenatally, seven subjects (0.101%) were subsequently referred for extended fetal echocardiography on account of an abnormal appearance of the fetal four chamber view. Another 14 (0,202%) subjects were referred because of other suspected congenital anomalies. Two cases of intra-uterine referral for suspected congenital heart disease could be confirmed on subsequent evaluation. Non-cardiac anomalies were detected more accurately; out of the 14 cases referred 12 proved to be affected.

*outcome of pregnancy*

Eventually, congenital anomalies were present in 118 (prevalence 2.22%; 95% C.I.: 1.84 - 2.65) cases. There were 62 (1.17%; 0.89 - 1.49) cases with congenital heart disease (6 of which also had other congenital anomalies). Non-cardiac anomalies were detected in 62 (1.17%; 0.89 - 1.49) cases. Furthermore, 5 cases of congenital heart disease occurred in combination with chromosomal anomalies. When evaluated according to categories (major, minor or unrecognisable) of anomalies, 80 (1.50%; 1.19 - 1.87) cases (major and minor) remained for secondary analysis. These included 44 cases of congenital heart disease (4 in combination with other malformations), and 40 cases of non-cardiac anomalies. The nature and number of the congenital anomalies encountered in these 80 cases is listed in table 1.

Table 1 Congenital anomalies detected in 80 cases during folow up with numbers detected prenatally in parenthesis

| | VSD | CoA | AVSD | ASD | PA | PS | TGA | HLH | HRH | DORV | Complex | ug | gi | extr | facial | cns | misc |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| total | 30 | 5 | 4 | 5 | 4 | 2 | 2 | 1 | 1 | 1 | 2 | 11 | 6 | 8 | 8 | 3 | 6 |
| major | 4 | | 4 | | | | | 1 | 1 | | 2 (2) | 4 (3) | 5 (3) | 8 | 4 | 2 | 6 (5) |

VSD = ventricular septal defect; CoA = coarctation of the aorta; AVSD = atrioventricular septal defect; ASD = atrial septal defect; PA = pulmonary atresia; PS = pulmonary stenosis; TGA = transposition of the great arteries; HLH = hypoplastic left heart; HRH = hypoplastic right heart; DORV = double outlet right ventricle; Complex = complex cardiac anomalies; ug = uro-genital; gi = gastro-intestinal; extr = extremities; cns = central nervous system; misc = miscellaneous

A table displaying all cases detected in 5,319 fetuses is presented in appendix G.

*performance of ultrasound*

In the categories of cardiac anomalies, non-cardiac anomalies and all anomalies combined a distinction has been made between the number of major and minor anomalies together and a sub-sample of major anomalies, likely to have generated an abnormal image at 20 weeks gestational age. This is reflected in separate tables and analyses according to case severity. Tables 2a-c show the findings of routine prenatal screening for congenital anomalies of the heart, other organs/parts and all anomalies combined, respectively.

Tables 2a-c Outcome of ultrasound screening for congenital anomalies and findings on follow-up

a

| | Follow-up | | | | | |
|---|---|---|---|---|---|---|
| Ultrasound | cardiac anomalies[1] | | normal | major cardiac anomalies | normal | total |
| abnormal 4CV | 2 | | 5 | 2 | 5 | 7 |
| normal 4CV | 42 | | 5,270 | 10 | 5,302 | 5,312 |
| total | 44 | (18)[2] (2)[3] | 5,275 | 12 | 5,307 | 5,319 |

b

| | Follow-up | | | | | |
|---|---|---|---|---|---|---|
| Ultrasound | non-cardiac anomalies[1] | | normal | major non-cardiac anomalies | normal | total |
| non-cardiac screen-positive | 12 | | 2 | 12 | 2 | 14 |
| non-cardiac screen-negative | 28 | | 5,277 | 18 | 5,287 | 5,305 |
| total | 40 | (22)[2] | 5,279 | 30 | 5,289 | 5,319 |

c

| | Follow-up | | | | | |
|---|---|---|---|---|---|---|
| Ultrasound | congenital anomalies[1] | | normal | major anomalies | normal | total |
| screen positive | 13 | (1)[4] | 7 | 13 | 7 | 20 |
| screen negative | 67 | (3)[4] (2)[5] | 5,232 | 26 | 5,273 | 5,299 |
| total | 80 | (38)[2] | 5,239 | 39 | 5,280 | 5,319 |

1 = major and minor anomalies
2 = cases not included; non-detectable anomalies
3 = non-detectable cardiovascular anomalies yet detectable non-cardiac anomalies
4 = number of cases with both cardiac and non-cardiac anomalies
5 = major anomalies

The sensitivity for cases of congenital heart disease was low (4.5%; 0.56 - 15.5) even if only major anomalies are considered (16.7%; 2.09 - 48.8). Sensitivity was somewhat higher for non-cardiac anomalies (30%; 16.6 - 46.5%) and higher still in case of major anomalies (40%; 22.7 - 59.4). The sensitivity for all anomalies combined was intermediate (overall: 16%; 8.95 - 26.2, major: 33%; 19.1 - 50.2). As expected, the specificity is high (>99%) for both categories of anomalies. Also the predictive value negative is high (99%). The predictive value positive varies considerably over the categories of anomalies and can not be established accurately, as illustrated by the wide confidence intervals. All test characteristics and prevalence figures are summarized in table 3.

Table 3 Test characteristics of routine fetal ultrasound

| | | cardiac anomalies | | other congenital anomalies | | overall | |
|---|---|---|---|---|---|---|---|
| sensitivity | -major and minor | 4.5 | (0.6 - 15) | 30.0 | (16.6 - 46.5) | 16.3 | (8.9 - 26.2) |
| | -major | 16.7 | (2.1 - 48.4) | 40.0 | (22.7 - 59.4) | 33.3 | (19.1 - 50.2) |
| specificity | | 99.9 | (99.8 - 100) | 99.9 | (99.9 - 100) | 99.9 | (99.7 - 100) |
| predictive value positive | | 29 | (3.7 - 71) | 86 | (57 - 98) | 65 | (41 - 85) |
| predictive value negative | | 99.2 | (98.9 - 99.4) | 99.5 | (99.2 - 99.7) | 98.7 | (98.4 - 99.0) |
| prevalence | -major and minor | 0.83 | (0.60 - 1.11) | 0.75 | (0.54 - 1.02) | 1.50 | (1.19 - 1.87) |
| | -all anomalies | 1.17 | (0.89 - 1.49) | 1.17 | (0.89 - 1.49) | 2.22 | (1.84 - 2.65) |

All figures are % with 95% confidence intervals in parenthesis. All anomalies; including non-detectable.

*validation*

As we were concerned about the possibility of selective participation of mothers with children that either have no anomalies or represent a population with a relatively high number of anomalies, a random sample of 1,500 ultrasound examinations (100 from each of the participating ultrasound units) was evaluated with regard to data on gestational age, referring obstetrician, indication of ultrasound, suspected presence of congenital malformations and referral for further evaluation. Because this random sample could not be selected on gestational age a wider gestational age range is represented. Furthermore, it appeared that slightly more examinations in the sample were requested by consultants. However, the (small) proportion of women referred on account of suspected fetal

anomalies was equal to that in the study population. In addition, we were able to study the data-base of the Division of Prenatal Diagnosis of the Department of Obstetrics and Gynaecology of Dijkzigt University Hospital, serving the Rotterdam metropolitan area as a tertiary referral centre, and check this data-base for cases not included in the study that would otherwise have qualified as participants. Only one case of a suspected anomaly of the fetal four chamber had been referred during the period of intake of the current study that was not known from the common follow-up.

## DISCUSSION

The objective of the present study was to evaluate the efficacy of the fetal four chamber view in routine screening of normal pregnancies to detect congenital heart disease. Our findings indicate that the fetal four chamber view, as evaluated during routine fetal ultrasound in the second trimester of pregnancy, does not provide an accurate screening-test. Even major anomalies, likely to create an abnormal fetal four chamber view, were not detected to a satisfactory degree prenatally.

Several factors may explain these results. The size of the fetal structures is related to gestational age. Hence, visualisation early in the second trimester, when the fetus is small, will be limited by the resolution of the ultrasound equipment. However, as is apparent from figure 2, the majority of scans was performed beyond 17 weeks gestational age, a time generally deemed appropriate for structural ultrasound examination. In addition, the proportion of fetal hearts that could not be assessed remained stable after 17 weeks of gestation; the scans appear to have been performed at an appropriate moment. Furthermore, all participating ultrasound units had state of the art equipment at their disposal. Conversely, other factors may be responsible for the results. The scans were performed by specialised technicians in over half of the cases and by sonographers with varying degrees of experience in the remainder of the group. We feel that this mix adequately reflects the current ultrasound practice of screening and, if anything, quality of procedures has been higher than usually encountered. Interestingly, the proportion of fetal four chamber views judged as not assessable did not differ among the categories of

sonographers. Also, all sonographers had taken similar additional training in the fetal four chamber view examination prior to the start of participation in the study. Furthermore, as we were aware of the fact that trainees performing ultrasound examinations tended to be replaced rather frequently, all participating ultrasound units were visited repeatedly. During these visits the progress of the study and demand for additional training of junior sonographers was assessed. By evaluating the number of inadequate four chamber view visualisations during the study the effect of increasing experience of the sonographers can be judged. However, the proportion of adequate ultrasound evaluations of the fetal heart did not materially fluctuate nor was there any indication of a particular trend during the period of participation. Therefore, it appears unlikely that variations in experience and skills have had a major impact on the efficacy of the screening procedure.
For non-cardiac congenital anomalies also a rather poor performance was observed with a 30 % sensitivity, resulting in a sensitivity of 16 % for all anomalies together. A discussion analogous to that on the fetal four chamber view applies to other congenital anomalies as well. Again, the results can not be readily explained by any of the variables discussed so far.

The nature of the anomalies encountered in routine screening explains part of the low sensitivity of prenatal detection observed in this study. Some malformations, for instance a small ventricular septal defect or an atrial septal defect, may not be visible with the current ultrasound equipment. The proportional distribution of congenital anomalies encountered at birth may clarify this argument. Approximately 30% of the cases have ventricular septal defects, 10% have a patent ductus arteriosus, 10% have atrial septal defects, 10% are pulmonary stenosis and a further 25% were cases of tetralogy of Fallot, coarctation of the aorta, aortic stenosis and transposition of the great arteries (16). It can be argued that approximately half may not be detectable (or only with great difficulty) by means of a fetal four chamber view. Furthermore, a congenital anomaly may not remain in a steady state. A duodenal obstruction, or a urinary tract obstruction for instance, may only become visible in late second trimester. The anatomical substrate may be present already, but may not yet have functional (recognisable) consequences at 20 weeks gestation. This may even apply in some severe cardiac anomalies like hypoplastic left

heart (17). Apparently, the sensitivity is partly determined by the (im)possibilities of detection by means of prenatal ultrasound and partly by the natural history of the specific anomalies. Nevertheless, even if anomalies of which possibilities for prenatal detection are debatable were left out of the analysis, low sensitivities were found. The exclusion of "minor" anomalies from evaluation could suggest that one considers these cases irrelevant from an obstetric and paediatric point of view. Yet, minor variants of congenital malformations may have an identical cause as major defects and may similarly be associated with other anomalies. In view of this it would seem irrational to consider such cases irrelevant.

Fetal echocardiography, e.g., the four fetal chamber view, has been advocated as a useful tool to detect congenital heart disease prenatally (11,12). Our data are not consistent with this view. It should be noted, however, that the authors concerned mostly were experts in the field of fetal ultrasound and tended to work in (tertiary) referral centres. Their results are likely not to apply to the routine ultrasound clinic, where sonographers may be less skilled, face crowded office hours and a non-selected population with a low prevalence of anomalies. Furthermore, the present prospective cohort-study has complete follow-up on the fetuses, whereas previous reports are limited to cases referred and detected. This may have caused a serious bias. Stillborn fetuses or infants affected may not reach (a tertiary) hospital or may not be examined routinely. When such false negative cases are not considered this will result in overestimated sensitivities. Recent reports on ultrasound in second trimester pregnancy, originating from ultrasound units employing regular personnel and scanning-time, show an efficacy of routine fetal ultrasound examination for detection of congenital anomalies that is compatible with our findings (18-22). The recent Radius study actually demonstrated completely similar results (18).

As discussed, the level of expertise and skills of the sonographers in the present study represents the level of quality in ultrasound examination currently observed in routine screening practice. Suggestions for additional training of the sonographers as well as additional scanning projections have been submitted (23,24). Great endeavour and substantial resources may be required to establish a level of ultrasound skills sufficient to have a major impact on detection rates. Even if achieved, a sizable proportion of cases may remain technically undetectable within the period of gestational age considered

optimal for screening. Despite obvious advantages of prenatal detection of individual cases, we feel that an overall net benefit of routine ultrasound screening has not been established. False negative diagnoses and false positive diagnoses will always occur and have to be taken into account. In addition, it may well be that in a major proportion of the cases potentially detectable, prognosis will not improve significantly by early detection (25,26).

In conclusion, the findings in this prospective study indicate that in the setting here described routine fetal echocardiography at 20 weeks gestational age by means of the fetal four chamber view does not suffice as a prenatal screening test for congenital heart disease.

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# CHAPTER 8

# EFFICACY AND YIELD OF TERTIARY CENTRE FETAL ECHOCARDIOGRAPHY FOR DIFFERENT HIGH RISK GROUPS

## INTRODUCTION

Technological advances in ultrasound equipment have enabled detailed anatomical and functional investigation of fetal structures including the heart (1-4). A prerequisite is that the personnel involved has adequate expertise in fetal ultrasound and detailed knowledge of fetal anatomy and functional status of the developing organs and structures. In addition, sufficient scanning time should be allocated to each patient. These conditions are scarce and expensive, restricting full fetal examination to teaching hospitals or other selected referral centres.

A number of risk-factors for congenital heart disease in the history of pregnant women has been recognized as indications for an extensive prenatal examination (5,6). The outcome of fetal echocardiography may prompt additional diagnostic tests and subsequent adjustment of obstetric management. Currently, increased risk for congenital heart disease in the offspring is considered on account of a previous infant, one of the parents or an other (second degree) relative affected, certain familial or genetic syndromes, maternal diseases, e.g., type 1 diabetes mellitus, (autoimmune) collagen diseases, phenyl ketonuria and rubella, maternal teratogen exposure.

As knowledge of the etiology of congenital heart disease is expanding and the technique of fetal echocardiography has become well established, the demand for prenatal ultrasound diagnosis is increasing rapidly and may exceed current capacity.

In the present paper the efficacy and yield of tertiary centre fetal echocardiography in women at known increased risk for congenital heart disease in their offspring is described using data on a 10 year experience.

## METHODS

### *subjects and appliances*

A total of 2852 anomaly scans was performed on patients with a known risk factor for (re-)occurrence of congenital heart disease in their offspring in the Division of Prenatal Diagnosis of the University Hospital Rotterdam - Dijkzigt between 01 01 1982 and 01 01 1992. The examinations were performed on a Diasonics Cardio Vue 100 mechanical

sector scanner (carrier frequency: 5.0 MHz) between 1982 and 1989, and on a Toshiba SSA-270 A curved linear array scanner (carrier frequency: 3.5 MHz) combined with colour coded Doppler flow imaging from 1989 onward.

The majority of scans (83%) was performed between 16 and 25 weeks of gestation (< 16 weeks: 1% and > 24 weeks: 16%) ensuring the best possibilities for visualization of the fetal cardiac and non-cardiac structures. The cardiac four chamber view, atrio-ventricular and ventriculo-arterial connections, the aortic arch, ductus arteriosus and venous inflow were examined in sagittal and short axis views (7). Colour-coded Doppler flow imaging may provide additional information on fetal cardiac flow characteristics in the presence of structural cardiac anomalies (8).

*data handling*

The reasons for referral, maternal age (years) and gestational age (weeks) at the time of the ultrasound examination, the nature of the anomaly and pregnancy outcome (normal, affected, intra-uterine or neonatal death or termination of pregnancy) were recorded. The prenatal and postnatal diagnosis of congenital malformations was recorded independently. Ascertainment of follow-up on all cases was pursued in various ways on a routine basis. If applicable, direct information from the referring midwife, general practitioner or obstetrician was obtained with regard to the first postnatal evaluation of the newborn. Otherwise, the attending general practitioner and/or paediatrician were approached for information on the neonatal status. In case an infant had been referred for cardiologic evaluation, the paediatric cardiologist was requested to make the diagnosis available. Occasionally, the only available information was a birth announcement sent by the parents stating that their infant was alive and well. The period of postnatal follow-up ranged from less than 1 week to over 9 years.

*validity*

The varying sources for follow up data led us to conduct a separate validation study. The available follow-up data of the years 1988 and 1989 (777 cases) were compared with a second set of follow-up data regarding potential congenital malformations, obtained by a separate request for information which was sent to the general practitioner. In addition,

the data-base of the Division of Paediatric Cardiology, Department of Paediatrics, Sophia Children's Hospital, a supra-regional referral institution, was checked for names of those pregnant women of whom definitive follow-up was missing.

*data analysis*

Taking the postnatal diagnosis as a gold standard, all prenatal ultrasound examinations were categorized as true positive in case a suspected anomaly was confirmed, false positive in case a suspected anomaly could not be confirmed, false negative in case an anomaly was missed by ultrasound examination or true negative in case no anomalies were present. The data were categorized according to the presence of congenital heart disease and/or other congenital anomalies. In addition, all anomalies were classified as potentially detectable prenatally; or definitely undetectable, such as patent ductus arteriosus or cryptorchism. The latter category (n = 13) was excluded from calculation of the test characteristics. The sensitivity and specificity, the predictive value positive and predictive value negative were calculated with corresponding exact 95 % binomial confidence intervals. In addition, the prevalence of congenital malformations (the proportion of infants affected) was calculated.

The relative risk of anomalies detected during fetal echocardiography and postnatally confirmed malformations associated with the various indications was estimated by means of a multiple logistic regression model (9). Firstly, as an approximation of the relative risk, a crude estimate of the odds ratio of an ultrasound diagnosis of a congenital anomaly was obtained for the various risk-factors, which was subsequently corrected for gestational and maternal age. Next, a similar model was applied to estimate the odds ratio of a definitive diagnosis at follow-up for the risk-factors. By mutually comparing the odds ratios or relative risks, an estimate of the relative yield of examination according to the various risk factors could be obtained.

## RESULTS

The mean gestational age at which the 2,852 fetuses were screened was 21 weeks (SD: 4 weeks). The mean maternal age at the time of examination was 29 years (SD: 4.9 years). Referral because of a previous infant with congenital heart disease occurred in 1,062 cases. This was followed by paternal cardiovascular anomalies: 562 cases, maternal cardiovascular anomalies: 326 cases, other relatives with cardiovascular anomalies: 150 cases, maternal use of anti epileptic drugs: 398 cases, maternal type 1 diabetes mellitus: 351 cases, maternal morphomimetics/drug abuse: 177 cases, and a miscellaneous group, e.g., retinoic acid use, maternal SSa antigen, alcohol abuse: 226 cases. Follow-up was obtained from the referring obstetricians, paediatricians, paediatric cardiologists or general practitioners in 2,024 cases (71%). In a further 604 cases only a birth announcement stating that the baby was alive and well was available, leaving 224 cases with incomplete follow-up. The names and addresses of these 828 women (fetuses) were verified in the hospital data-base. In 23 cases there was insufficient information to obtain the full name and address (mostly heroin addicted women). The names and addresses of the remaining 805 cases were matched with the data-base of Sophia Children's Hospital. Apart from a case of mild pulmonary stenosis and a case of perimembranous ventricular septal defect not yet known at the time of data-matching, no major pathology was revealed. Thus, the data of 2,829 fetuses were available for analysis (99%).

The validation sub-sample of 777 cases, of whom a second set of follow-up data was requested (>88% completed) revealed no additional anomalies. Follow-up data had to be updated in only two cases out of 20 occurring in the sub-sample.

In total, 80 cases with congenital malformations were detected in the cohort of 2,829 fetuses (prevalence 2.83%; 95% C.I. 2.25 - 3.51). Subsequently, 13 cases considered undetectable were excluded: 3 cases of patent ductus arteriosus, one of which combined with a rest foramen ovale; a case of absent right pulmonary artery; a case of aplasia of the right earlobe; a case of hypospadias; 4 cases with dysmorphic features; a case of cleft palate; a case of oesophageal atresia with fistula; and a case with webbed neck and hypoplasia of the lungs (residual prevalence 2.4%; 95% C.I. 1.8 - 3.0). There were 43 cases (1.5%; 1.1 - 2.0) of congenital heart disease and 31 cases (1.1%; 0.8 - 1.6) with

other anomalies (table 1). There were 8 cases with both cardiac and other anomalies. Twenty-five out of 43 cardiac anomalies were not detected; 7 of which on account of the documented minute size of the anomaly (a small ventricular septal defect, 3x) or severe maternal obesity (coarctation of the aorta, hypoplastic left heart syndrome, truncus arteriosus) or associated with unfavourable fetal position (coarctation of the aorta). The remaining 18 cases were not detected in spite of the current procedure of fetal echocardiography. However, 5 of these cases were ventricular septal defects which were only recognised on auscultation and were not verified by means of echocardiography postnatally. Another fetus was suspected to have a ventricular septal defect, which could not be confirmed postnatally. Though spontaneous intra-uterine closure is a likely explanation, this case was included as a false positive diagnosis. Twelve out of the 31 non-cardiac anomalies were not detected, 5 of which on account of the minute size of the anomaly (a dysmorphic hand, a case with multiple minor anomalies (dysmorphic features)), or anomalies which may not yet have been functionally obstructive at about 21 weeks gestational age (multiple bowel atresia, oesophageal atresia) or associated with severe maternal obesity (multiple skeletal anomalies).

Table 1 Nature of the anomalies observed in 70 cases; detected - undetected

| Diagnosis<br>- additional anomalies per case | number of cases<br>detected | <br>undetected |
|---|---|---|
| VSD | 3 | 11 (3#) (5‖) |
| - ASD (1x) | | |
| - radial aplasia (1x) | 1 (non-cardiac) | |
| ASD | 1 | |
| - aplasia of extremities | 1 (non-cardiac) | |
| AVSD | 1 | |
| - oesophageal atresia and hypospadias | | 1# (non-cardiac) |
| TOF | 5 (1*) | 2 |
| - hydrocephalus, multi-cystic kydney, skeletal malformations | 1 (non-cardiac) | |
| - cleft lip palate | 1 (non-cardiac) | |
| COA | | 5 (2#) |
| - tricuspid anomaly | | |
| - bicuspid aortic valves | | |
| - ASD, PDA | | |
| PS | 1* | 2 |
| AS | | 2 |
| - peripheral pulmonary hypoplasia | | |
| TGA | 2 | |
| - DILV, DORV, VSD, mitral insufficiency | * | |
| - VSD, straddling tricuspid valve | | |
| DORV | 1 | |
| - VSD, right sided aorta | | |
| HLH | 1 | |
| - mitral atresia, APVD, aortic atresia | | 1# |
| HRH | 1 | |
| - DILV, DORV, TGA, PA, straddling tricuspid valve | | |
| Univentricular heart | 1 | |
| - truncus arteriosus, ASD, APVD | | |
| Truncus arteriosus | | 1# |
| - multiple skeletal anomalies | | 1# (non-cardiac) |
| Ectopia Cordis | 1 | |
| - gastroschizis, hygroma colli | | 1 (non-cardiac) |
| Multiple minor anomalies; cardiac (VSD), | | 1 |
| non-cardiac (dysmorphic features) | | 1# (non-cardiac) |

| | | |
|---|---|---|
| Urogenital anomalies: | | |
| - bilateral hydronephrosis | 1 | |
| - polycystic kidneys, polydactyly | | 1 |
| - hypospadias, cleft lip | 1 (cleft lip missed) | |
| Gastro-intestinal anomalies: | | |
| - multiple bowel atresia | | 1# |
| Skeletal anomalies: | | |
| - multiple | 1 | |
| - agenesis left hand, foot | 1 | |
| - clubfoot | | 1 |
| - dysmorphic hand | | 1# |
| - fibular aplasia | | 1 |
| Facial anomalies: | | |
| - cleft lip and palate | 1 | 2 |
| Central nervous system anomalies: | | |
| - anencephaly | 4 | |
| - hydrocephalus, cleft lip and palate | 1 (cleft missed) | |
| - hydrocephalus, spina bifida | 5 (spina missed 1x) | |
| - spina bifida | 1 | 1 |

VSD = ventricular septal defect; ASD = atrial septal defect; AVSD = atrioventricular septal defect; TOF = tetralogy of Fallot; COA = coarctation of the aorta; PDA = patent ductus arteriosus; PS = pulmonary stenosis; AS = aortic stenosis; TGA = transposition of the great arteries; DILV = double inlet left ventricle; DORV = double outlet right ventricle; HLH = hypoplastic left heart; HRH = hypoplastic right heart; PA = pulmonary atresia; APVD = abnormal pulmonary venous drainage; * = anomaly detected but misclassified; ‖ = anomalies verified by means of auscultation only; # = anomaly not detected as a result of the minute size of the anomaly, maternal obesity or unfavourable fetal position

All results, both including and excluding the cases not detected on account of specific reasons or conditions, are summarized in tables 2a-c. Subsequently, sensitivity for detectable cases, specificity, predictive value positive, predictive value negative and prevalence are presented in table 3. In addition, the sensitivity of fetal echocardiography was estimated after excluding the 5 cases of ventricular septal defect detected on auscultation only.

Tables 2a-c Outcome of tertiary ultrasound examination for congenital anomalies and findings on follow-up

a Congenital heart disease

| | Follow-up | | | | | |
|---|---|---|---|---|---|---|
| Ultrasound | cardiac anomalies | | normal | detectable cardiac anomalies[1] | normal | total |
| suspected | 18 | | 1 | 18 | 1 | 19 |
| normal | 25 | | 2,785 | 18 | 2,792 | 2,810 |
| total | 43 | (4)[2] | 2,786 | 36 | 2,793 | 2,829 |

b Non-cardiac malformations

| | Follow-up | | | | | |
|---|---|---|---|---|---|---|
| Ultrasound | non-cardiac anomalies | | normal | detectable non-cardiac anomalies[1] | normal | total |
| suspected | 20 | | - | 20 | - | 20 |
| normal | 12 | | 2,797 | 7 | 2,822 | 2,809 |
| total | 32 | (9)[2] | 2,797 | 28 | 2,822 | 2,829 |

c All anomalies combined

| | Follow-up | | | | | |
|---|---|---|---|---|---|---|
| Ultrasound | congenital anomalies | | normal | detectable anomalies[1] | normal | total |
| anomaly suspected | 34 | (4)[3] | 1 | 34 | 1 | 35 |
| normal | 33 | (4)[3] | 2,761 | 24 (1)[3] | 2,770 | 2,794 |
| total | 67 | (13)[2] | 2,762 | 58 | 2,771 | 2,829 |

1 = excluding cases missed on account of specific reasons or conditions
2 = non-detectable anomalies (cases not included in calculation of test characteristics)
3 = cases with both cardiac and non-cardiac anomalies

Table 3 Test characteristics of extensive fetal ultrasound examination.
All figures are % with 95% confidence intervals in parenthesis

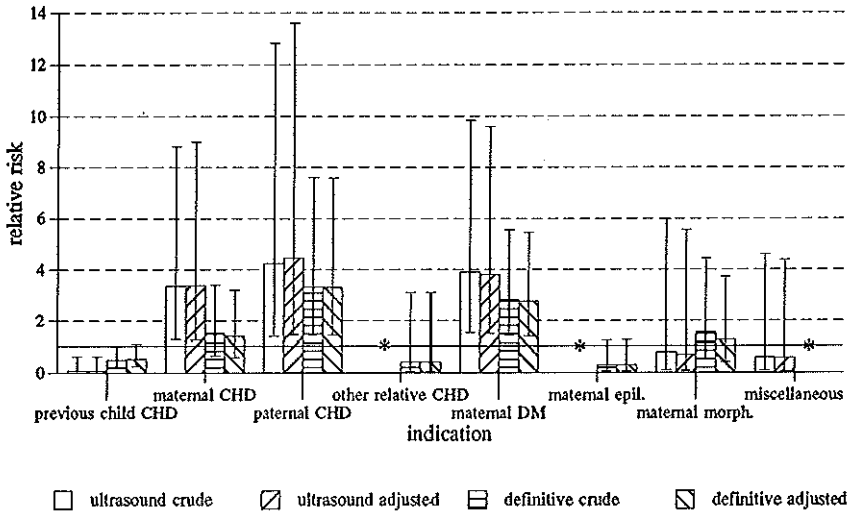
| | | cardiac anomalies | | non-cardiac anomalies | | overall | |
|---|---|---|---|---|---|---|---|
| sensitivity | detectable | 50 | (33 - 67) | 74 | (54 - 89) | 59 | (45 - 71) |
| | confirmed | 58 | (39 - 75) | | | 64 | (50 - 77) |
| specificity | | 99.9 | (99.8 - 100) | 99.9 | (99.9 - 100) | 99.9 | (99.8 - 100) |
| predictive value positive | | 95 | (74 - 100) | 100 | (87 - 100) | 97 | (85 - 100) |
| predictive value negative | | 99.1 | (98.7 - 99.4) | 99.5 | (99.2 - 99.7) | 98.8 | (98.3 - 99.1) |
| prevalence | | 1.52 | (1.10 - 2.04) | 1.13 | (0.78 - 1.59) | 2.37 | (1.84 - 3.00) |
| | total | 1.66 | (1.22 - 2.20) | 1.45 | (1.04 - 1.96) | 2.83 | (2.25 - 3.51) |

detectable = excluding cases missed on account of specific reasons or conditions
confirmed = excluding the cases of ventricular septal defect verified by means of auscultation only
total = including undetectable anomalies (excluded in calculation of test characteristics)

When all postnatally reported cases are considered the sensitivity of fetal echocardiography was 42% (95% C.I. 27 to 58). However, if cases known to be difficult or impossible to detect are excluded the sensitivity was 50% (95% C.I. 33 to 67). For non-cardiac anomalies and overall the sensitivity was 63% (95% C.I. 44 to 79) and 51% (95% C.I. 38 to 63) respectively. When excluding the non-cardiac cases difficult to detect (n = 5) the sensitivity was 74% (95% C.I 54 to 89) and 59% (95% C.I. 45 to 77) respectively. Finally, as a number of cases of ventricular septal defect had been verified by means of auscultation only, the data were analysed excluding this group. This brought the sensitivity of fetal echocardiography and overall to 58% (95% C.I. 39 - 75) and 64% (95% C.I. 50 - 77) respectively. Specificity and predictive value negative were high (99%) with narrow confidence intervals (< 1%). Predictive value positive was also high (> 95%).

Figure 1 displays the relative risks of obtaining an ultrasound diagnosis and a definitive diagnosis of congenital heart disease given the various risk factors, both crude and adjusted for gestational and maternal age. Accordingly, figure 1 displays the attained yield of the various risk factors relative to one another.

Figure 1 Relative risk of a diagnosis of congenital heart disease by indication




Legend: CHD = congenital heart disease; DM = type 1 diabetes mellitus; epil. = anti epileptic drug use; morph. = morphomimetic/drug abuse; * = number of cases affected too low for estimation of relative risk

Parental congenital heart disease and maternal diabetes mellitus are associated with the highest yield (relative risk) regarding prenatal diagnosis of fetal congenital heart disease. This in contrast to risk factors such as a previous child affected, other relatives affected and maternal epilepsy, which seem to (relatively) decrease this yield. Based on the postnatal diagnosis of congenital heart disease, the highest yield of congenital heart disease is restricted to paternal congenital heart disease and maternal type 1 diabetes mellitus. Maternal morphomimetics abuse and some miscellaneous factors also seem to be associated with a relatively low yield of congenital heart disease.

## DISCUSSION

The results of ultrasound examinations in our tertiary referral centre for prenatal diagnosis over a 10 year period display a high validity. Follow-up was virtually complete or validated (99%), resulting in an update of only two cases of minor anomalies.

The overall prevalence of congenital malformations was 2.5% and for cardiac anomalies 1.5 % (2.8% and 1.7%, respectively if undetectable anomalies are included). Though this is approximately equal to the prevalence of congenital malformations found in the general population the proportion of cardiac anomalies is almost twice as high, confirming the increased overall risk of congenital heart disease (10). Nevertheless, some authors have reported a prevalence of congenital heart disease in excess of our estimate, detected in programs for fetal echocardiography (4,11). These results were, however, obtained from different patient populations including patients with fetal growth retardation, poly or oligohydramnios and anomalies already suspected during a previous routine ultrasound examination. We found comparable results in a similar referral group (3).

The efficacy of tertiary centre known high risk scanning for cardiac anomalies by far exceeds that of routine screening in a low risk population (Buskens, submitted). In our hands, the overall results of extensive fetal ultrasound examination appear to be reasonable with an estimated overall sensitivity of 50%: 42% for congenital heart disease and 60% for non-cardiac anomalies. These estimates include cases of gross cardiac pathology, which are detectable by means of diagnostic ultrasound, but were not detected as a result of unfavourable fetal position or severe maternal obesity. Included are also cases of (small) cardiac defects which may be difficult or impossible to detect at the time of examination, despite optimal scanning conditions. When excluding these cases, the sensitivity improves from 42 to 50% for congenital heart disease and from 63 to 74% for non-cardiac anomalies. In addition, as the diagnosis of 5 cases of cardiac anomalies may not been established accurately the sensitivity of fetal echocardiography may have been underestimated. Nonetheless, these results imply that even in a more or less optimal clinical setting, i.e., expert staff, state of the art ultrasound equipment and sufficient scanning time per patient, not all congenital anomalies will be diagnosed. Apparently, the sensitivity of a diagnostic test is influenced by several factors, some of which are beyond

our control.

Moreover, the test characteristics are subject to the type, severity and prevalence of the anomalies observed. Major structural pathology may be readily recognized especially if the prevalence is high. Accordingly, potent teratogenic agents or risk factors which result in serious anomalies in a large proportion of exposed fetuses may display a higher sensitivity and yield when compared with mild teratogens or the general (non-exposed) population. Conversely, as case severity and the proportion of fetuses affected may be considered a derivative of the aetiology of congenital malformations, the test characteristics and yield are likely to be risk-factor specific. Therefore, the various risk factors for the occurrence of congenital malformations should be assessed independently when evaluating the yield of a high risk screening procedure. In addition, population characteristics such as maternal age and ethnic background can be considered potential risk factors and should therefore be included in the evaluation of a diagnostic test. In the present study information is restricted to maternal and gestational age.

Our data were limited to women scanned on account of known risk factors. The findings presented in figure 1 are the result of a mutual comparison of the current risk factors or reasons for referral. Parental congenital heart disease and maternal diabetes mellitus may be considered relatively strong risk factors whereas other risk factors such as a previously affected infant, second degree relatives affected, use of anti-epileptic drugs and morphomimetic abuse and some miscellaneous risk factors appear to predict a diagnosis of cardiovascular anomalies less then average (relative risk $< 1$). These risk factors may subsequently be less relevant regarding the yield of cases affected. Adjustment for maternal and gestational age did not essentially alter the results. Similarly, the distinction between prenatal diagnosis and postnatally confirmed diagnosis of congenital heart disease did not reveal systematic variation of the results.

Interestingly, within the group of parental congenital heart disease, paternal anomalies appeared a stronger risk factor than maternal anomalies (figure 1). Nora and Nora have found opposite results (12). However, in view of the wide confidence intervals definite inference is not possible.

In order to establish a proper assessment of the reasons for referral a comparison with the (expected) yield of extensive fetal echocardiography in the general population should be

available. However, this is not a feasible approach. Alternatively, a theoretical approach of such a comparison between the various risk groups and the general population may be obtained by comparing the respective proportions of affected fetuses or infants. The best estimate of the prevalence of congenital heart disease in the general population is 0.8% (10), which is just over half (0.53) of the overall prevalence of congenital heart disease (1,5%) established in our high risk group. Assuming that the test characteristics of fetal echocardiography would not change, and a similar proportion of detectable and undetectable anomalies would occur, the solid line in figure 1 (relative risk = 1) may thus at most display a shift to the position of the current figure of 0.53, when comparing the high risk group to the general population. Some indication groups would subsequently show a yield slightly over the "adjusted" nil effect (modified relative risk = 1) level. However, in view of the wide confidence limits more data are needed to be able to infer whether the current reasons for referral would result in a significant yield. Furthermore, as the psychological impact of performing prenatal diagnosis in these high risk groups has not been assessed, definitive conclusions can not be provided.

In conclusion, screening for congenital heart disease in a high risk population by means of extensive fetal echocardiography shows a moderate effectiveness. Clear differences in yield appear to be present across currently accepted risk factors.

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# CHAPTER 9

# ROUTINE SCREENING FOR CONGENITAL HEART DISEASE; WHAT CAN BE EXPECTED? A DECISION ANALYTIC APPROACH

## INTRODUCTION

Over the last decade many reports have appeared on the possibilities of ultrasound for prenatal detection of congenital heart disease. A limited number of authors, however, has tried to assess the actual yield of a (routine) screening program for cardiac anomalies by means of fetal echocardiography (1-15). A distinction can be made between two screening policies. Either can fetal echocardiography be offered routinely to all expectant women or it can be offered to those considered to be at (high) risk for fetal congenital heart disease.

In the first approach, all pregnant women should undergo a routine ultrasound examination, including a fast and simple evaluation of the fetal heart, at a certain optimal gestational age. Subsequently, upon suspicion of a congenital anomaly referral to further establish a diagnosis and appropriate obstetric policy should follow. The screening procedure of choice currently suggested for evaluation of the fetal heart is the four chamber view, incorporated in routine fetal ultrasound, between 16 and 24 weeks pregnancy (3,6).

In the high risk approach, extended structural ultrasound examination is offered to a selection of women that have a history of increased risk of congenital heart disease in their offspring. The type of anomalies encountered in this sub-sample are likely to be more severe, more complex and occur more frequently. The ultrasound examination in these patients is referred to as extensive structural (or tertiary) fetal echocardiography. In addition to the four chamber view, the cardiac connections and cardiac functional status are evaluated (16). Obviously, this can only be accomplished by highly skilled experts during a lengthy and detailed examination in a referral centre.

It would appear that, in order to be able to recommend prenatal screening in low risk pregnancies, followed by tertiary ultrasound examination in case of suspected fetal pathology, an assessment of the yield and benefit that may be expected is needed. However, based on an assumed favourable effect routine fetal ultrasound, comprising a four chamber view evaluation, is now offered to the majority of pregnant women in several countries including the Netherlands. To our knowledge, this has not been preceded by an appropriate evaluation. Accordingly, we suggest that before formal introduction of routine fetal ultrasound screening the actual risk of bearing an affected fetus, the efficacy

of the proposed screening test, including additional tests required, the natural history of the anomaly(ies) concerned and, finally, the valuation or impact of the anomaly(ies), related to psychological, social and economic aspects, should be assessed. Medical decision analysis offers a possibility to integrate the issues involved and, in addition, evaluate the influence of variability of these factors.

We set out to answer the question whether the benefits of routine fetal ultrasound for the detection of cardiac anomalies are sufficiently clear to merit routine examination of all expectant women. Finally, an estimate of the impact of routine screening of low risk pregnancies is provided.

## METHODS

### *Structure of the model*

The present report proceeds from an inventory of currently available literature data. Subsequently, these data have been assimilated in a decision analysis model centred on the problem to either offer routine fetal echocardiography to all expectant women or omit this screening test. Decision Maker software (New England Medical Centre: 1988) was applied to structure the model and convey the options and chances future parents and clinicians, or policy makers, face at 16 to 24 weeks gestational age (figure 1). The high risk approach as a separate option has not been entered into the model as its benefits are less debatable (6,8,17-20). In addition, the occurrence of spontaneous abortion or intra-uterine death prior to any prenatal diagnostic procedure was assumed not to influence the choice between the two strategies. The probability of an affected fetus (with either minor or major congenital heart disease) was entered into the model at the first chance node. The subsequent chance node in the model represents the test of interest; routine fetal echocardiography. Given a malformation in the fetus, the chance of a positive test result is the true positive rate or sensitivity. Conversely, a negative test given an anomaly is the false negative rate (or 1-sensitivity). Similarly, the chance node given the absence of malformations applies to the true negative rate or specificity and in case of a false positive test result the false positive rate (or 1-specificity).

The subsequent branch of the model represents referral upon suspicion of a malformation

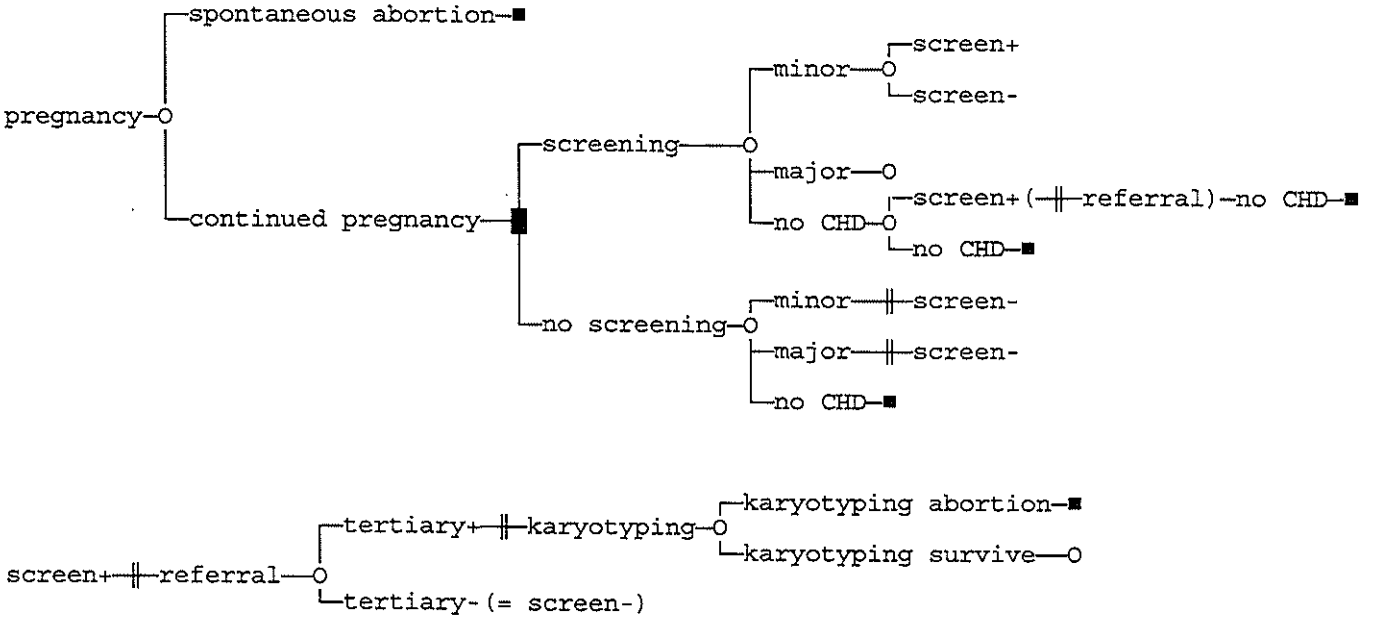
or pregnancy pathology during screening. Thus, extended fetal echocardiography is offered to those screened and suspected of a fetal anomaly, to those screened and not suspected despite being affected and in addition presenting (pregnancy) pathology, and to those not screened yet presenting (pregnancy) pathology. In this respect specific signs of possible fetal anomalies, e.g., growth discrepancy, lack of fetal movements or an abnormal fetal heart rate, are taken as pregnancy pathology.

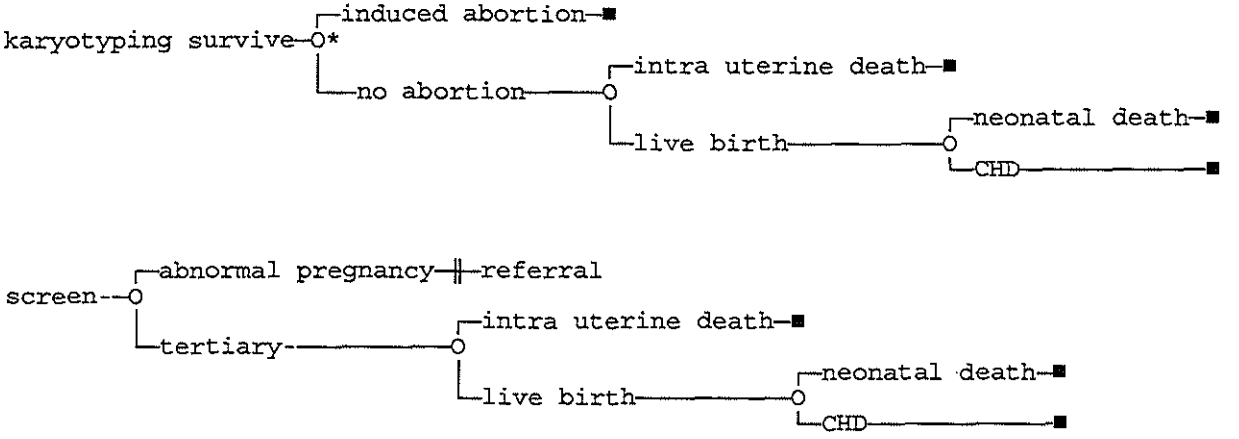
With respect to initial false positive screening results we assumed that subsequent extensive fetal echocardiography would always reveal previous diagnostic errors (100% specificity), thus excluding false positive diagnosis. This appears to be a reasonable simplification of the model since further diagnostic steps or policy adaptation are presently not offered unless justified by suspicion of a significant anomaly. Non-adoption of screening implies that extended ultrasound is available only in the event of clinically suspected fetal or pregnancy pathology.

Similar to the probabilities at the level of screening, the test characteristics of extended fetal echocardiography pertain to the probabilities of the corresponding chance nodes in the model.

Furthermore, in case an anomaly is confirmed during extensive structural fetal ultrasound examination, fetal karyotyping is offered; e.g., chorion villus sampling, amniocentesis or cordocentesis. These techniques have a (low) risk of inducing abortion which is represented by the corresponding chance node in the model. The next step is the decision parents face after having obtained all relevant information concerning the diagnosis and prognosis of their (affected) fetus. They may either choose to terminate pregnancy or carry to term. Obviously, an unaffected or slightly affected fetus is likely to be carried to term. In case the gestation of a fetus with a congenital heart disease is continued two outcomes are possible. Either, intra uterine death may occur, or an infant with a cardiac anomaly is born, which may as a result of the anomaly die. This risk of a fatal outcome again represented by a chance node. The situation is essentially similar if parents, informed about the presence of a (severe) fetal anomaly, decide not to terminate pregnancy, or in case an anomaly is not detected, or if screening does not take place.

Figure 1 Diagrams of the decision model






Legend:
O = chance node
▉ = decision node
■ = outcome
╫ = implicit action
minor = minor anomaly
major = major anomaly
CHD = congenital heart disease
screen = test result of prenatal ultrasound screening
tertiary = test result of extensive ultrasound examination
* This chance node could also be represented by a dicision node as it is an (parental) option to terminate pregnancy after detection of a severe anomaly.

*Assignment of probabilities*

All variables implemented in the model are summarised in table 1. A number of problems in the assignment of probabilities need to be discussed. An estimate of the chance of bearing a fetus with congenital heart disease is preferably provided by the prevalence of cardiac anomalies at 16 to 24 weeks gestation. However, whereas a large number of reports is available on the prevalence of congenital heart disease at birth, a reliable estimate of the prevalence at about 20 weeks gestational age is difficult to obtain. We assumed that newborns with a birth prevalence of cardiac anomalies of approximately 0.008 (21) originated from a larger cohort of fetuses of which a proportion has aborted spontaneously or ended in premature death. Thus, the fraction affected required to reach 8 per thousand neonates with congenital heart disease was calculated backward, given a non-screening situation. In addition, the notion that only about half the cardiac anomalies found in neonates are major or echocardiographically detectable is taken into account (22). The probabilities reflecting the test characteristics of routine and extended ultrasound evaluations are based on a literature survey. Reports that apply exactly to the situation described above are scarce. To account for problems of interpretation arising from differences in study design we adopted a case-severity based approach. The sensitivity of the fetal four chamber view for detecting severe cases of congenital cardiac anomalies is estimated to be 50%. This is in accordance with the upper range of the figures reported in the literature (1-15). The lower range of the sensitivity reported, below 10%, is taken to apply to minor anomalies. The specificity of the screening test is reported to be very high (99%) and has a narrow range, hence, does not need further comment. The test characteristics of extended ultrasound evaluation appear to be superior and have been reported with a much more narrow range (6,8,17-20). More detailed data on extended fetal echocardiography provided the possibility to calculate the test characteristics with the specific indication of suspected fetal (cardiac) pathology (8,19,20). A high sensitivity (95%) and specificity (99%) is generally reported. The chance of induced abortion after fetal karyotyping is low (less then 1%) (23). Reports on the chance of pregnancy pathology in relation to congenital heart disease were not found. Hence, we submitted this issue to a panel of obstetricians at the University Hospital Rotterdam and obtained an estimated probability of less than 1%.

In case a malformation is detected, parents informed about the nature of the anomaly face a decision. Specific literature on this subject is scarce. Pryde et al. evaluated several factors influencing the parental decisions regarding pregnancy outcomes of congenitally malformed offspring (24). The prognosis given appeared to be of major influence; two out of three parental couples opted to terminate pregnancy if the outlook was grim. Termination was never decided in case of minor anomalies. Subsequently, we compared the results by Pryde et al. to the proportion of pregnancies that were reported to have been terminated on account of the prognosis given after extended fetal echocardiography (8,19,20,24). An identical proportion emerged and, hence, is taken to represent the chance of termination of pregnancy in case of a severe fetal anomaly. Apparently, the cases detected during routine fetal ultrasound examination and subsequently referred are a selection of the total number of fetal anomalies present at 20 weeks gestational age, that is, a sample of severe cases. The probabilities of intra uterine death of an affected fetus (37%) and infant death after live birth (59%) were again obtained from the reports on fetal echocardiography (19,20).

As we consider the probabilities derived above to apply to cases of major anomalies, we submit data on live-born children (mortality less then 10%) as a substitute for the effect on survival of minor cardiac malformations; the majority of minor cases have no hemodynamic consequences prenatally and, accordingly, survive to term.

Finally, a sensitivity analysis was conducted over plausible ranges of the estimated probabilities (as presented in the right-hand side of table 1), to obtain an impression of the impact of variation in the estimates on the outcome of the model.

Table 1 Probabilities entered in the decision model.
In the sensitivity analysis a distinction is made between major and minor anomalies. The plausible range is given in parenthesis, if possible based on 95% confidence intervals.

| | point estimate | lower value | upper value | major | | minor | |
|---|---|---|---|---|---|---|---|
| prevalence[22,23,Buskens] | 0.008 | 0.003 | 0.012 | 0.004 | | 0.004 | |
| prenatal prevalence * | 0.013 | | | 0.0063 | (0.01 - 0.005) | 0.004 | |
| level 1 sensitivity[1-15] | 0.07 | 0.07 | 0.50 | 0.50 | (0.20 - 0.80) | 0.07 | (0.01 - 0.20) |
| level 1 specificity[1-15] | 0.99 | 0.99 | 1.0 | | | | |
| level 2 sensitivity[6,8,17-19] | 0.95 | 0.927 | 0.974 | | | | |
| level 2 specificity[6,8,17-19] | 0.99 | 0.987 | 0.993 | 1.00 | | 1.00 | |
| p(abnormal pregnancy \| CHD)[P.C.JWW] | 0.01 | | | 0.01 | (0 - 0.03) | 0.01 | (0 - 0.03) |
| p(karyotyping abortion)[23] | 0.01 | | | | | | |
| p(induced abortion \| CHD)[8,19,20] | 0.678 | 0.571 | 0.773 | 0.68 | (0 - 1.0) | 0.0 | |
| p(intra uterine death \| CHD)[19,20] | 0.370 | 0.194 | 0.576 | 0.37 | (0.20 - 0.60) | 0.0 | |
| p(neonatal death \| CHD)[19,20] | 0.588 | 0.329 | 0.816 | 0.59 | | 0.1 | |

major - minor = category of congenital malformation
p( ) = chance of event between brackets
CHD = congenital heart disease
* = expected prevalence at 20 weeks gestation calculated backward; varies according to p(intra uterine death | CHD).

## RESULTS

A first estimate of the impact of routine fetal ultrasound screening in low risk pregnancies is obtained by comparing the numbers of corresponding outcomes of the two strategies. Table 2 reflects the results from a model based on the estimates in table 1. The estimates pertain to one million 2nd trimester pregnancies. In the Netherlands, which has an annual birth rate of approximately 190.000, these events would accordingly take about five years to occur.

Table 2 Estimated pregnancy outcomes of a million 2nd trimester pregnancies (fetuses of 16 to 24 weeks gestational age). No screening versus screening and subtraction.

| Outcome | no scr | scr | Δ scr |
|---|---|---|---|
| CHD major | 1629 | 1104 | -525 |
| CHD minor | 3600 | 3597 | -3 |
| neonatal death | 2745 | 1988 | -757 |
| induced abortion | 41 | 2046 | 2005 |
| karyotyping abortion | 1 | 33 | 32 |
| intra uterine death | 2334 | 1582 | -753 |
| no CHD (false positive) | 0 | 9897 | 9897 |
| no CHD | 989651 | 979754 | -9897 |

no scr = no screening
Δ scr = subtraction: scr - no scr
CHD = congenital heart disease

With a relatively low sensitivity for major anomalies of 50% it is estimated that the number of children born with severe congenital heart disease decreases by a third in case routine screening is offered to all pregnant women. The number of intra uterine deaths shows a similar trend. The impact of routine screening on minor congenital heart disease is numerically negligible. However, the number of terminations of pregnancy would increase 50-fold and a substantial number of almost 9,900 false positive screening tests would result. A further point of interest may be the fact that screening would also imply a loss of 32 fetuses, 28 cases of major anomalies and 4 cases with only minor anomalies, because of the risk of invasive procedures for karyotyping. (As we consider the specificity

of extended fetal echocardiogrphy to be 100%, no unaffected fatalities will occur.)

Table 3 provides the results of sensitivity analysis, demonstrating the effects for different estimates of the sensitivity of routine fetal ultrasound, the proportion of parents opting for termination of pregnancy in case of a severely affected fetus, the likelihood of pregnancy pathology and the likelihood of intra-uterine death due to congenital heart disease. An increase in sensitivity (to 80% and 20% for major and minor anomalies respectively) reduces the number of cases with an unfavourable outcome of pregnancy. However, increased numbers of termination of pregnancy are a consequence. In addition, as increased numbers of anomalies are detected with high sensitivity subsequent fetal karyotyping is performed more often causing an additional loss of 23 (affected) fetuses.
Parental inclination toward termination of pregnancy in case of severe malformations appears to have a very much similar effect as increased sensitivity of routine ultrasound on the outcome of pregnancy. In case all pregnancies are continued very little effect remains.
Also, an abnormal development of pregnancy does not seem to have a significant impact.
The likelihood of intra-uterine death resulting from congenital anomalies does not affect the number of affected infants born. However, with increasing probability of premature death, a larger number of pregnancies is terminated that would otherwise have resulted in spontaneous abortion or intra-uterine death.

Table 3 Estimated pregnancy outcome per million 2nd trimester pregnancies (fetuses of 16 to 24 weeks gestational age); results of the sensitivity analysis. Subtraction of the results of screening - no screening.

| Outcome | sensitivity routine ultrasound | | p(induced abortion) | | p(abnormal pregnancy) | | p(intra uterine death) | |
|---|---|---|---|---|---|---|---|---|
| | high (80%; 20%)* | low (20%; 1%)* | high (100%) | low (0%) | high (3%) | low (0%) | high (60%)# | low (20%)# |
| | Δ scr | Δ scr | Δ scr | Δ scr | Δ scr | Δ scr | Δ scr | Δ scr |
| CHD major | -841 | -210 | -772 | -8 | -516 | -531 | -525 | -525 |
| CHD minor | -7 | 0 | -3 | -3 | -3 | -3 | -3 | -3 |
| neonatal death | -1211 | -303 | -1111 | -11 | -742 | -764 | -757 | -757 |
| induced abortion | 3208 | 802 | 2957 | 0 | 1967 | 2024 | 3158 | 1579 |
| karyotyping abortion | 55 | 12 | 32 | 32 | 32 | 33 | 50 | 26 |
| intra uterine death | -1205 | -301 | -1105 | -11 | -738 | -760 | -1923 | -321 |
| false positive | 9897 | 9897 | 9897 | 9897 | 9897 | 9897 | 9897 | 9897 |
| no CHD | -9897 | -9897 | -9897 | -9897 | -9897 | -9897 | -9897 | -9897 |

Δ scr = subtraction: scr - no scr
CHD = congenital heart disease
* = sensitivity of routine fetal echocardiography for major and minor anomalies respectively
# = with regard to cases of major CHD, a high chance (60%) of intra uterine death implies a high (1%) prenatal prevalence of CHD, whereas, a low chance of intra uterine death (20%) implies a low prenatal prevalence (0.5%)

*Chapter 9*

# DISCUSSION

In the model it was presumed that approximately half of the severe anomalies would be detected. The future parents and fetus may benefit from these results. Obstetric policy may be adapted, timing, mode and location of delivery can be optimised, or, in case of severe or fatal anomalies, termination of pregnancy can be offered (19,20,25-27). The fact that fewer children are born with severe congenital heart disease may be considered a benefit of routine fetal ultrasound. However, a routine fetal ultrasound programme according to current specifications has disadvantages as well. Several remarks can be made with regard to the "side-effects" of screening and are illustrated using data from an imaginary cohort of one million pregnancies. Apparently, preventing the birth of 1,285 cases of congenital heart disease, 525 major cases, 3 minor cases and 757 cases of infant death, means that over 2,000 induced abortions are needed, 753 of which would have ended in spontaneous abortion in absence of intervention, and 32 losses of pregnancy due to complications of karyotyping. The model also indicates that almost 9,900 false positive screening-tests would result. The women involved may subsequently have to face the anxiety caused by the alarming result of routine fetal ultrasound and require subsequent referral for extended fetal echocardiography to be reassured that no anomaly is present.

As some of the literature estimates of the probabilities applied in the model may be liable to dispute, the impact of variability of the respective probabilities is important to assess. We did not vary the prevalence of congenital heart disease in the model. Clearly, with increasing prevalence the numbers of cases detected will increase proportionally and vice versa. However, given a constant specificity, the number of false positive cases would remain the same. A higher sensitivity of routine fetal ultrasound, as for instance may be achieved in a specialised centre, would increase the yield in numbers of births of infants with congenital heart disease prevented, and also increase the number of terminations of pregnancy required. In case the sensitivity does not reach the levels reported in the literature the yield would decrease proportionally.

The effect of parental preference regarding termination of pregnancy in case of severe anomalies detected in their fetus has been approached by varying the proportion of terminations. If parents invariably were to accept induced abortion the yield appears to

equal that of a high sensitivity of routine fetal ultrasound. However, with decreasing proportions of termination of pregnancy, despite severe anomalies, the yield would also decrease. Hence, especially, in a community or society that has constraints concerning interference with intra-uterine life possible advantages would be limited to adapted obstetric policies.

A change in the likelihood of an abnormal course of pregnancy does not importantly affect the impact of screening. As an abnormal pregnancy is an indication for referral in any event, an anomaly would likely have been detected during subsequent extensive ultrasound examination.

The impact of the natural history of fetal congenital heart disease requires additional discussion. We accepted that the birth prevalence of congenital heart disease remains unchanged irrespective of the natural history prenatally. However, with an increased probability of intra-uterine death a larger number of affected fetuses would have to be present to result in the same number of affected neonates. Note that the number of terminations of pregnancy increases by 1,153, i.e., 3,158 induced abortions in case of a high proportion of intra uterine death (60%) versus 2,005 in case of the original literature estimate (37%), (almost) equal to the decrease in spontaneous intra-uterine deaths, i.e., -1,923 versus -753 (tables 2 and 3). Thus, severe anomalies causing fetal loss in a large proportion can be viewed a natural screening process. The yield of screening, expressed as births of affected neonates prevented remains stable. Consequently, the relative yield of screening decreases because the fetuses with severe anomalies would not have been live born anyhow. With a less severely affected fetus, e.g., not resulting in fetal loss, yet, facing a severe prognosis postnatally, future parents may be inclined to have pregnancy terminated. Accordingly, for such cases screening does have additional (and increased relative) yield.

Finally, an additional remark may be made regarding the specificity of extensive structural fetal ultrasound examination. The specificity applied in the model was presumed to be 100%. Therefore, in the model no far-reaching consequences were attached to false positive screening tests. However, it may be that this is not correct. Recently, cases of apparently severe fetal congenital heart disease have been described that were not terminated. Postnatally they proved to have only mild to moderate anomalies (28).

According to the best available estimates of the test characteristics of prenatal screening for congenital heart disease by means of the fetal four chamber view, the yield, expressed as the prevention of the birth of a critically ill neonate, appears to be numerically modest. In addition, a sizable number of pregnant women require referral for additional diagnostic testing on account of a false positive screening test. In case the sensitivity of prenatal screening would in practice be substantially lower, i.e., within the lower range currently reported, or the majority of parents faced with a severely affected fetus would opt for continued pregnancy, the yield would decrease to marginal.

When factors that may (significantly) influence on the yield of a routine fetal ultrasound screening program are considered, only a few appear accessible for improvement. The test characteristics of extensive structural ultrasound can already be considered more or less optimal. Also, fetal karyotyping is not likely to achieve still lower rates of complications. At present, little is known about the natural history of congenital malformations in utero, i.e., the chance of pregnancy pathology and intra-uterine death. Moreover, even less information is available on factors affecting natural history in utero. Next, the final decision parents take once a serious fetal anomaly is detected is culturally, socially and economically determined. Evidently, a strategy for termination of pregnancy generally applicable is inconceivable. Remaining factors are the prevalence of congenital anomalies and the sensitivity of routine fetal echocardiography. The actual prevalence of congenital malformations is a given hardly accessible to intervention, and, moreover, if accessible would imply possibilities for primary prevention. However, it may be possible to select patients on account of increased risk, thus creating a subgroup with increased prevalence.
Pivotal in such a policy of increased risk screening is the quality of the diagnostic test, that is, fetal echocardiography. Currently attained results in screening programs for routine antenatal detection of congenital heart disease seem insufficient to merit such a strategy (14). Furthermore, this would also imply that in low risk pregnancies formal screening is abolished.
Alternatively, the currently proposed screening test, the fetal four chamber view examination, could be optimised. An adequate screening test can, however, only be obtained if sufficient numbers of experienced staff with extensive scanning expertise and

high quality ultrasound equipment would be available, requiring a large investment. In spite of the results of the present (decision) analysis, that has shown that the yield in births of affected infants prevented would be limited numerically and, in addition, only apply to a sub-sample of the severe cases detectable. Furthermore, it is important to realise the consequences of such a strategy of limited (only severe cases) anomaly screening; it implies that the appreciation of a prenatal screening program comes to depend on the significance and valuation of the detectable sub-sample of cardiovascular anomalies. Also, following a negative screening test, future parents should be told that only a minority of severe cardiac anomalies could be excluded.

The significance and valuation of the cases detected, the cases not detected, the false positive test results and their subsequent outcomes have not been assessed in the present analysis. This can be attempted by estimating the psychological relief or burden that can be attained or by means of estimating the financial consequences. Pauker et al. and Heckerling et al. have described such a method (23,29,30). They have, after parental assessment, assigned specific values or utilities to the various outcomes of pregnancy in a prenatal Down syndrome screening programme, and subsequently tried to establish the utility of screening. Ekwo et al. have, similarly, reported on the outcome of pregnancy with regard to congenital anomalies and their perceived consequences or burden (31). Again it appeared that parents have a specific opinion on the outcomes of pregnancy which can be expressed on a preference scale. However, at present, reliable data on parental attitudes towards congenital heart disease are lacking. Yet, as parental assessment of the various outcomes may, ultimately, have a considerable impact on the appreciation and efficacy of a prenatal screening program for congenital anomalies, further research seems necessary.

In conclusion, the results of our analysis suggest only a limited overall advantage of routine prenatal ultrasound screening for congenital heart disease. However, data on the efficacy of routine screening are scarce and hardly allow definite inference. Moreover, an assessment of utilities of various outcomes and parental attitudes and valuation does clearly call for additional research.

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# CHAPTER 10

# GENERAL DISCUSSION

# GENERAL DISCUSSION

Congenital malformations, in particular cardiovascular anomalies, have a prominent position throughout the current dissertation. Through lack of substantial evolution in knowledge on (preventable) causes and still limited possibilities for curative treatment of severe cardiovascular anomalies, prenatal detection has attracted a great deal of attention. Promising early results prompted initiatives to adopt routine fetal ultrasound screening programmes. However, as the utility of such a screening test has not been established confidently an effort to clarify the efficacy was initiated. The assessment of the efficacy of routine prenatal screening for congenital heart disease is the main theme of this thesis. Additional information on various aspects of congenital heart disease, e.g., causes, frequency of occurrence, treatment (options) and possibilities for early detection, is provided to comprehend screening adequately. In this chapter the main conclusions and implications for screening and future research will be given.

The prospective study on routine ultrasound examination for congenital heart disease in a inherently low risk population has shown that screening does not lead to a sufficient level of detection. Several explanations for these results may be considered.
Firstly, the prevalence of congenital (cardiovascular) anomalies is low in a routinely screened population. Furthermore, the scanning-time allocated to each examination is limited and the technicians or sonographers may not have sufficient experience and expertise in a routine setting. Finally, it is important to realise the technical restrictions of the procedure with regard to visualisation of certain anomalies. Conversely, ultrasound examination of a high risk population performed in referral centres by specialised personnel has shown to be far more effectice.

In view of the above, there appears to be little basis to propose large scale routine ultrasound screening in low risk populations. Yet, screening in high risk populations may be recommended and could be expanded to include certain additional risk groups. In addition, it is as yet unclear to what extent all pregnancies belonging to currently recognized high risk groups are identified to take maximal advantage of screening.

Defining and identifying high risk pregnancies that justify extensive ultrasound examanition will require additional research. In particular, the expansion of the indications for high risk screening while maintaining adequate screening performance may necessitate further study.

# SUMMARY

As congenital heart disease occurs relatively often, and improvement of prognosis has not kept pace with that achieved in infectious diseases, it has become rather an important infant health problem (chapter 1).

Currently, the occurrence of only a minority (10 to 20%) of the cases of congenital heart disease can be accounted for by specific factors (chapter 2). Likely, this proportion will increase in the next decades as a result of research in epidemiology, embryology, genetics and molecular biology. Knowledge of factors that induce malformations could make these determinants accessible to treatment or primary prevention. Meanwhile, secondary prevention, that aims to avert pre and postnatal morbidity once a fetal anomaly has occurred remains the main treatment option.

Several attempts have been made to estimate the magnitude of the problem of congenital heart disease with varying results (chapter 3). Apparently, the methodology applied to establish the proportion of fetuses or infants affected is not unequivocal. A number of characteristics of study design may influence the estimated (birth) prevalence of congenital heart disease. Duration of follow-up and case ascertainment, including diagnostic work-up and case definition appear to be important determinants of the estimated prevalence reported, in particular for minor anomalies. A satisfactory overall estimate of the birth prevalence of congenital heart disease appears to be difficult to attain. An estimate of the proportion of affected fetuses, at a certain gestational age, is even more difficult to obtain. Reliable information on these cases (preferably autopsy) would allow estimating the impact of congenital anomalies on fetal survival. Moreover, incidence figures, that is the proportion of embryos or fetuses that actually develop an anomaly, are not available at present and may be obtained. As this kind of information is essential in etiologic research, further study is warranted.

Besides numerical information, on the occurrence of congenital heart disease, data on the impact of anomalies on longevity and morbidity are also important in estimating the consequences and magnitude of the problem. Therefore, a brief overview of current knowledge and experience of paediatric cardiology for the majority of cardiovascular anomalies found in neonates is provided (chapter 4). Furthermore, the impact of these anomalies on fetal survival is assessed. It seems likely that the infants that are (live) born with a cardiovascular anomaly are a selection of cases that exist earlier in pregnancy. Those cases that end in (early) intra-uterine death are not, or only infrequently accounted

for at present. As mentioned above, valuable information is lost with the dead fetus if a diagnosis is not provided.

In addition to describing the consequences of cardiovascular anomalies for the fetus and neonate, the possibility and significance of prenatal detection by means of ultrasound have been addressed. It appeared that a large proportion of the cases that present after birth may not be detectable by means of the currently available technique. Also, the prognosis of affected fetuses appears to be difficult to improve.

Nevertheless, routine fetal ultrasound screening for congenital heart disease has been strongly advocated on account of initial reports. A careful assessment of the original studies did reveal some explanations for the contradictory results compared to more recent research (chapter 5). For instance a number of the early studies have relied on retrospective data for follow-up of screen negative cases, thus introducing possible bias as some diagnoses may remain obscure. Furthermore, the skills and interest of the sonographers involved may have been superior as compared to that observed in regular ultrasound clinics. Accordingly, prior to general adoption of a routine prenatal screening program a thorough evaluation in a realistic clinical setting should be available.

The core of this thesis is an account of the design, conduct and findings of a prospective cohort study in 6,922 fetuses scanned routinely (chapter 6 & 7). After successful follow-up on the majority (>81%) of fetuses only 4.5% of the cardiovascular anomalies appeared to have been detected prenatally. Non-cardiac anomalies, checked for during the same ultrasound session, were detected in 30% of the cases. These results provide little support for the introduction of routine fetal ultrasound screening as a mandatory part of obstetric care.

Tertiary referral centres, in contrast, have reported far better results. Especially, the proportion of cases detected prenatally is high (60 to 85%). Yet, it is important to realise that the sonographers in these centres are far more experienced and that scanning time allocated to each examination is not limited to a maximum of 10 to 15 minutes. In addition, the patients involved are a selection, considered at increased risk of having affected offspring. The accumulated experience of a tertiary referral centre in Rotterdam, the Netherlands gives evidence of similar results with 40 to 60% of the cases detected prenatally in women at a known increased risk for congenital heart disease in their offspring (chapter 8). However, the actual yield, that is the proportion of affected fetuses

fetuses in the cohort screened, appeared to vary considerably within this high risk group. Therefore, the risk factors for fetal cardiovascular malformations, currently applied as an indication for tertiary ultrasound examination may need reappraisal. Selection of cases referred may further improve the yield of a high risk screening program.

Finally, the attainable yield of routine fetal echocardiography has been assessed in decision analysis model, reflecting the choices and chances that (future) parents, the fetus and obstetrician face (chapter 9). It could be demonstrated that even with more or less optimal results of population screening still a limited impact can be anticipated. The more so, as such optimal results can only be achieved if all pregnant women are screened routinely at about 20 weeks gestation, the prognosis would improve upon detection of a severe anomaly and, well trained well equipped sonographers would be available at sufficient time and locations.

In conclusion, routine fetal ultrasound screening for detection of congenital anomalies appears to achieve an insufficient level of detection in the setting of the present study to merit general introduction. Improved training of the sonographers is required to realise a better detection rate. Moreover, it may be difficult to achieve a sufficient yield in a low risk population. On the other hand, ultrasound examination performed in referral centres for prenatal diagnosis on account of a known increased risk of fetal anomalies appears to be far more efficient. Merely, identifying the reasons for referral that justify extensive ultrasound examination may need additional research.

# SAMENVATTING

Aangeboren hartafwijkingen komen relatief vaak voor. Voorts is de ontwikkeling, en derhalve de verbetering van de prognose, minder snel gegaan dan bij infectieziekten, zodat aangeboren hartafwijkingen bij zuigelingen een niet te verwaarlozen gezondheidsprobleem vormen (hoofdstuk 1).

Op dit moment kan slechts bij een minderheid (10 tot 20%) een mogelijke oorzaak worden aangewezen voor het optreden van een aangeboren hartafwijking (hoofdstuk 2). Binnen enkele tientallen jaren zal, naarmate het samenwerkingsverband tussen epidemiologie, embryologie, genetica en moleculaire biologie vruchten gaat afwerpen, dit verklaarbare deel toenemen. Bekend zijn met risico- of oorzakelijke factoren zou deze determinanten wellicht toegankelijk maken voor behandeling of primaire preventie. Ondertussen blijft secundaire preventie gericht op het voorkomen van verdere gezondheidsproblematiek, nadat eenmaal een afwijking is opgetreden, het beste alternatief.

Meerdere pogingen om de omvang van het probleem van aangeboren hartafwijkingen te beschrijven hebben geresulteerd in uiteenlopende schattingen (hoofdstuk 3). Klaarblijkelijk verschilden de gebruikte methoden om de proportie aangedane foetussen of zuigelingen (prevalentie) te schatten. Een aantal kenmerken van studie-opzet bleken in dit verband bepalend. Met name voor geringe afwijkingen waren duur van vervolging binnen het onderzoek en de vaststelling van afwijkingen, waaronder diagnostische techniek en de gebruikte definities, van belang. Het blijkt moeilijk te zijn om een bevredigende schatting van de prevalentie van aangeboren hartafwijkingen bij levendgeborenen te verkrijgen. Voor een schatting van het deel van de foetussen (bij bepaalde zwangerschapsduur) dat is aangedaan geldt dit in nog grotere mate. Indien betrouwbare informatie (liefst autopsie verslagen) aanwezig zou zijn behoorde het wellicht tot de mogelijkheden om een inschatting te verkrijgen van de invloed van aangeboren afwijkingen op de foetale overleving. Bovendien zou een schatting van de incidentie, de proportie foetussen waarbij zich een afwijking voordoet, verkregen kunnen worden. Dergelijke gegevens zijn, alhoewel momenteel niet beschikbaar, essentieel voor het wetenschappelijk onderzoek naar oorzakelijke factoren, zodat aanvullend onderzoek vereist is.

Voorts is het, om de consequenties en omvang van het probleem van aangeboren hartafwijkingen te kunnen inschatten, van belang om over informatie omtrent overleving en veroorzaakte "ziekte" te beschikken. Derhalve werd een beknopt overzicht van de stand van zaken binnen de kindercardiologie opgenomen (hoofdstuk 4). Tevens werd een

oordeel gegeven over het belang van hartafwijkingen voor de foetale overleving. Het ligt voor de hand dat levendgeborenen met een aangeboren hartafwijking kunnen worden beschouwd als een selectie van de aangedane embryo's of foetussen die reeds in een vroeger stadium van de zwangerschap aanwezig waren. Gevallen van (vroege) intra-uteriene sterfte worden slechts zelden in ogenschouw genomen. Zoals reeds opgemerkt gaat met het abortus materiaal waardevolle informatie verloren indien geen diagnose wordt gesteld.

Naast een beschrijving van de mogelijke gevolgen van aangeboren hartafwijkingen voor de foetus en pasgeborene werd ook de mogelijkheid tot, en het belang van, prenatale detectie door middel van ultrageluidsonderzoek toegelicht. Het bleek dat een groot deel van de afwijkingen dat zich na de geboorte openbaart met de huidige techniek prenataal waarschijnlijk niet is vast te stellen. Voorts bleek dat het moeilijk zou zijn om de prognose van aangedane foetussen te verbeteren.

Desalniettemin is routinematig prenataal ultrageluidsonderzoek ter opsporing van aangeboren hartafwijkingen op grote schaal aanbevolen op grond van initiële publikaties. Een grondige evaluatie van deze vroege studies gaf enige verklaringen voor de tegenstrijdige resultaten in vergelijking met meer recent werk (hoofdstuk 5). Zo bleek dat bij een aantal vroege studies, voor foetussen met een negatieve test-uitslag, gebruik was gemaakt van reeds eerder verzamelde gegevens omtrent de uitkomst. Hiermee werd een potentiële vertekening van de resultaten geïntroduceerd omdat men niet kan uitsluiten dat een aantal pasgeborenen met een afwijking buiten beschouwing zijn gebleven. Bovendien betrof het experts op het gebied van ultrageluidsonderzoek zodat de verkregen resultaten minder representatief zijn voor reguliere klinieken voor ultrageluidsonderzoek. Een grondige evaluatie van routinematig uitgevoerd ultrageluidsonderzoek, in een realistische klinische omgeving, lijkt op zijn plaats alvorens over te gaan tot algemene toepassing.

Het hoofd-onderwerp van dit proefschrift betreft een verslag van het ontwerp, de uitvoering en de resultaten van een prospectief vervolg-onderzoek bij een groep van 6.922 foetussen, allen routinematig onderzocht met behulp van ultrageluidsonderzoek (hoofdstuk 6 & 7). Nadat van de meerderheid van de foetussen (> 81%) uitkomst gegevens waren verkregen bleek dat slecht 4,5% van de hartafwijkingen voor de geboorte was ontdekt. Overige aangeboren (niet hart-) afwijkingen werden in 30% van de gevallen voor de geboorte ontdekt. Dergelijke resultaten lijken geen aanleiding te geven om routinematig

uitgevoerd ultrageluidsonderzoek als een vereist onderdeel van de verloskundige zorg in te voeren.

Vanuit gespecialiseerde verwijs centra, echter, zijn veel betere resultaten gerapporteerd. Met name de proportie aangeboren afwijkingen die reeds voor de geboorte ontdekt wordt is hoog (60 tot 85%). Hierbij is het van belang dat men zich realiseert dat het om zeer ervaren personeel gaat en dat de duur van het ultrageluidsonderzoek niet gelimiteerd is tot maximaal 10 tot 15 minuten. Bovendien betreft het een selecte groep patiënten waarvan verondersteld wordt dat zij een verhoogd risico hebben voor het optreden van aangeboren hartafwijkingen. Bij vrouwen met tevoren bekend verhoogd risico voor het optreden van hartafwijkingen in het nageslacht werden vergelijkbare resultaten geboekt; in 40 tot 60% van de foetussen met een aangeboren hartafwijking werd deze reeds voor de geboorte ontdekt (hoofdstuk 8). Echter, binnen deze hoog-risico groep bleek de proportie van gevallen met afwijking(en) een behoorlijke spreiding te vertonen. Derhalve verdient het aanbeveling om de momenteel gebruikte indicaties of risicofactoren voor gedetailleerd ultrageluidsonderzoek nader te evalueren. Aanpassing van selectiecriteria voor verwijzing zou de opbrengst van hoog-risico ultrageluidsonderzoek kunnen vergroten.

Tenslotte werd met behulp van een beslis analyse model, waarin de keuzen en kansen van (toekomstige) ouders, de foetus en de verloskundige weergegeven worden, getracht de bereikbare opbrengst van routinematig uitgevoerd ultrageluidsonderzoek naar aangeboren hartafwijkingen te schatten (hoofdstuk 9). Het bleek mogelijk om aan te tonen dat, zelfs met min of meer optimale resultaten van routinematig ultrageluidsonderzoek, de invloed hiervan gering zou zijn. Te meer, daar dergelijke optimale resultaten slechts kunnen worden bereikt indien alle zwangere vrouwen na omstreeks 20 weken zwangerschap routinematig zouden worden onderzocht, er daadwerkelijk verbetering van de prognose van voor de geboorte ontdekte ernstige gevallen zou optreden, en goed geschoold personeel met adequate apparatuur beschikbaar zou zijn.

Samenvattend kan gesteld worden dat routinematig uitgevoerd ultrageluidsonderzoek om reeds voor de geboorte aangeboren afwijkingen te kunnen opsporen, in het kader van het huidige project, van onvoldoende kwaliteit blijkt om een aanvaardbaar resultaat te bereiken. Een verbeterde opleiding in de verloskundige echoscopie is noodzakelijk om tot een meer effectieve opsporing van aangeboren afwijkingen te komen. Bovendien lijkt het

hoe dan ook moeilijk om een acceptabel effect te behalen binnen een laag risico groep (de algemene bevolking). Ultrageluidsonderzoek uitgevoerd in gespecialiseerde centra voor prenatale diagnostiek, op grond van tevoren bekend verhoogd risico voor aangeboren afwijkingen, is daarentegen duidelijk veel efficiënter. Slechts het onderkennen van indicaties voor uitgebreid ultrageluidsonderzoek verdient nader onderzoek.

№ 04316

datum onderzoek : .. - .. 199 ..

laatste menstruatie : .. - .. 199 ..
☐ onbekend

zwangerschapsduur : .. weken ( ca. 16 - 24 weken )

aanvrager echo-onderzoek :
☐ verloskundige
☐ huisarts
☐ gynaecoloog ( eigen polikliniek )

reden echo-onderzoek :
☐ routine inspectie
☐ termijndiscussie
☐ overige .....

vierkamerverdeling :
☐ normaal
☐ abnormaal: ☐ anatomie
☐ ritme
☐ niet te beoordelen / niet gezien

andere afwijkingen :
☐ nee
☐ ja .....

Heeft u verwezen naar het
Academisch Ziekenhuis Rotterdam : ☐ nee
Dijkzigt ? ☐ ja

*Appendix B*

effectiviteit routine
intra - uteriene
echocardiografie
Instituut
Epidemiologie
en Biostatistiek

**№ 04316**

| Uw brief | Ons kenmerk | Datum |
|---|---|---|
| | | 15 januari 1991 |
| Onderwerp | Faxnummer | Doorkiesnummer |
| | 010-408 7494 | 010-408 7475 |

Zeer geachte mevrouw,

In samenwerking met de Nederlandse Hartstichting gaan de Erasmus Universiteit, het ziekenhuis waar u wordt onderzocht en het consultatie-buro voor zuigelingen, na hoe effectief het echo-onderzoek is dat u zojuist heeft ondergaan. Met andere woorden; wij willen te weten komen of er misschien afwijkingen zijn die niet gezien kunnen worden met dit onderzoek. Het gaat hierbij vooral om afwijkingen van het hart.

Wij willen hiervoor graag uw medewerking vragen en verzoeken u de bijgevoegde formulieren bestemd voor het consultatie-buro (of eventueel een andere arts die uw kind zal onderzoeken) bij het eerste bezoek af te geven. Verder hoeft u niets te doen.

Uiteraard worden alle verzamelde gegevens strikt vertrouwelijk verwerkt en blijven medisch beroeps geheim.

Mocht u vragen hebben dan kunt u mij op werkdagen van 09.00 - 17.00 uur bereiken op telefoonnummer 010 - 4087475.

Wij danken u bij voorbaat hartelijk voor uw medewerking.

Met vriendelijke groet,

E. Buskens, arts.

Dr. D.E. Grobbee
Instituut Epidemiologie
Erasmus Universiteit Rotterdam

Prof. Dr. J.W. Wladimiroff
afdeling Gynaecologie/ Verloskunde
Academisch Ziekenhuis Dijkzigt

Prof. Dr. J Hess
afdeling Kindercardiologie
Sophia Kinderziekenhuis

effectiviteit routine
intra - uteriene
echocardiografie

Instituut
Epidemiologie
en Biostatistiek

aan de consultatie-buro arts c.q.
arts jeugd gezondheidszorg 0 - 4
jarigen.

| Uw brief | Ons kenmerk | Datum |
|---|---|---|
| | | 15 januari 1990 |
| Onderwerp | Faxnummer | Doorkiesnummer |
| | 010-408 7494 | 010-408 7475 |

Geachte collega,

Van de huidige methode van intra-uteriene echocardiografie, als onderdeel van het routine prenatale screenings-onderzoek, is de effectiviteit onbekend. Derhalve wordt met subsidie van de Nederlandse Hartstichting, een grootschalig onderzoek uitgevoerd door de afdelingen Epidemiologie, Gynaecologie/Verloskunde en Kindercardiologie van de Erasmus Universiteit, naar de waarde van deze diagnostiek bij het vaststellen van aangeboren hartafwijkingen. Tevens is de Stichting Samenwerkende Rotterdamse Kruisverenigingen, bij monde van dhr. R.E. Juttmann, districtsarts jeugdgezondheidszorg Rotterdam, frequent geconsulteerd in verband met de praktische uitvoering van dit project. Wij vragen voor dit onderzoek graag ook uw medewerking.

Van de baby, waarop deze brief betrekking heeft, zijn de gegevens van routinematig vervaardigde intra-uteriene echocardiografie bij ons reeds bekend. Indien u bij het consultatie-buro onderzoek aanwijzingen heeft gevonden voor de aanwezigheid van een hartafwijking, vernemen wij dat graag van u. Bij verwijzing naar een kindercardioloog van het Sophia Kinderziekenhuis Rotterdam of het Academisch Ziekenhuis Leiden, zullen wij de gegevens verkregen bij intra-uteriene echocardiografie kunnen vergelijken met die verkregen bij nadere klinische diagnostiek. Wilt u daarom aangeven of u de huisarts heeft voorgesteld het kind te verwijzen.

Het is voor het onderzoek van groot belang dat u de bijgesloten briefkaarten invult en vervolgens opstuurt. Eén na het eerste onderzoek en de tweede, na contrôle, een half jaar later of eerder indien u verwijzing naar een kindercardioloog geïndiceerd acht.

Dr. D.E. Grobbee
Instituut Epidemiologie
Erasmus Universiteit Rotterdam

Prof. Dr. J.W. Wladimiroff
afdeling Gynaecologie/ Verloskunde
Academisch Ziekenhuis Dijkzigt

Prof. Dr. J Hess
afdeling Kindercardiologie
Sophia Kinderziekenhuis

Wij danken u bij voorbaat hartelijk voor uw medewerking. Mocht u over het onderzoek nadere informatie wensen dan kunt u op werkdagen kontakt opnemen met ondergetekende op telefoonnummer 010 - 4087475, tussen 09.00 en 17.00 uur, of met mevr. I.M.E. Frohn-Mulder, kindercardioloog, Sophia Kinderziekenhuis Rotterdam, ( ma., di. & vrij.) op telefoonnummer 010 - 4656566 tst. 2293.

Met collegiale hoogachting,

Mede namens Prof. Dr. J. Hess, kindercardioloog,
Prof. Dr. J.W. Wladimiroff, gynaecoloog, en
Dr. D.E. Grobbee, epidemioloog

E. Buskens, arts

*Appendix D*

**№ 04316**

datum onderzoek : . . - . . 199 . .
geboortedatum : . . - . . 199 . .
geslacht : ☐M
☐V

Het betrokken kind is voor de eerste maal gezien op het C.B..

☐ Geen afwijkingen waargenomen; verdere contrôle zal op gebruikelijke wijze plaatsvinden.

☐ **Anders**; namelijk: .....
.....
(bijvoorbeeld: direct indicatie verwijzing, ander specialisme, andere aangeboren afwijkingen enzovoorts.)

Aub. na eerste bezoek versturen.

*Appendix E*

**№ 04316**

datum onderzoek : . . - . . 199 . .
geboortedatum : . . - . . 199 . .

☐ Bij hercontrôle wederom geen afwijkingen waargenomen.

☐ Gelet op symptomen passend bij hartafwijkingen, zoals afbuigen van de groeicurve, voedingsproblematiek, ademhalingsproblematiek, cyanose, afwezige liespulsaties of een hartgeruis, is verwijzing, door de huisarts, naar een kindercardioloog geïndiceerd

☐ **Anders**; namelijk: .....
.....
(bijvoorbeeld: verwijzing ander specialisme, eventueel symptomen of diagnose)

Aub. in dossier bewaren en na eindbeoordeling versturen.

*Appendix F*

The following clinics for routine prenatal ultrasound participated in the study: Holy Ziekenhuis, Vlaardingen, Ikazia Ziekenhuis, Rotterdam, Jacobus Ziekenhuis, Zwijndrecht, 't Lange Land Ziekenhuis, Zoetermeer, Merwede Ziekenhuis, Dordrecht, Reinier de Graaf Gasthuis, Delft, Refaja Diakonessenhuis, Dordrecht, Schieland Ziekenhuis, Rotterdam, Sint Franciscus Gasthuis 1e lijn, Rotterdam, Sint Franciscus Gasthuis 2e lijn, Rotterdam, Stichting Trombosedienst en Artsenlaboratorium Rotterdam, University Hospital Rotterdam - Dijkzigt, Rotterdam, Westeinde Ziekenhuis, Den Haag, IJsselland Ziekenhuis, Rotterdam, Zuider Ziekenhuis, Rotterdam.

## CONGENITAL HEART DISEASES AND OTHER ANOMALIES ASCERTAINED

R = Routine U = Undetermined
GA = Gestational age
M = Miscellaneous

| Diagnosis | Remarks | Indication US | Outcome US | Gestational age (weeks) |
|---|---|---|---|---|
| Valvular pulmonary stenosis. | Paediatric cardiologist. Chronic obstructive airway disease. | GA | - | 18 |
| VSD small, murmur. | Paediatric cardiologist. | R | - | 20,1/7 |
| PA: complex heart defect; levo isomerism syndrome, 2 morphological left-atria, large VSD, hypoplastic pulmonary artery, ASD, etc. | Structural ultrasound: complex CHD; hypoplastic left-heart, isomerism/heterotaxia. | R | + | 16,3/7 |
| Large VSD + ASD. | Corrected surgically. | R | - | 23 |
| Aortic valve insufficiency; coarctation juxtaductal. | Corrected surgically. | R | - | 20,6/7 |
| Small VSD, dysmature, deformation of skull. | Corrected surgically. | GA | - | 24 |
| Large VSD, ASDII, sinus coronarius absent. | Paediatric cardiologist; corrected surgically. | R | - | 22 |
| Routine utrasound: no anomalies. Follow-up: under-development of right-ventricle with reduced compliance + varying right/left shunting through the foramen ovale. | Structural ultrasound: ASD, probably VSD, Hypoplastic right-ventricle, microcephalic, left clubfoot. | R | - | 18,5/7 |
| ASDII, VSD. | Developing heart failure. Paediatric cardiologist. | R | U | 20 |
| Coarctation, PDA, VSD. | Corrected surgically. | GA | - | 16,3/7 |
| Small apical muscular VSD. | Paediatric cardiologist. | R | - | 19,1/7 |
| VSD, Pulmonary artery atresia, PDA. | Paediatric cardiologist; corrected surgically: Blalock Goretex shunt left. | R | - | 19,1/7 |
| VSD closed spontaneously. First examination: III/VI systolic murmur + echocardiography; shunt flow. Follow-up: I/VI no anomalies. | Cardiologist. | R | U | 23 |
| Pulmonary atresia, VSD, PDA. | Paediatric cardiologist; corrected surgically: aortic/pulmonary Goretex shunt. | R | - | 18,3/7 |
| AVSD; incomplete atrial component only. | Paediatric cardiologist. Corrected surgically | GA | - | 18,6/7 |
| VSD, PDA. | Trisomy 21 | R | - | 16 |
| Small VSD. | Paediatric cardiologist. | R | - | 19,2/7 |
| Second fetus of triplets. Multiple CHD, advanced ascites. | Structural ultrasound 24 weeks: right-ventricular reduction, probable VSD. PA: - Children 1 + 3: no anomalies. | R | U | 19 |
| Pulmonary atresia, VSD, PDA. | Corrected surgically. | R | - | 20 |
| PDA + muscular apical VSD. | Follow-up: no murmur, spontaneous closure. | GA | - | 20,3/7 |

| | | | | |
|---|---|---|---|---|
| Loud murmur, small perimembranous VSD. | Paediatric cardiologist. | R | - | 17,4/7 |
| Hypoplastic left-heart, small ascending aorta. | Paediatric cardiologist; deceased 3 days postnatally. | R | - | 18,3/7 |
| Systolic murmur, small perimembraneus VSD. | Paediatric cardiologist. | R | - | 18,6/7 |
| Routine ultrasound: anatomy 4CV abnormal. | Structural ultrasound: no anomalies. Postnatally no anomalies. | GA | + | 18 |
| Routine ultrasound: anatomy 4CV abnormal; no/small atrial septum. | Structural ultrasound: no anomalies. Postnatally no anomalies. | R | + | 21 |
| Large muscular VSD + coarctation preductal. | Paediatric cardiologist. | R | - | 21 |
| Routine ultrasound: anatomy + rhythm abnormal. | Structural ultrasound: no obvious structural anomalies, normal rhythm. | R | + | 18 |
| Transposition great arteries. | Paediatric cardiologist. Corrected surgically; artial switch-operation. | R | - | 17,3/7 |
| Routine ultrasound: Cardiac connections: double outlet. 4CV normal. | Structural ultrasound: no anomalies. | GA | + | 19 |
| Perimembraneus VSD, ASDII, PDA with left/right shunt. | Paediatric cardiologist; corrected surgically. | R | - | 20,5/7 |
| Systolic murmur; perimembranous VSD. | Paediatric cardiologist; spontaneous closure. | R | - | 20 |
| Neonatal echocardiogaphy: d-Transposition great arteries. | Paediatric cardiologist; corrected surgically: arterial switch-operation. Deceased 3 days postnatally due to post operative pulmonary haemorrhage. | R | - | 20 |
| Atrioventricular septal defect. | Paediatric cardiologist. Trisomy 21. | R | - | 21 |
| Small innocent VSD. | Paediatric cardiologist; spontaneous closure. | R | - | 18,3/7 |
| VSD. | Paediatric cardiologist. | R | - | 20,3/7 |
| Systolic murmur III/IV; VSD. | Paediatric cardiologist. | R | - | 20 |
| VSD, perimembraneus "outlet". | Paediatric cardiologist. | R | U | 19 |
| Coarctation of aorta. | Corrected surgically. Pylorus stenosus. | R | - | 19,3/7 |
| VSD, muscular. | Paediatrician. Follow-up: 03-03-95. | R | - | 17 |
| Systolic murmur, VSD, pulmonary stenosis + double outlet right ventricle. | Paediatric cardiologist. | R | - | 17 |
| Atrio-ventricular septal defect, chondro ectodermal dysplasia, IUD. | Ellis v. Creveld syndrome. PA: chondro ectodermal dysplasia. | R | - | 23,4/7 |
| Coarctation juxtaductal, patent ductus arteriosus. | Paediatric cardiologist. | R | - | 21,3/7 |
| VSD, ASDII, PDA. | Corrected surgically. Trisomy 21 | R | - | 19 |
| Systolic murmur II/VI, VSD. | Paediatric cardiologist. | R | - | 21 |
| Medium size perimembranous VSD. | Paediatric cardiologist. | R | - | 22 |
| Pulmonary atresia + VSD, PDA. | Paediatric cardiologist; corrected surgically: Blalock Goretex shunt. | R | - | 20 |

| | | | | |
|---|---|---|---|---|
| Routine ultrasound: density in left ventricle, bradycardia. | Structural ultrasound: so-called 'golfball' + occasional bradycardia. | GA | + | 16,3/7 |
| Incomplete AVSD. | Paediatric cardiologist. Trisomy 21. | R | - | 23 |
| Omphalocèle, exstrophia cloacae. | Paediatrician. Premature, decaesed 3 days postnatally. PA: + | R | + | 21,3/7 |
| Cystic structure in liver: 15x18mm. | Structural ultrasound: no anomalies. | R | + | 19,3/7 |
| Oesophagus atresia, PDA. | Paediatrician.: Died despite surgical correction. | R | - | 20,3/7 |
| Oesophagus atresia + tracheo-oesophageal fistula. | Corrected surgically. | R | - | 22 |
| Gastro-schizis. | Structural ultrasound: omphalocèle. Paediatrician: Beckwitt-Wiedeman syndrome, dysmorfia. | GA | + | 16,2/7 |
| Diaphragmatic hernia (detected prenatally). | Structural ultrasound. | R | - | 21 |
| Diaphragmatic hernia, Prune Belly, polyhydramnios. | Paediatrician. Hydrocephalus. | GA | + | 24,3/7 |
| Hydronephrosis, bilateral compensated subpelvine stenosis. | Paediatrician. | R | - | 24,3/7 |
| Hydronephrosis. | Paediatrician. Double sided reflux III. | R | - | 19,6/7 |
| Primary obstructive mega-urethra left. | Paediatrician | GA | - | 22 |
| Hydronephrosis double sided + hydro-ureters. | Paediatrician. Corrected surgically. | R | + | 20,3/7 |
| Primary obstructive mega-urethra left, hydronephrosis left. | Paediatrician. | GA | - | 21,4 |
| Extrophia vesicae. | Paediatrician. Corrected surgically | R | - | 17,3/7 |
| Double sided hydronephrosis; urethra-valves. | Paediatrician. | R | - | 23 |
| Hydronephrosis right, microcephaly, multiple dysmorphia, PDA, ASD. | PA: + Chromosomes 46,XY,del(7),(q34). | R | + | 18 |
| Cystic kidneys. | Paediatrician. | GA | - | 18 |
| Hydronephrosis left. | Paediatrician: no hydronephrosis. Follow-up: post natally more or less doubled left kidney. | R | + | 23 |
| IUGR, Wolf's syndrome, palato-schizis, hypertelorism, additional ears, dysmorphia. | Kidney-dysplasia | GA | + | 22 |
| Double-sided Cheilo-gnato-palato schizis. | Paediatrician; schizis-team. | R | - | 18 |
| Double-sided Cheilo-gnato-palato schizis. | Paediatrician; schizis-team. | R | - | 16,6/7 |
| Apert's syndrome. | Craniosynostosis, mid-facial hypoplasia, syndactyly, ocular anomalies. | GA | - | 19,1/7 |
| Cheilo-gnato-palato schizis. | Paediatrician; schizis-team. | GA | - | 21 |
| Palato schizis, micrognatia. | Paediatrician. | R | - | 19,2/7 |
| Palato schizis, glossoptosis. | Paediatrician. Pierre Robin's Syndrome. | GA | + | 22 |

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|---|---|---|---|---|
| Unilateral enlarged cerebral ventricle. | Structural ultrasound: no anomalies (probably "drop-out"). | R | + | 19 |
| Hydrocephalus caused by osteopetrosis. | Corrected surgically; lumbo-peritoneal drain. | R | - | 20,4/7 |
| Occipital encephalocèle. | Paediatrician. | M | - | 16 |
| Spina Bifida, systolic murmur I/VI. | Paediatrician. Dysmorphia. | R | - | 19,6/7 |
| Essentially absent left foot. | Paediatrician | R | - | 20 |
| Clubfoot. | Corrected surgically. | R | - | 21,5/7 |
| Amelia distal left arm. | Paediatrician | R | - | 16,2/7 |
| Left clubfoot. | Paediatrician | R | - | 19 |
| Syndactyly right/left foot, left-hand, hypoplasia dig. II to V. | Paediatrician; orthopaedic/plastic surgery, clinical genetics. | R | - | 24 |
| Clubfoot. | Paediatrician. | R | - | 23 |
| Clubfeet, PDA. | Dysmorphia | R | - | 19,3/7 |
| Scoliosis, body stalk anomaly. Autopsy: VSD. | Termination of pregnancy. | R | + | 16 |
| Osteogenesis imperfecta. | Termination of pregnancy at 20,3/7 weeks. | R | + | 18 |
| Klippel Trenauny Weber. | Termination of pregnancy at 21 weeks. | R | + | 20,3/7 |
| Hydrops fetalis + hygroma colli, IUD eci. | Intra-uterine referral. PA: extensive maceration, hydrops fetalis + hygroma colli. | GA | + | 19 |

indication M = mother Askermans syndrome

DANKWOORD

Eigenlijk meer dan woorden kunnen zeggen ben ik dank verschuldigd aan de medewerkers van het Instituut Epidemiologie en Biostatistiek van de Erasmus Universiteit Rotterdam, de afdeling Kindercardiologie van het Sophia Kinderziekenhuis, en de afdeling Prenatale Diagnostiek van het Academisch Ziekenhuis Rotterdam Dijkzigt. Zij vormden de afgelopen vier jaar het motiverend gezelschap dat door zijn positieve sfeer heeft bijgedragen aan het tot stand komen van mijn proefschrift. Naast dit algemene woord van dank wil ik echter een aantal mensen in het bijzonder danken voor hun onmisbare inbreng. Allereerst de toekomstige ouders die deelnamen aan het onderzoek. De gegevens die zij ons ter beschikking stelden vormen de basis voor dit proefschrift. Een volgende onmisbare schakel in het geheel was de enthousiaste medewerking van "collega-echografisten" en hun medewerkers. Zij hebben zorg gedragen voor het verrichten en de verslaglegging van bijna 7.000 echo-onderzoeken. Daarnaast was er meestal ook nog tijd voor een kop koffie tijdens mijn "ophaalronden" op de motor, en nader overleg als er van onze kant onduidelijkheid bestond over de echo-gegevens. Voorts hebben vele consultatie-bureau artsen verslag gedaan van hun bevindingen bij de zuigelingen uit het onderzoek. Ook huisartsen, kinderartsen en kindercardiologen vonden wij bereid ons de noodzakelijke informatie te verschaffen.

Aan de wieg van het project stonden naast mijn promotores onder andere Rikard Juttmann, Ingrid Frohn-Mulder en Patricia Stewart. Hun inbreng en ideeën waren onontbeerlijk om tot een uitvoerbaar onderzoeksvoorstel te komen. Patricia Stewart was daarnaast gelukkig ook nog bereid om zo nu en dan met een kritisch oog naar mijn Engels te kijken. Vervolgens heeft Marcel Eijgermans, samen met Gerrit-Anne van Es, een data-base ontworpen zodat de verkregen gegevens konden worden opgeslagen en bewerkt. In een later stadium kon ik bij Marcel ook altijd terecht als ik weer eens een specifieke selectie van gegevens nodig had.

Dat het controleren, invoeren, bijhouden en desnoods aanvullende informatie opvragen voor een omvangrijke data-base een formidabele inzet vereist kunt u zich wellicht voorstellen. Andrina Cleveringa, Sharmila Bhikha, Petra Steenman-Fontein, Agnes van der Voorn en Desiré de Kruijff hebben wat dat betreft lief en leed met mij gedeeld. In

tijden van tegenspoed gaven zij morele steun en in tijden van voorspoed waren zij er om de vreugde te delen. Of de meerderheid van hen zich door het onderzoek heeft laten inspireren weet ik niet. Een feit is wel dat Andrina, Petra en Agnes vervolgens ook zelf voor prenatale echodiagnostiek in aanmerking kwamen.

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Dat aan de overstap op epidemiologie een moeilijke afweging vooraf ging zullen enkele van mijn junioren-collega's (-kamergenoten) kunnen beamen. Door met hen de gedachten en twijfels te delen kwam mijn keuze tot stand. Cuno Uiterwaal, met wie ik gedurende een groot deel van de tijd op één kamer heb gezeten, wil ik hier met name noemen en danken. Cuno ik ben blij dat jij paranimf bent. Jan Luyendijk, vriend en ook paranimf, jij nam mij mee uit jagen en vissen. Deze totaal andere bezigheden, gepaard met de nodige gezellige uurtjes (met name achteraf), vormden een zeer welkome afwisseling en punten van rust. Ik hoop dat wij hier samen nog lang mee door kunnen gaan. Andere vrienden en familieleden die ik met name het laatste jaar te weinig heb gesproken dank ik voor hun geduld. Als ik straks de race tegen de klok heb voltooid is er weer tijd om de draad op te pikken.

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CURRICULUM VITAE

Erik Buskens werd op 13 juni 1962 te Rotterdam geboren. In Oud Beyerland rondde hij aan de Rijksscholengemeenschap in 1979 het H.A.V.O. af en vervolgens in 1981 het Atheneum. In aansluiting hierop begon hij aan de Erasmus Universiteit Rotterdam de studie Geneeskunde, hetgeen in februari 1988 werd afgerond met het Arts-examen. Vervolgens werkte hij, in het kader van de militaire dienstplicht, van mei 1988 tot en met maart 1990 als arts bij de Koninklijke Landmacht. Van mei tot september 1990 was hij werkzaam als assistent geneeskundige, op de afdeling inwendige geneeskunde van het Interconfessioneel Ziekenhuis de Baronie te Breda (J.A.M. Hoskam, internist). Per september 1990 werd hij aangesteld als arts-onderzoeker bij de afdeling Kindergeneeskunde, subafdeling Cardiologie, van het Sophia Kinderziekenhuis (Prof. Dr J. Hess), in nauwe samenwerking met het Instituut Epidemiologie en Biostatistiek van de Erasmus Universiteit Rotterdam (hoofd: Prof. Dr A. Hofman, begeleiding: Prof. Dr D.E. Grobbee) en de afdeling Gynaecologie en Verloskunde van het Academisch Ziekenhuis Rotterdam - Dijkzigt (Prof. Dr J.W. Wladimiroff), in verband met een epidemiologisch onderzoek naar de effectiviteit van prenatale echodiagnostiek van aangeboren hartafwijkingen, hetgeen resulteerde in het onderhavige proefschrift. Naast zijn coördinerende taak ten behoeve van het onderzoek, organisatie van seminars in 1991 en coördinatie van het congres voor de Vereniging voor Epidemiologie in 1992, werd hij in de gelegenheid gesteld epidemiologisch en statistisch onderwijs te volgen zodat in 1993 registratie tot epidemioloog A kon plaatsvinden. Sinds september 1994 werkt hij als klinisch epidemioloog bij het Academisch Ziekenhuis Utrecht.