

# MASTERS PROJECT



## Fetal Heart Screening In Low-Risk Pregnancies

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# FETAL HEART SCREENING IS LOW-RISK PREGNANCIES

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## ABSTRACT

**Objectives:** *The purpose of this review is to evaluate the indication for prenatal ultrasonography in the detection of congenital heart disease, specifically in low-risk obstetric populations.*

**Design:** *Multistudy Review*

**Methods:** *Published studies were identified by a National Library of Medicine PubMed search using the terms, “ultrasonography, echocardiography, ultrasound, sonography, fetal, fetus, prenatal, heart defect, cardiac, and anomalies” along with several other inclusion and exclusion criteria. An official validity and level of evidence assessment was completed for each study.*

**Results:** *Three large prospective studies were selected; 3/3 studies were given level 1b evidence ratings. Study #1: overall sensitivity 15%, specificity 99.9%, positive predictive value 50%, negative predictive value 99.6%. Study #2: overall sensitivity 43.8%, specificity 99.7%, positive predictive value 70.4%, negative predictive value 99.3%. Study#3: overall sensitivity 88.5%; specificity 100 %, positive predictive value 100%, negative predictive value 99.8%.*

**Conclusion:** *All studies evaluated suggest that a fetal heart screening program in a low-risk obstetric population is justified, although sensitivity levels varied from 15-88% in the detection of CHD. Detection rates would be potentially elevated with universal increase in sonographer training and experience, and with the utilization of developing technology.*

## INTRODUCTION

Congenital heart disease (CHD) is one of the most frequent abnormalities observed at birth with an incidence of about 8/1000<sup>1</sup>. In the United States, approximately 32,000 children are born with a heart defect each year<sup>2</sup>. Defects can range from mild to complex in severity. The ability to detect, diagnose, and properly intervene has progressed rapidly within the last four decades.

Currently, fetal echocardiography is extensively utilized only in high-risk obstetric groups, or if suspicion is noted on the level 1 obstetric ultrasound. High-risk groups include one or more of the following<sup>3</sup>:

- Parent or sibling with a history of CHD
- Certain maternal diseases (e.g. diabetes mellitus, collagen vascular disease)
- Maternal exposure to certain medications (e.g. lithium, amphetamine, anticonvulsants, addictive drugs, progesterone, or other teratogens)
- Advanced maternal age (>35yrs)

- Fetal cardiac arrhythmias
- Fetal chromosomal anomalies
- Fetal extracardiac anomalies (e.g. diaphragmatic hernia, omphalocele, hydrops)
- Fetal polyhydramnios or oligohydramnios

However, statistics show that **up to 50% of neonates diagnosed with a CHD have no known risk factors**, and most have undergone several obstetrical ultrasounds during the pregnancy that did not detect a cardiac defect<sup>4</sup>. With the introduction of improved resolution ultrasound equipment and color flow Doppler, the question arises, **should low-risk populations also be extensively screened?** In order to explore this, the efficacy of current screening programs must be assessed.

Several retrospective and prospective studies have been organized within the last decade to assess screening efficacy. In the literature, the sensitivity of the detection of CHD varies from 4.5% for the four-chamber view<sup>5</sup>, to 95% for a detailed examination done under ideal conditions<sup>6</sup>. This discrepancy is likely due to a number of reasons, including: (1) *Wide variability in sonographer education and experience.* The ranges of personnel performing the exams include obstetric trainees, obstetric physicians, radiologists, perinatologists, and pediatric cardiologists. (2) *Ultrasound techniques are not standardized.* Techniques range from the basic four-chamber view to a detailed examination of five plus chamber views with color flow Doppler. Also, timing of the initial screening varies from the 14<sup>th</sup> week of gestation, to anytime thereafter during pregnancy. (3) *It is often difficult to distinguish between cardiac malformations and variations of normal anatomy.* Awkward fetal positioning or severe maternal obesity can obscure image clarity. Additionally, normal fetal physiology may preclude the diagnosis of certain cardiac defects, such as ventricular septal defects, atrial septal defects, patent ductus arteriosus, coarctation of the aorta, and mild valve abnormalities<sup>1</sup>. (4) *The American College of Obstetricians and Gynecologists (ACOG) does not currently recommend universal screening ultrasounds<sup>7</sup>.*

With such obstacles and low sensitivity yields, one may wonder whether routine fetal heart screening is justified. The benefits of fetal diagnosis of CHD must also be considered, including appropriate planning for delivery, identification of urgent post-natal conditions, early tertiary care intervention, opportunities for genetic counseling, psychological preparation, parental education, and choice of pregnancy termination<sup>8,9</sup>. Experts argue that low sensitivity is better than zero sensitivity in the detection of potentially lethal malformations.

Therefore, the purpose of this review is to further investigate the question, **“Is fetal heart screening for the detection of cardiac anomalies indicated in low-risk populations?”** Three large prospective studies are critically appraised in the following sections below.

## METHODS

A PubMed search was completed January 2003 using the search terms, “(ultrasound OR ultrasonography OR echocardiography) AND (fetal OR fetus OR prenatal) AND (cardiac OR heart defect OR anomalies)”, yielding 44 articles. The only search limit applied was publication dates 1996-2003, due to the fact that equipment and fetal heart screening technique was largely primitive before this time. Similar searches on Cochrane, TRIP, and InfoPoems Database were also performed with limited results. Additional articles and background material were obtained through the Primary Children’s Medical Center in Salt Lake City, Utah, specifically through the Pediatric Cardiology Department. The collected articles were then included based on the following criteria: (1) *Prospective studies.* (2) *Consecutive series.* (3) *Low-risk or unselected pregnancies.* (4) *Techniques outlined.* (5) *Sensitivity and specificity values included.* (6) *>3,000 pregnancies screened.* (7) *Publication dates 1996-2003.* (8) *Study initiation 1991 or later.* Articles were excluded based on the following criteria: (1) *Retrospective studies.* (2) *High-risk or selected populations.* (3) *Limited in available statistics.* (4) *Published prior to 1996.* (5) *Initiated prior to 1991.*

Three large, prospective published studies were identified using the above criteria. These studies were individually evaluated for relevance and validity using standardized criteria, then assigned a level of evidence rating (Oxford Centre for Evidence-based Medicine). The primary outcome measurement for the purposes of this review is the sensitivity values of prenatal vs. postnatal detection of CHD in unselected populations.

## RESULTS

### Study #1

A study by Todros et al<sup>10</sup> was conducted in the Piemonte Region of Italy. Sonograms were performed on 8,299 pregnancies, and conducted within 17 different ultrasound units by various obstetricians. The study objective was to assess the accuracy of the four-chamber view as a screening test for the prenatal detection of CHD in a low-risk population. **Validity assessment: Study design:** This is a prospective observational study. Duration of the study is adequate, consisting of a four-year time period (1991-1995). Patients in the study are well-representative of a low-risk population; all subjects with a known risk factor for CHD were purposefully excluded (exclusion criteria stated and consistent with the high-risk indications listed in the Intro of this review). Racial diversity and ages of subjects screened were not included. **Study conduct:** An adequate number of patients were enrolled in the study. Scans were performed at 18-34 weeks gestation by various part-time obstetricians with experience ranging from 1-10 years (mean 9.4 years). Educational training appears inadequate considering only 30% attended a “short-training course” on the four-chamber view offered prior to starting the study. Technology utilized is limited, utilizing medium-level ultrasound machines to assess a four-chamber view of the heart only. Scans were performed transabdominally.

With inter-operator variation, bias may have occurred. Follow-up was marginal, consisting of a minimum of five days, or until the newborn was discharged from the hospital. No detail was given regarding follow-up methods. Lost to follow-up was not indicated. **Study results:** Incidence was recorded as 3.3/1000. Cardiac malformations were diagnosed in 40 newborns postnatally (4.8/1000). Only six of these (15%) were diagnosed *in utero* through the four-chamber view assessment (0.7/1000). The following values were calculated: overall sensitivity 15%, specificity 99.9%, positive predictive value 50%, and negative predictive value 99.6%. The sensitivity was calculated separately for cases scanned before 24 weeks, resulting in 9.5%. When malformations that were not associated with an abnormal four-chamber view were excluded from the analysis, the sensitivity increased to 35.3%. **Study conclusions:** The authors concluded that the sensitivity found in this study is low, but comparable to that reported of other multicentric, multi-operator studies utilizing similar techniques. They advocate that this study is probably realistic of current screening practice. They acknowledge the potential of routine screening programs to detect CHD. They advocate better training of the sonographers and extending the examination to include ventriculo-arterial connections. Level of evidence assessment: 1b.

## Study #2

A study by Hafner et al<sup>11</sup> was conducted in a National Health Service hospital in Vienna, Austria. Sonograms were performed on 6727 pregnancies by three experienced physicians (specialties not specified) through one antenatal unit. The study objective was to evaluate the efficacy of level II ultrasound screening for the detection of CHD in a low-risk population. **Validity assessment: Study design:** This is a prospective study. Duration of the study is adequate, consisting of a four-year time period (1992-1996). Patients in the study are well-representative of a low-risk population; all subjects referred to the department for a suspected CHD were purposefully excluded (exclusion criteria not described). Racial diversity and ages of subjects screened were not included. **Study conduct:** An adequate number of patients were enrolled in the study. Scans were performed at  $\leq 22$  weeks of gestation. Experience and training of operators appears adequate. Scans were performed by three doctors who had completed at least 1000 fetal ultrasounds prior to the study, and specially trained to scan various cardiac views. Technique utilized is acceptable, including three standardized cardiac sections obtained transabdominally: (1) apical four-chamber view (2) sagittal four-chamber view (3) right and left outflow tracts with crossing over of the great arteries. In relatively few cases of sonographer suspicion, color-Doppler and additional images were obtained. Follow-up was acceptable, consisting of a cardiac exam performed by an experienced neonatologist at day one, three, and five (although a pediatric cardiologist may improve sensitivity). Echocardiogram was additionally performed with the evidence of prenatal cardiac anomalies, striking murmurs, or poor oxygenation despite adequate artificial respiration. An acceptable number of patients were lost to follow-up due to delivering elsewhere (3%). Patients who entered the study were properly accounted for at its conclusion. **Study results:** Incidence was sited as 8/1000. Cardiac malformations were diagnosed in 87 newborns postnatally (13/1000). 43.8% of these were diagnosed *in utero* (5.7/1000). The following values were calculated: overall sensitivity 43.8%, specificity 99.7%,

positive predictive value 70.4%, and negative predictive value 99.3%. Detection rate was 20.8% in the presence of VSD, ASD2, or combined ASD2+VSD (thus decreasing overall sensitivity); the detection rate was 74.3% in the presence of other forms of CHD. Of the 39 cases diagnosed prenatally, 55.4% of pregnancies were electively terminated, 13% were planned to deliver in a hospital with the capacity of pediatric heart surgery, and 21% had a neonatologist present at birth. **Study conclusions:** The authors acknowledge that the yield of fetal sonography is extremely sonographer and technique dependent. They believe that their approach to screening in a low-risk population is a practical method considering that the study was performed in a public hospital with level two qualifications. They conclude that perinatal morbidity and mortality may be reduced through appropriate screening and intervention. Level of evidence assessment: 1b.

### Study #3

A study by Stümpflen et al<sup>12</sup> was conducted through the University of Vienna Medical School in Vienna, Austria. Sonograms were performed on 3,085 pregnancies, and conducted within one antenatal unit by one investigator. The study objective was to assess the prenatal detection of CHD by detailed fetal echocardiography in an unselected group of pregnant women. **Validity assessment: Study design:** This is a prospective study. Duration of the study is narrow, consisting of a 21 month time period (1993-1994). Patients in the study are marginally representative of a low-risk population, with 2,181 subjects (70.7%) having no known risk factors for CHD (high-risk criteria stated and consistent with the high-risk indications listed in the Intro of this review), 540 (17.5%) were considered high risk for CHD, 364 (11.8%) were referred for sonographically detected abnormalities. Racial diversity and ages of subjects screened were not included. **Study conduct:** An adequate number of patients were enrolled in the study. Scans were performed at 18-28 weeks gestation by one investigator. Sonographer experience and training was not described. Technique utilized is favorable, including the following transabdominal views: (1) apical four-chamber view (2) right and left outflow tracts (3) color-flow Doppler. Additional M-mode investigations were done when appropriate. Follow-up was ideal for suspected CHD patients, consisting of detailed diagnostic interventions and pediatric cardiology follow-up until the age of four, according to the Austrian federal screening program. Postnatal follow-up methods for all participants were otherwise not described. An acceptable number of patients were lost to follow-up (1.8%). Patients who entered the study were properly accounted for at its conclusion. **Study results:** Incidence was cited as 8/1000. Cardiac malformations were diagnosed in 52 newborns postnatally (16.9/1000). 88% of these were diagnosed *in utero* (14.9/1000). Prevalence for the cases exclusively with no risk factors was 6.9/1000. The following values were calculated: overall sensitivity 88.5%; specificity 100 %, positive predictive value 100%, negative predictive value 99.8%. Of the pregnancies with prenatally detected cardiac malformations, 37% were found to have a concomitant chromosomal abnormality, 47% were electively terminated. **Study conclusions:** The authors conclude that prenatal diagnosis of cardiac malformations by ultrasonography may significantly lower perinatal mortality, while allowing parents to make informed decisions about the further course of pregnancy. They found early diagnosis of cardiac defects lead to otherwise undiagnosable chromosomal abnormalities. They believe that

the use of a standard four-chamber view is insufficient for screening; inclusion of the outflow tracts in routine screening is recommended. They conclude that routine fetal screening for CHD is justified in an unselected population. Level of evidence assessment: 1b.

Table 1: Summary of study characteristics

	Year Published	Study Period	Location	Patients Screened	Population Selection	Gestational Age (wk)	Exam Techniques	#Operators
Todros	1997	1991-1995	Italy	8299	Low-risk	18-34	(1) 4C	Multiple
Hafner	1998	1992-1996	Austria	6727	Low-risk	≤22 wk	(1) apical 4C (2) sagittal 4C (3) right and left outflow tracts.	3
Stümpflen	1996	1993-1994	Austria	3085	Unselected	18-28 wk	(1) apical 4C (2) right and left outflow tracts (3) color-Doppler.	1

4C=four chamber view.

Table 2: Summary of validity assessments

	Similarity to Primary care Populations	Operator Training	Operator Technique	Patient Accounting & Follow-up	Level of Evidence Rating
Todros	A	I	I	I	1b
Hafner	A	A	M	M	1b
Stümpflen	M	U	A	A	1b

A=Adequate M=Marginal I=Inadequate U=Unknown

Table 3: Summary of study results

	Incidence	Prevalence	Sensitivity	Specificity	PPV	NPV
Todros	3.3/1000	4.8/1000	15%	99.9%	50%	99.6%
Hafner	8/1000	13/1000	43.8%	99.7%	70.4%	99.3%
Stümpflen	8/1000	16.9/1000† 6.9/1000‡	88.5%	100 %	100%	99.8%

†overall prevalence; ‡low-risk population prevalence.

Table 4: Summary of additional studies for routine screening of CHD

	Year Published	Study Design	Patients Screened	Population Selection	Gestational Age (wk)	Exam Techniques	Sensitivity
Rustico <sup>8</sup>	1995	Prospective	7024	Low-risk	20-22 wk	4C and venous returns	35%
Buskens <sup>5</sup>	1996	Prospective	6922	Low-risk	16-24 wk	4C	4% for 4C; 16% overall
Ott <sup>13</sup>	1995	Prospective	1136	Low-risk	U	4C and LV outflow tracts	14%
Tegnander <sup>14</sup>	1995	Prospective	7459	Low-risk	18 wk	2 parts, one with 4C view	26% for critical heart disease
Klein <sup>1</sup>	1999	Retrospective	97,245	Unselected	22,32 wk	4C, outflow tracts, & color-Doppler if CHD suspicion	34.8%
Bronshstein <sup>15</sup>	2002	Prospective	36323	High and low-risk	11-17 wk	Transvaginal	≈59.5%
Berghella <sup>6</sup>	2001	Retrospective	U	Unselected	U	U	95%

U=Unknown

## DISCUSSION

### Evaluation of study trends

All three prospective studies conclude that routine heart screening in low-risk populations should be potentially utilized. Although such conclusions are made, variation in sensitivity ranges from 15- 88.5%, and can be further compared to comparable studies ranging from 4- 95%<sup>5,6</sup>. Although specificity values are high, this range in sensitivity is a significant barrier in determining the accuracy of the screening test.

It is highly acknowledged in all articles that the four-chamber view is outdated as a solitary screening technique. Studies show that the diagnostic yield increases by at least 23% when visualizing the five-chamber view<sup>9</sup>. The five-chamber view includes visualization of the four chambers of the heart, in addition to the left ventricular outflow tract (aortic root), and the right ventricular outflow tract (pulmonary arteries). Studies #2 and #3 had fairly good sensitivity values when utilizing the five-chamber view. This technique appears practical as screening time averaged 3-20 minutes, and 4 minutes respectively.

Additional variables include dissimilarity in definition criteria. For example, postnatal follow up in study #1 was pursued until the newborn was discharged from the hospital, vs. study #3 which potentially pursued follow-up of CHD individuals until the age of four. None of the studies had sufficient long-term follow up for all study participants, which is a major flaw considering that ventricular septal defects, atrial septal defects, patent ductus arteriosus, coarctation of the aorta, and minor valve abnormalities are typically diagnosed postnatally during the first year of life<sup>1</sup>. Further studies with longer follow-up are needed to make conclusions on detection rates.

Additional imperfections in the studies were the exclusion of individual ages and ethnicity. Study #3 included data for women  $\geq 35$  years, but ages were otherwise unlisted. Also, the fact that these studies were performed in Italy and Austria may lead to incongruent results in comparison to the United States. It should be acknowledged that termination rates may vary with ethical variation between cultures. Termination rates are important because they affect birth prevalence and cost-benefit ratios. Additionally, the included studies were published between 1996 and 1998. Perhaps higher and more consistent sensitivity levels have been established in more recent trials.

A favorable aspect of the studies is that most study participants were representative of primary care populations. Study #1 and #2 specifically included only low-risk individuals. Study #3 included 70.7% low-risk individuals, with separate calculations for this low-risk group. These studies were uniquely different from numerous available studies due to their focus on screening low-risk populations. Overall prevalence was shown to be elevated in study #2 and #3; both studies attribute this to a possible bias that may have occurred when actively searching aneuploidies and other malformations detected *in utero*. This finding is reasonable considering the specificity values are close to 100%. It can be concluded that with thorough scanning, more cardiac anomalies may be detected.

Overall, the power and quality of the three selected studies is positive, considering the high number of study participants, and prospective study methods. Methods were described in sufficient detail to permit its replication. Specificity, sensitivity, positive predictive values, and negative predictive values were all readily available. The criteria for testing to be uniformly blind did not apply. The consistency of these level 1 studies merit a Grade of Recommendation Level A on the Oxford Centre Level of Evidence Criteria.

### **Consideration of screening factors**

When considering whether fetal heart screening is worthwhile as a diagnostic test, factors such as frequency, severity, risk, availability, amenability to treatment, cost-benefit ratios, emotional impact, and accuracy must be evaluated<sup>13</sup>. Although the focus of this review is based on the accuracy or sensitivity of the detection of CHD in low-risk populations, a brief abstract of each of these factors are listed below:

**Frequency:** Malformations of the cardiovascular system are the most frequent congenital disease in the newborn, although it is currently one of the least diagnosed *in utero*<sup>10</sup>. “True” incidence of CHD is probably higher than reported if fetal losses are taken into account<sup>9</sup>. **Severity:** Approximately 2.5/1000 live births represent the prevalence of severe CHD requiring cardiac surgery or catheterization<sup>16</sup>. Proper intervention is the often life-saving. **Risk:** Ultrasound equipment is considered safe providing the operators abide by the displayed safety indices (thermal and mechanical). Even with the trend in fetal screening at earlier stages in development, safety in younger fetuses has been assured. Doppler equipment has no conclusive epidemiological data on the exact safety levels of exposure to be instituted, although minimal levels are also considered safe<sup>17</sup>. **Availability:** Developed countries have more advanced equipment available. Within developed countries, Real-time gray-scale ultrasound and two-dimensional echocardiography are widespread. High image resolution and color Doppler are currently less utilized, but increasing in availability<sup>18</sup>. **Amenability to treatment:** Early data is suggestive that fetal diagnosis improves morbidity, although studies are conflicting in demonstrating improved mortality in patients prenatally diagnosed with CHD<sup>9,12</sup>. **Cost-benefit ratios:** Meticulous screening time and specialized operator training may heighten costs. Survivors with CHD heighten costs<sup>9</sup>. Termination of pregnancy is considered cost-beneficial when CHD is detected through decreasing hospital, surgical, and transplantation costs<sup>13</sup>. Benefits of social and psychological costs of a child with CHD are not quantifiable, but must be considered. **Emotional impact:** Emotional outcome appears positive from a maternal perspective according to a prospective questionnaire-based study<sup>19</sup>. **Accuracy:** The three prospective studies in this review particularly address the accuracy of whether routine heart screening in low-risk populations is justified. If all trials had the consistency of study #3 (88.5% sensitivity), the argument for universal screening in low-risk populations would be easier to explore.

### **Implementation of the screening procedure**

When compiling all of the above factors into a global picture, it seems that fetal heart screening is a blossoming potential. In order to turn this potential into a universal reality for low-risk populations, the following needs to be done:

(1) *Increase in sonographer education and experience.* The range of trained specialists performing the exam may include obstetric physicians, radiologists, perinatologists, and pediatric cardiologists, as long as the examiner is properly skilled. Quality-control criteria may need to be implemented to assure sonographer accreditation. (2) *Standardization of ultrasound techniques.* Techniques at this time should include a detailed examination of five plus chamber views with color flow Doppler. Additional views such as sagittal, short axis, aortic arch, and ductal arch are also of value, but may not be practical in terms of time for a screening test. Suggested timing of the initial screening is currently 18-21 weeks, as visualization is limited before 18 weeks, and state legality regarding termination ends at 21 weeks of gestation. (3) *Utilization of advancing technology.* Color Doppler is of definite value in determining the direction of blood flow and velocity in the fetal heart. Also, recent articles have been published regarding the precision of three-dimensional echocardiography<sup>20</sup>. This type of technology is currently

utilized primarily in developing research; its limitations include cumbersome probes, time-consumption, increased required computer space, and heightened costs<sup>9</sup>. Three-dimensional echocardiography, magnetic resonance imaging, *in utero* surgical intervention, and other developing techniques are also limited in practicality, but a taste of the future. (4) *Continued trials*. Future trials should further examine the accuracy of fetal heart screening, as well as explore factors such as frequency, severity, risk, availability, amenability to treatment, cost-benefit ratios, and emotional impact as discussed in the previous section. Trials should examine possible differences in ethnicity, cultures, and ages of conception. Trials with long term follow up methods are needed to more accurately determine detection rates. (4) *ACOG's public avocation*. ACOG's universal recommendation for fetal heart screening in high and low-risk pregnancies will enhance the implementation process.

## CONCLUSION

In relation to the presented clinical question, **“Is fetal heart screening for the detection of cardiac anomalies indicated in low-risk populations?”** I believe that the answer is yes. With the realization that up to 50% of neonates diagnosed with a CHD have no known risk factors, I believe that routine fetal heart screening is indicated regardless of identified risk-factors. However, it is obvious that the implementation of this process may take some time. As the above studies reflect, current efficacy is largely variable as sensitivity levels range across the board. With specialized training, advancing technology, standardization, and continued trials, sensitivity levels should progressively stabilize, while the global arguments for fetal heart screening will likely increase. It can be projected that more efficacious, extensive fetal heart screening in low-risk populations is a potential and reality for the future.

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