The mathematical limitations of fetal echocardiography as a screening tool in the setting of a normal second-trimester ultrasound

Samuel Bellavance, Mikhail-Paul Cardinal, Laurence Gobeil, Marie-Ève Roy-Lacroix, Frédéric Dallaire

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Authors

Samuel Bellavance,[1] Mikhail-Paul Cardinal, BSc,[1] Laurence Gobeil,[1] Marie-Eve Roy-Lacroix, MD,[2] and Frédéric Dallaire, MD PhD[1]

Affiliations

1. Department of Pediatrics, Université de Sherbrooke and Centre de Recherche du Centre Hospitalier Universitaire de Sherbrooke

2. Department of Obstetrics and Gynecology, Université de Sherbrooke and Centre de Recherche du Centre Hospitalier Universitaire de Sherbrooke

Address for correspondence

Frédéric Dallaire, MD PhD FRCPC, Department of Pediatrics, Université de Sherbrooke and Centre de Recherche du Centre Hospitalier Universitaire de Sherbrooke, 3001, 12e Avenue Nord, Sherbrooke, Quebec, Canada, J1H 5N4, tel: (819) 346-1110 (70454), e-mail: frederic.a.dallaire@usherbrooke.ca

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BRIEF SUMMARY

In this simulation study, the authors show that the addition of a fetal echocardiography in pregnancies at high-risk of CHD increases sensitivity by only 1.8 percentage points. The number needed to screen to detect additional cases of severe CHD was high and the rate of additional detected cases was low. They conclude that the addition of FE in pregnancies at high-risk of CHD yielded marginal benefits at the expense of significant resource utilization.

ABSTRACT

Background: The effectiveness of screening strategies targeting pregnancies at higher-risk of congenital heart disease (CHD) is reduced by the low prevalence of severe CHD, increasing CHD detection rates by 2nd trimester ultrasound (U/S), and the high proportion of severe CHD in low-risk pregnancies. We aimed to determine in which situations additional screening by fetal echocardiography (FE) would result in a significant increase in sensitivity and a sizable decrease in the false-negative rate of severe CHD.

Methods: We simulated the change in the numbers of detected severe CHD cases when a FE is offered to women with a normal 2nd trimester U/S who have a higher risk of bearing a child with CHD, compared to U/S alone. The primary outcome was the increase in sensitivity. Secondary outcomes were the number needed to screen (NNS) and the reduction in the rate of missed cases.

Results: For an U/S sensitivity of 60%, the addition of a FE in pregnancies at high-risk of CHD (risk ratio 3.5, range: 2 to 5) increased sensitivity by 2.4 percentage points (1.1 to 7.9). The NNS to detect one additional case of severe CHD was 436 (156 to 952). The rate of additional severe CHD cases detected by FE was 4 per 100,000 pregnancies (2 to 32).

Conclusion: The addition of FE to U/S for severe CHD prenatal screening in pregnancies at high-risk of CHD yielded marginal benefits in terms of increased sensitivity and decreased rates of false negatives, at the expense of significant resource utilization.

INTRODUCTION

In 2004, the American Society of Echocardiography recommended performing a fetal echocardiogram (FE) in addition to the 2nd trimester obstetrical ultrasound (U/S) for fetuses with an increased risk of congenital heart disease (CHD) such as increased nuchal translucency, family history of CHD, maternal diabetes or maternal exposure to teratogens during pregnancy.[1] This recommendation was reinforced in 2014 in a scientific statement from the American Heart Association: "[…] risk levels of ≥2% to 3% as defined by prenatal screening tests […] result in a recommendation for consideration for additional testing; therefore, it is reasonable to perform fetal echocardiography at this risk level, whereas if risk exceeds 3%, fetal echocardiography should be performed."[2]

The rationale for recommending a FE for these pregnancies is based on the assumptions that: 1) the prevalence of CHD is increased in these fetuses, 2) a proportion of these extra CHD cases may be missed by 2nd trimester U/S, and 3) the necessary FE resources would be compensated by a significant increase in detection rates. Evidence supporting the effectiveness of referring these higher-risk pregnancies with a normal 2nd trimester U/S for a FE is surprisingly scarce and inconclusive. The very noble endeavour of increasing detection rates by offering FE to women with higher-risk pregnancies has likely been hampered by increasing detection rates by 2nd trimester U/S in the last two decades,[3-6] by a possible overestimation of the risk of severe CHD in high-risk pregnancies,[7, 8] and by the fact that >90% of severe fetal CHDs occur in pregnancies without risk factors.[3, 7-9] Furthermore, the relatively low prevalence of severe CHD – the CHD we must not miss in any prenatal screening set-up – will result in a very high negative predictive value, even with a fairly low sensitivity. Mathematically, it will require a high number of additional tests to obtain a modest increase in negative predictive value. In other words, many FEs will be needed to significantly decrease the rate of false negatives.

In this study, we present theoretical models built to help determine in which situation additional screening of pregnancies at high-risk of CHD by FE would result in a significant increase in sensitivity and in a significant decrease in the false-negative rate of severe CHD. Specifically, we estimated the number needed to screen (NNS) and the increase in overall sensitivity to detect severe CHD when FE is performed for frequent maternal or fetal indications in the setting of a normal 2nd trimester U/S. We also calculated the impact of the relative risk of a given risk factor on the NNS.

METHODS

Overview of the study design

This is a simulation study. We computed series of contingency tables to assess the change in the numbers of detected and undetected severe CHD cases when a FE is offered to women with a higher risk of bearing a child with CHD compared to the 2nd trimester U/S alone. We defined "high-risk pregnancies" as pregnancies with a normal 2nd trimester U/S and with maternal, familial or fetal risk factors for CHD. We targeted frequent FE indications, such as familial history of CHD, pre-gestational diabetes, maternal medication, and increased nuchal translucency, as they represent a high level of activity in many North American fetal cardiology divisions.

Our framework was based on the trajectory of care of pregnant women in Quebec, Canada. It is recommended that all women undergo a 2nd trimester U/S performed by an obstetrician or a radiologist. In accordance with the scientific statement from the American Heart Association,[2] pregnancies with maternal, familial or fetal risk factors for CHD are also referred for a FE in a tertiary care centre, even if the 2nd trimester U/S is normal. In Canada, the cost of all pregnancy follow-ups and imaging is covered by the government universal health care insurance.

Contingency tables and outcomes were calculated with and without this additional FE in high-risk pregnancies. This enabled the comparison between the outcomes in a population for which FE is offered to women with higher-risk pregnancies and those of an identical population where FE was not offered. Outcomes were calculated when the theoretical sensitivity of the 2nd trimester U/S varied from 20 to 100%, and for three scenarios of CHD prevalence, of risk ratios of CHD in high-risk pregnancies and of proportions of high-risk pregnancies in the population of pregnant women, as detailed below.

Outcomes of interest

The primary outcome was the increase in sensitivity to detect severe CHDs when FE is offered to women with high-risk pregnancies with a normal 2nd trimester U/S. Severe CHD was defined as a congenital heart lesion that would require specialized care or intervention within the first months of life, such as single ventricle physiology, transposition of the great arteries, critical outflow track obstructions, common arterial trunk, double-outlet right ventricles and tetralogy of Fallot.

The secondary outcomes were: 1) the number needed to screen (NNS) (i.e., the number of FEs needed to detect one additional severe CHD), 2) the number needed to screen to increase the sensitivity by 1 percentage point, and 3) the reduction of the rate of missed severe CHD cases per 100,000 pregnancies. The equations to compute these outcomes as well as all other parameters needed to perform the simulations are available in the supplemental material (see Supplementary Table S1).

Definition of the simulation scenarios

Mathematically, the yield of FE as a screening tool will increase in the following settings: a higher-risk ratio of CHD in high-risk pregnancies compared to low-risk pregnancies, a higher prevalence of at-risk pregnancies, and a higher prevalence of severe CHDs in the screened population. These numbers are not

always known and may vary across populations. Hence, we have built simulations for a best-case, a worst-case and a realistic scenario. The three scenarios are detailed in Table 1.

The realistic scenario was based on recent data from the province of Quebec. In 2018, we set up the FREQUENCY study, a large retrospective population-based study that aims to assess the performance of prenatal CHD screening in Quebec on >650,000 mother-child dyads.[10] We used the preliminary results[11, 12] of the FREQUENCY study to feed the initial assumption of our theoretical models: a prevalence of severe CHD of 1.82/1000 pregnancies and a prevalence of high-risk pregnancies of 19.1/1000. The risk ratio of CHD in high-risk pregnancies cannot be calculated with the FREQUENCY study data. The risk ratio was based on the level of risk for frequent FE indications, which have risk ratios ranging from 2 to 8 according to previous studies.[2, 13-19]

The worst-case and best-case scenarios were based on data available in scientific literature. Despite a thorough review of the scientific literature, several assumptions had to be made. The worst-case and best-case scenarios were developed using the full range of prevalences and risk ratios reported in the literature. For example, the worst-case scenario was built using the prevalence and risk ratios that would decrease the efficiency of FE: lowest prevalence of severe CHD, lowest prevalence of high-risk pregnancies and lowest risk ratio of CHD in high-risk pregnancies. The final numbers represent what was thought to be a conservative margin of error that would encompass most situations in populations where FE is used as a screening tool in high-risk pregnancies.

Number needed to screen according to relative risk

To measure how the level of risk influences the NNS, we performed a simulation in which the relative risk for a given risk factor varies from 1 to 20 (the risk severe CHD for pregnancies with this risk factor

compared to pregnancies without this risk factor). We then calculated the NNS as the reciprocal of the proportion of newly CHD identified per pregnancy.

For all scenarios, the sensitivity of the FE to identify severe CHDs was conservatively set at 95%.[8, 20] All calculations were performed using SAS for Windows version 9.4. The SAS programs used are available in the supplemental material (see Supplementary Appendix S1). As this is a simulation study, no statistical inferences were sought.

RESULTS

Our simulation is based on a population of 100,000 pregnancies, which is approximately the annual number of pregnancies in Quebec, Canada (population of 8.5 million).[21] Results are presented for the realistic scenario, with the worst-case and best-case scenarios between brackets. We report outcomes for U/S sensitivities of 60% and 75%, which represent the bracket of observed sensitivities in the last decade.[3-6, 22] Outcomes for the full spectrum of U/S sensitivities are presented in the figures and in Table 2.

Number of severe CHD and gain in sensitivity

For 100,000 pregnancies, we estimated that the number of severe CHD cases was 180 (140 to 400). The number of severe CHD cases missed by the U/S was 72 (56 to 160) if the U/S sensitivity was 60%, and 45 (35 to 100) if the U/S sensitivity is 75%. The proportion of severe CHD occurring in the high-risk pregnancies was 6.3% (2.9% to 20.8%).

Figure 1 shows the increase in sensitivity to detect severe CHDs when FE is performed for all high-risk pregnancies, according to U/S sensitivity. The gain in sensitivity by adding a FE was marginal and decreased as the sensitivity of U/S increased. The addition of a FE in high-risk pregnancies resulted in

an increase in sensitivity of 2.4 percentage points (1.1 to 7.9) if the U/S sensitivity is 60%, and of 1.5 percentage point (0.7 to 4.9) if U/S sensitivity is 75%.

Number needed to screen and number of missed CHD

Figure 2 shows the number needed to screen (NNS), i.e., the number of FEs that need to be performed to detect one severe CHD case, according to U/S sensitivity. The NNS was high and increased rapidly as the U/S sensitivity increased. The NNS to detect a missed case of CHD in high-risk pregnancies was 436 (156 to 952) for a U/S sensitivity of 60%, and 697 (249 to 1523) for a U/S sensitivity of 75%.

Figure 3 shows the number of FEs that would need to be performed to increase the sensitivity of detecting a severe CHD case by one percentage point. We found that for a U/S sensitivity of 60%, as many as 785 FEs (625 to 1333) were needed to increase the combined sensitivity from 60 to 61%. For a U/S sensitivity of 75%, the number of FEs needed would be 1255 (998 to 2132).

Figure 4 shows the number of missed severe CHDs by U/S that would be detected by FE for a population of 100,000 pregnancies, according to U/S sensitivity. The numbers were low overall and decreased rapidly as U/S sensitivity increased. The number of additional severe CHDs detected by FE was 4 per 100,000 pregnancies (2 to 32), for a U/S sensitivity of 60%, and 3 per 100,000 pregnancies (<1 to 20) for a U/S sensitivity of 75%.

We calculated that in the realistic scenario, any measures that would increase U/S sensitivity from 60% to 65% would reduce the number of undetected severe CHDs by 12.5%. For a population of 100,000 pregnancies, 3,920 FEs would be needed to produce the same results. This number of FEs is twice higher than the theoretical number of 1,904 high-risk pregnancies in the same population.

Influence of relative risk on the number needed to screen

To help determine in which situation the NNS would be low enough to justify performing a FE, we estimated how the NNS varies in the setting of a wide range of relative risks. Figure 5 shows the NNS according to the relative risk in the setting of a severe CHD prevalence of 1.8 cases per 1,000 pregnancies. If the U/S sensitivity is 75%, we found that a RR ~10 is needed to yield a NNS below 250. The NNS remained above 100 for risk factors with relative risk >20. In the setting of a lower U/S sensitivity of 60%, the NNS fell below 250 at a relative risk of ~6. A relative risk ~15 is needed to obtain NNS below 100.

DISCUSSION

In this study, we explored theoretical models to evaluate the potential incremental benefit of additional screening of high-risk pregnancies by FE in the setting of a normal 2nd trimester U/S. We found that in the usual environment in which these screening FEs are performed, there was a very modest increase in sensitivity to detect severe CHDs, at the expense of a high utilization of specialized medical resources. This was mostly driven by the low prevalence of severe CHD and by the low absolute number of severe CHDs in higher-risk pregnancies, compared to low-risk pregnancies. We also showed that to identify FE indications with NNS below 250 – which is still relatively high – we should target factors with a risk of severe CHD that is at least 6 times that of the general population. We acknowledge that this study is a pure mathematical exercise, and that the usefulness of FE is much broader than an increase in sensitivity. Nevertheless, our simulations help predict the expected gain when FE is used as a screening tool in the setting of a normal 2nd trimester U/S.

We have empirically observed that the large volumes of high-risk pregnancy referrals place tremendous pressure on already stretched pediatric cardiology resources with unclear benefit. To substantiate this,

we initiated two parallel research projects. First, we undertook the FREQUENCY study,[10] a population-based retrospective cohort evaluating the actual performance of prenatal screening in the province of Quebec. The study is ongoing. We acknowledge that variations in healthcare systems, expertise and operator experience may limit the generalizability of the results of the FREQUENCY study in some settings. Hence, we designed this current simulation study specifically to shed light on possible situations in which FE screening of high-risk pregnancy would yield better outcomes.

Prenatal diagnosis of CHD has always relied heavily on the identification of abnormal cardiac images during the 2nd trimester obstetrical U/S. Prenatal detection rates have been found to be quite variable.[3, 5, 6, 23-25] Detection rates of <50% have been reported for some critical CHDs requiring immediate specialized care at birth, such as transposition of the great arteries,[9, 22-28] although more recent experience points toward increasing detection rates with time.[3-6] As a way to increase prenatal detection rates, experts have argued that the presence of maternal or fetal factors that increase the risk of fetal CHD should prompt a referral for a fetal echocardiogram (FE), even in the setting of a normal 2nd trimester U/S performed by the obstetrician or the radiologist.[1, 2, 29]

The theoretical modelling presented in the current work suggests that performing screening FE in high-risk pregnancies may have been the wrong target, at least in regions with modestly sensitive fetal ultrasound practice. We should continue to strive to increase the prenatal detection rate of severe CHD, but we believe that the benefits of FE as a screening tool will be limited in most settings. This study highlights that these limitations are due to the low prevalence of severe CHD, even in high-risk pregnancies, the very high proportion of missed CHDs in the low-risk group, and the increasing detection rate at the 2nd trimester U/S.

Evidence supporting the effectiveness of referring high-risk pregnancies with normal 2nd trimester U/S for FE is scarce. In 2015, an interrogation of the Danish birth registry showed that only a minority of CHDs were identified by adding a FE in high-risk pregnancies.[27] In 2016, Nayak et al. found a paradoxically lower CHD prevalence in high-risk pregnancies compared to low-risk pregnancies, although the study was relatively underpowered.[7] In that study, 92% of CHDs occurred in the low-risk group, which is similar to our simulations. Others have also observed that most CHDs are identified during the 2nd trimester U/S and that referring high-risk pregnancies for a FE did little to increase overall detection rates.[8, 9, 30]

Our model suggests that improving the overall sensitivity of the 2nd trimester U/S has a much better potential to reduce the number of undiagnosed severe CHDs. A recent study in Canada highlighted the important regional variability of the 2nd trimester U/S, with sensitivities ranging from 14% to 72% for the prenatal detection of the transposition of the great arteries.[22] In our realistic scenario, it was mathematically impossible to increase the sensitivity by >5% by adding a FE in high-risk pregnancies, even with a 2nd trimester US sensitivity of <20%. It has been shown that detection rates can be increased to 75-85% by the addition of cardiac views and by enhancing awareness and training.[3-6] This approach has the benefit of targeting pregnancies in both the high-risk *and* low-risk categories. We believe that even a modest reduction in the variability of the detection rate between regions would outperform the entire high-risk pregnancy FE screening strategy. We fully recognize that FE has great value in specific screening settings, such as for early signs of potentially progressing obstructive lesions, myocardial diseases and other subtle but clinically important CHDs. Initiatives to increase the overall sensitivity of the 2nd trimester U/S combined with a more focused strategy to refer these higher-risk pregnancies is likely to bear fruit.

While strategies to improve detection rates are desirable and necessary, we have a responsibility to ensure that currently and widely used strategies are effective, efficient and well targeted, especially if such strategies are costly and strenuous on human and material resources. The setting of the best-case scenario may be one where screening by FE would be valuable, although such a combination of favorable parameters is not probable. Additional screening has a better yield in situations where both the risk ratio and baseline prevalence of CHD are high. Future research should guide us on FE indications that meet these criteria. Our preliminary results[12] and other previously published studies[7, 27] suggest that pre-gestational diabetes, family history, maternal medication and isolated small increased nuchal translucency may not fulfill these criteria.

This study has limitations. Results are based on simulation data. Real-life data could be different and will vary between regions, countries, and healthcare settings. We believe that most populations where FE is performed would fall between the best-case and worst-case scenarios in developed countries with accessible healthcare. Our simulations are based on detection of severe CHDs and the added benefit of FE in detecting these CHDs. We fully recognized that fetal cardiology consultation and FE have many other important purposes in the trajectory of care of pregnant women. Not all CHDs have the same detection rate and using a combined CHD detection rate may provide a somewhat incomplete picture. Finally, our simulation strictly focuses on detection rates. The financial and clinical impact of missed diagnoses of CHD, as well as of false positive FE results were not considered, although they play an important role in the assessment of any screening strategy.

CONCLUSION

This study suggests that the current epidemiological parameters are such that the benefit of referring high-risk pregnancies that have a normal 2nd trimester U/S for FE is likely limited. Given the high proportion of severe CHDs in low-risk pregnancies, screening approaches that do not target all

pregnancies will likely yield disappointing results despite high resource utilization. More research is needed to assess the actual performance of prenatal CHD screening, as well as to draw a more complete picture of the economical, logistical and psychological impact of the use of FE as a screening tool.

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The authors have nothing to disclose.

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TABLES

Table 1 – Simulation parameters

Parameters	Values in literature	Worst case	Realistic	Best case
Prevalence of high-risk pregnancies	1.5 to 5% [16, 31-35]	1.5%	1.9%	5%
Risk ratio of CHD in high-risk	1 to 5 [2, 7, 8, 13-19]	2	3.5	5
Prevalence of severe CHD	0.14 to 0.4% [36-39]	0.14%	0.18%	0.4%

CHD = congenital heart disease.

Table 2 – Number of CHDs and outcomes according to the 2nd trimester U/S sensitivity

Ultrasound sensitivity (%)	New CHD cases detected by FE per 100,000 pregnancies	Number needed to screen to detect one CHD	Number needed to screen to increase sensitivity by 1 percentage point	Increase in sensitivity (percentage point)
20	8.7 [3.1 - 63]	219 [79 - 477]	393 [315 - 667]	4.8 [2.2 – 15.8]
25	8.2 [2.9 - 59]	233 [84 - 508]	420 [335 - 712]	4.5 [2.1 – 14.8]
30	7.6 [2.8 - 55]	250 [90 - 545]	449 [359 - 763]	4.2 [2.0 – 13.9]
35	7.1 [2.6 - 51]	269 [97 - 586]	484 [386 - 821]	3.9 [1.8 – 12.9]
40	6.5 [2.4 - 48]	291 [105 - 635]	524 [418 - 889]	3.6 [1.7 – 11.9]
45	6.0 [2.2 - 44]	317 [114 - 693]	571 [456 - 970]	3.3 [1.5 – 10.9]
50	5.5 [2.0 - 40]	349 [125 - 762]	628 [501 - 1067]	3.0 [1.4 – 9.9]
55	4.9 [1.8 - 36]	388 [139 - 847]	698 [556 - 1185]	2.7 [1.3 – 8.9]
60	4.4 [1.6 - 32]	436 [156 - 952]	785 [625 - 1333]	2.4 [1.1 – 7.9]
65	3.8 [1.4 - 28]	498 [178 - 1088]	897 [714 - 1524]	2.1 [1.0 – 6.9]
70	3.3 [1.2 - 24]	581 [208 - 1269]	1046 [832 - 1777]	1.8 [0.8 – 5.9]
75	2.7 [<1 - 20]	697 [249 - 1523]	1255 [998 - 2132]	1.5 [0.7 – 4.9]
80	2.2 [<1 - 16]	871 [312 - 1904]	1568 [1246 - 2665]	1.2 [0.6 – 4.0]
85	1.6 [<1 - 12]	1161 [415 - 2538]	2090 [1660 - 3553]	0.9 [0.4 – 3.0]
90	1.1 [<1 - 8]	1741 [622 - 3806]	3134 [2488 - 5329]	0.6 [0.3 – 2.0]
95	<1 [<1 - 4]	3481 [1243 - 7612]	6266 [4973 - 10656]	0.3 [0.1 – 1.0]

The numbers between brackets are the range obtained using the worse-case and the best-case scenarios. CHD = congenital heart disease; FE = fetal echocardiography.

FIGURE

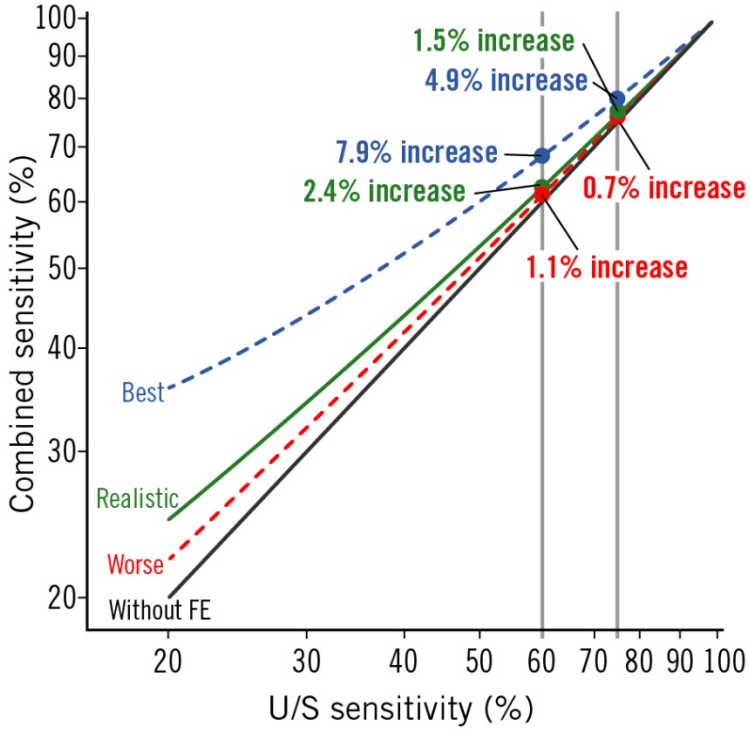

Figure 1. Combined sensitivity (U/S + FE) to detect severe CHD cases, according to U/S sensitivity. U/S = 2nd trimester obstetrical ultrasound. FE = fetal echocardiogram.

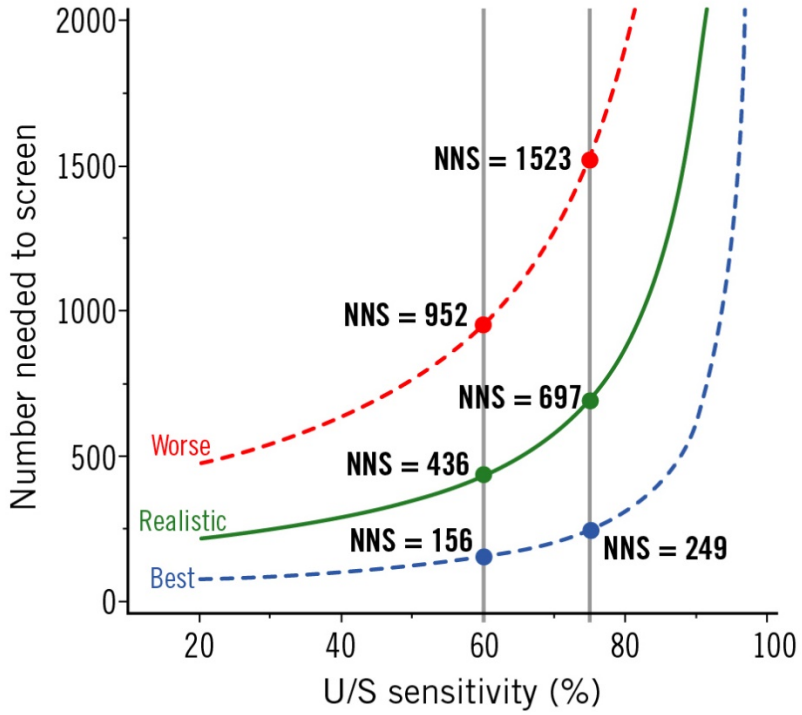

Figure 2. Number needed to screen (NNS) to detect one severe CHD case, according to U/S sensitivity.

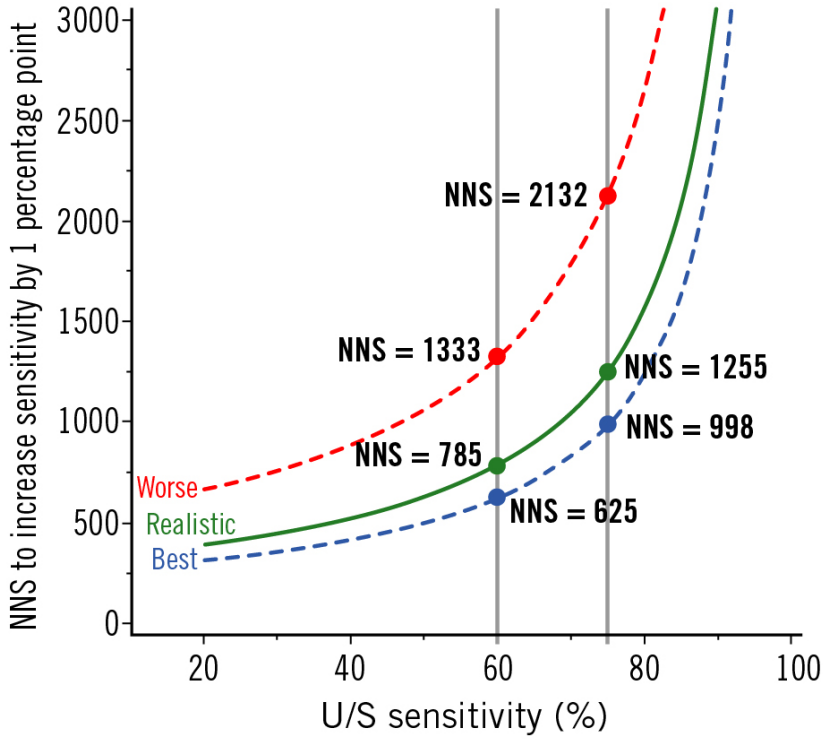

Figure 3. Number needed to screen (NNS) to increase the combined sensitivity of detecting severe CHDs by one percentage point, according to U/S sensitivity.

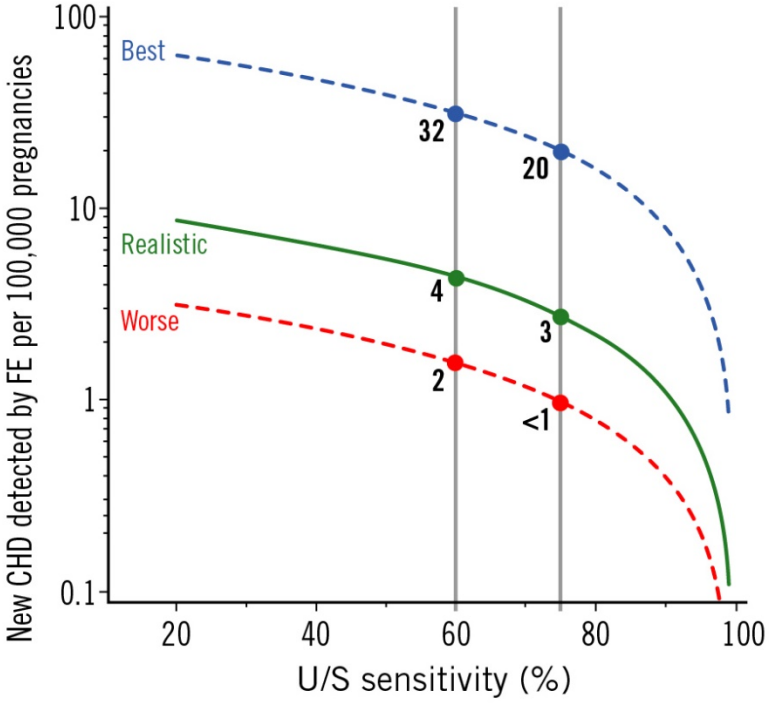

Figure 4. Rate of additional severe CHDs detected by fetal echocardiography (FE) per 100,000 pregnancies, according to U/S sensitivity.

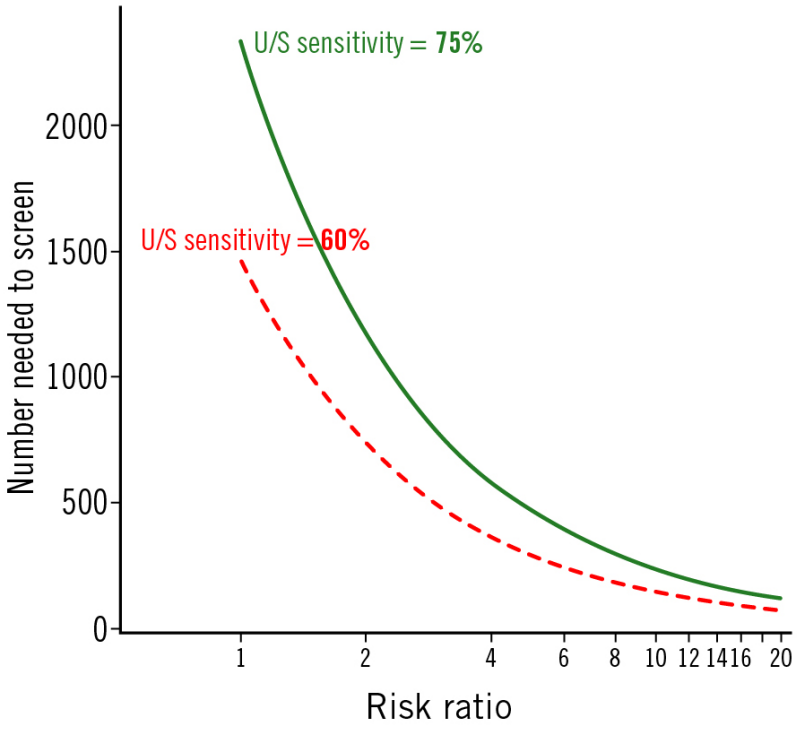

Figure 5. Number needed to screen according to the risk ratio. U/S = ultrasound.

-- Supplemental material --

The mathematical limitations of fetal echocardiography as a screening tool in the setting of a normal second trimester ultrasound

Samuel Bellavance, Mikhail-Paul Cardinal, BSc, Laurence Gobeil, Marie-Eve Roy-Lacroix, MD, and Frédéric Dallaire, MD PhD

Supplementary Table S1. List of parameters and the corresponding equations used in the simulation

Parameter	Equation
All severe CHD	Nb pregnancies × severe CHD prevalence
All non-CHD pregnancies	Nb pregnancies – severe CHD
Nb CHDs in at risk pregnancies	$nb\ pregnancies\ \times CHD\ prevalence\ \times \frac{prevalence\ at\ risk \times at\ risk\ RR}{(prevalence\ at\ risk \times at\ risk\ RR)+(1-prevalence\ at\ risk\ )}$
Nb CHDs in not at risk pregnancies	All severe CHD – Nb CHDs in at risk pregnancies
Severe CHD detected by US	All severe CHD × US sensitivity
Severe CHD undetected by US	All severe CHD × (1 – US sensitivity)
Severe CHD detected by US in at risk pregnancies	Nb CHDs in at risk pregnancies × US sensitivity
Severe CHD undetected by US in at risk pregnancies	Nb CHDs in at risk pregnancies × (1 – US sensitivity)
Nb of FEs to do (at risk pregnancies with a negative US screening)	(Nb pregnancies × Prevalence of at-risk pregnancies) – CHD detected by US in at risk pregnancies
New CHD detected by fetal echography in at risk pregnancies	CHD undetected in at risk pregnancies × FE sensitivity
Missed cases reduction rate by FE per 10,000 pregnancies	(New CHD detected by FE ÷ Nb pregnancies) × 10,000
FE and US combined sensitivity (system's sensitivity)	(CHD detected by US + New CHD detected by FE) ÷ all CHD
Number needed to screen to find a new CHD by FE	Number of FEs to do ÷ New CHD detected by FE Or 1 ÷ proportion of newly identified CHD per pregnancy
Number needed to screen by FE to increase the system's sensitivity by 1%	All severe CHD × 1% × Number needed to screen to find a new CHD by FE

Supplementary Appendix S1

SAS program to compute the contingency tables.

```
/* Values for simulation parameters */
/* These values are assigned to macro variables */

/* 1. Setting parameters and scenarios */
/* 1.1 Fixed parameters */
%LET FE_sens = 0.95; /* Sensitivity of FE for severe CHD = 95% */
%LET FE_spec = 0.99; /* Specificity of FE for severe CHD = 99% */
%LET US_spec = 0.98; /* Specificity of U/S for severe CHD = 98% */
%LET pop = 100000; /* Number of pregnancies in Quebec per year */

/* 1.2 Scenario parameters*/
/* 1.2.1 Best case */
%LET chd_prev1 = 0.004; /* Prevalence of severe CHD */
%LET at_risk_prev1 = 0.05; /* Prevalence of high-risk pregnancies  */
%LET at_risk_RR1 = 5; /* Relative risk of CHD in high-risk pregnancies */

/* 1.2.2 Worse case */
%LET chd_prev2 = 0.0014;
%LET at_risk_prev2 = 0.015;
%LET at_risk_RR2 = 2;

/* 1.2.3 Realistic */
%LET chd_prev3 = 0.0018;
%LET at_risk_prev3 = 0.0191;
%LET at_risk_RR3 = 3.5;


/* 2. Computing simulation data for contingency tables */
/* 2.1 Simulation 1 (best case) */
data _sim1;
       /* Fixed parameters */
       all_chd = &pop * &chd_prev1; /*Total number of CHDs */
       all_non_chd = &pop - all_chd; /* Total number of non-CHD pregnancies */
       CHD_in_at_risk =  &pop * &chd_prev1 * ((&at_risk_prev1 * &at_risk_RR1) / ((&at_risk_prev1 *
&at_risk_RR1) + ( 1 - &at_risk_prev1)))  ; /* Number of CHD in high-risk pregnancies */
       CHD_in_not_at_risk = all_chd - CHD_in_at_risk; /* Number of CHD in low-risk pregnancies */

       /* Looping for all possible values of 2nd trimester US */
       /* Sensitivity of US */
       us_sens = 0; /* First, we set the value at 0 */
       do i=0 to 0.99 by 0.01; /* We create an index variable (i) */
              us_sens = i; /* We assign the value of i to the new variable us_sens at each iteration */

              /* We compute the variables that are dependent on the sensitivity */
              chd_detected_by_us = all_chd * us_sens;
              chd_undetected_by_us = all_chd - chd_detected_by_us;
              chd_detected_in_at_risk_preg = CHD_in_at_risk * (us_sens);
              chd_undetected_in_at_risk_preg = CHD_in_at_risk * (1 - us_sens);

              us_tp = chd_detected_by_us;
              us_fp = all_non_chd * (1-&US_spec);
              us_fn = chd_undetected_by_us;
              us_tn = all_non_chd - us_fp;
              us_for = us_fn / (us_fn + us_tn);

              nb_fe_to_do = (&pop * &at_risk_prev1) - chd_detected_in_at_risk_preg;
              new_chd_detected_by_fe = chd_undetected_in_at_risk_preg * &FE_sens;
              miss_case_reduction_rate = new_chd_detected_by_fe / &pop;
              miss_case_reduction_per_10000 = (new_chd_detected_by_fe / &pop)*10000;

              chd_undetected_by_system = chd_undetected_by_us - new_chd_detected_by_fe;

              fe_false_positive = (nb_fe_to_do - new_chd_detected_by_fe)* (1-&fe_spec);
```

```
                us_fe_sens = ((new_chd_detected_by_fe + chd_detected_by_us) / all_chd);
                fe_sens_increase = us_fe_sens - us_sens;

                nns = nb_fe_to_do / new_chd_detected_by_fe; /* Number needed to screen */
                nns_to_increase_sens_by_five = 0.05 * all_CHD * nns;
                nns_to_increase_sens_by_one = 0.01 * all_CHD * nns;

                /* Variable in percentage value */
                us_sens_perc = us_sens * 100;
                us_fe_sens_perc = us_fe_sens * 100;
                fe_sens_increase_perc = fe_sens_increase * 100;
                output;
        end;
        drop i;
run;

/* 2.2 Simulation 2 (worse case) */
data _sim2;

        all_chd = &pop * &chd_prev2;
        all_non_chd = &pop - all_chd;
        CHD_in_at_risk =  &pop * &chd_prev2 * ((&at_risk_prev2 * &at_risk_RR2) / ((&at_risk_prev2 *
&at_risk_RR2) + ( 1 - &at_risk_prev2)))  ;
        CHD_in_not_at_risk = all_chd - CHD_in_at_risk;

        us_sens = 0;
        do i=0 to 0.99 by 0.01;
                us_sens = i;

                chd_detected_by_us = all_chd * us_sens;
                chd_undetected_by_us = all_chd - chd_detected_by_us;
                chd_detected_in_at_risk_preg = CHD_in_at_risk * (us_sens);
                chd_undetected_in_at_risk_preg = CHD_in_at_risk * (1 - us_sens);

                us_tp = chd_detected_by_us;
                us_fp = all_non_chd * (1-&US_spec);
                us_fn = chd_undetected_by_us;
                us_tn = all_non_chd - us_fp;
                us_for = us_fn / (us_fn + us_tn);

                nb_fe_to_do = (&pop * &at_risk_prev2) - chd_detected_in_at_risk_preg;
                new_chd_detected_by_fe = chd_undetected_in_at_risk_preg * &FE_sens;
                miss_case_reduction_rate = new_chd_detected_by_fe / &pop;
                miss_case_reduction_per_10000 = (new_chd_detected_by_fe / &pop)*10000;

                chd_undetected_by_system = chd_undetected_by_us - new_chd_detected_by_fe;
                fe_false_positive = (nb_fe_to_do - new_chd_detected_by_fe)* (1-&fe_spec);

                us_fe_sens = ((new_chd_detected_by_fe + chd_detected_by_us) / all_chd);
                fe_sens_increase = us_fe_sens - us_sens;

                nns = nb_fe_to_do / new_chd_detected_by_fe;
                nns_to_increase_sens_by_five = 0.05 * all_CHD * nns;
                nns_to_increase_sens_by_one = 0.01 * all_CHD * nns;

                us_sens_perc = us_sens * 100;
                us_fe_sens_perc = us_fe_sens * 100;
                fe_sens_increase_perc = fe_sens_increase * 100;
                output;
        end;
        drop i;
run;

/* 2.3 Simulation 3 (realistic) */
data _sim3;

        all_chd = &pop * &chd_prev3;
        all_non_chd = &pop - all_chd;
        CHD_in_at_risk =  &pop * &chd_prev3 * ((&at_risk_prev3 * &at_risk_RR3) / ((&at_risk_prev3 *
&at_risk_RR3) + ( 1 - &at_risk_prev3)))  ;
        CHD_in_not_at_risk = all_chd - CHD_in_at_risk;
```

```
	us_sens = 0;
	do i=0 to 0.99 by 0.01;
		us_sens = i;

		chd_detected_by_us = all_chd * us_sens;
		chd_undetected_by_us = all_chd - chd_detected_by_us;
		chd_detected_in_at_risk_preg = CHD_in_at_risk * (us_sens);
		chd_undetected_in_at_risk_preg = CHD_in_at_risk * (1 - us_sens);

		us_tp = chd_detected_by_us;
		us_fp = all_non_chd * (1-&US_spec);
		us_fn = chd_undetected_by_us;
		us_tn = all_non_chd - us_fp;
		us_for = us_fn / (us_fn + us_tn);

		nb_fe_to_do = (&pop * &at_risk_prev3) - chd_detected_in_at_risk_preg;
		new_chd_detected_by_fe = chd_undetected_in_at_risk_preg * &FE_sens;
		miss_case_reduction_rate = new_chd_detected_by_fe / &pop;
		miss_case_reduction_per_10000 = (new_chd_detected_by_fe / &pop)*10000;

		chd_undetected_by_system = chd_undetected_by_us - new_chd_detected_by_fe;
		fe_false_positive = (nb_fe_to_do - new_chd_detected_by_fe)* (1-&fe_spec);

		us_fe_sens = ((new_chd_detected_by_fe + chd_detected_by_us) / all_chd);
		fe_sens_increase = us_fe_sens - us_sens;

		nns = nb_fe_to_do / new_chd_detected_by_fe;
		nns_to_increase_sens_by_five = 0.05 * all_CHD * nns;
		nns_to_increase_sens_by_one = 0.01 * all_CHD * nns;

		us_sens_perc = us_sens * 100;
		us_fe_sens_perc = us_fe_sens * 100;
		fe_sens_increase_perc = fe_sens_increase * 100;
		output;
	end;
	drop i;
run;

/* 2.4 Merging datasets*/
/* 2.4.1 Renaming scenario variables */
data _sim2; set _sim2;
	rename nns = nns2;
	rename nns_to_increase_sens_by_five = nns2_to_increase_sens_by_five;
	rename nns_to_increase_sens_by_one = nns2_to_increase_sens_by_one;
	rename new_chd_detected_by_fe = new2_chd_detected_by_fe;
	rename us_fe_sens_perc = us2_fe_sens_perc;
	rename chd_undetected_by_system = chd_undetected_by_system2;
	rename CHD_in_not_at_risk = CHD_in_not_at_risk2;
	rename CHD_in_at_risk = CHD_in_at_risk2;
run;
data _sim3; set _sim3;
	rename nns = nns3;
	rename nns_to_increase_sens_by_five = nns3_to_increase_sens_by_five;
	rename nns_to_increase_sens_by_one = nns3_to_increase_sens_by_one;
	rename new_chd_detected_by_fe = new3_chd_detected_by_fe;
	rename us_fe_sens_perc = us3_fe_sens_perc;
	rename chd_undetected_by_system = chd_undetected_by_system3;
	rename CHD_in_not_at_risk = CHD_in_not_at_risk3;
	rename CHD_in_at_risk = CHD_in_at_risk3;
run;

/* 2.4.2 Merging datasets*/
/* The NNS variable contains the NNS of the first simulation, and the NNS2 variable those of the
second, etc... */
data _sim;
	set _sim1 _sim2 _sim3;

	/* Identify data points for graphs labels */
	if (round(us_sens_perc) = 60 or round(us_sens_perc) = 75) and nns ne . then do;
		nns_point = nns;
```

```
                nns_label = "NNS = " || compress(round(nns));
                nns_to_increase_point = nns_to_increase_sens_by_one;
                nns_to_increase_label = "NNS = " || compress(round(nns_to_increase_sens_by_one));
                new_chd_point = new_chd_detected_by_fe;
                new_chd_label = "Nb detected = " || compress(round(new_chd_detected_by_fe));
                if new_chd_detected_by_fe <1 then new_chd_label = "Nb detected = <1";
        end;

        if (round(us_sens_perc) = 60 or round(us_sens_perc) = 75) and nns2 ne . then do;
                nns2_point = nns2;
                nns2_label = "NNS = " || compress(round(nns2));
                nns2_to_increase_point = nns2_to_increase_sens_by_one;
                nns2_to_increase_label = "NNS = " || compress(round(nns2_to_increase_sens_by_one));
                new2_chd_point = new2_chd_detected_by_fe;
                new2_chd_label = "Nb detected = " || compress(round(new2_chd_detected_by_fe));
                if new2_chd_detected_by_fe <1 then new2_chd_label = "Nb detected = <1";
        end;

        if (round(us_sens_perc) = 60 or round(us_sens_perc) = 75) and nns3 ne . then do;
                nns3_point = nns3;
                nns3_label = "NNS = " || compress(round(nns3));
                nns3_to_increase_point = nns3_to_increase_sens_by_one;
                nns3_to_increase_label = "NNS = " || compress(round(nns3_to_increase_sens_by_one));
                new3_chd_point = new3_chd_detected_by_fe;
                new3_chd_label = "Nb detected = " || compress(round(new3_chd_detected_by_fe));
                if new3_chd_detected_by_fe <1 then new3_chd_label = "Nb detected = <1";
        end;
run;

/* 3. Outcomes
/* 3.1 Sensitivity of the system with and without fetal echo */
proc sort data=_sim; by us_sens_perc; run;
proc sgplot data = _sim noautolegend;
        Where us_sens_perc>20;
        series x=us_sens_perc y=us_sens_perc /curvelabel="Without FE" curvelabelpos=start
lineattrs=(pattern=solid color=black);
        series x=us_sens_perc y=us_fe_sens_perc /curvelabel="Best" curvelabelpos=start
lineattrs=(pattern=mediumdash color=blue);
        series x=us_sens_perc y=us2_fe_sens_perc /curvelabel="Worse" curvelabelpos=start
lineattrs=(pattern=mediumdash color=red);
        series x=us_sens_perc y=us3_fe_sens_perc /curvelabel="Realistic" curvelabelpos=start
lineattrs=(pattern=solid color=green);
        xaxis type=log logbase=10 label="U/S sensitivity (%)";
        yaxis type=log logbase=10 label="System sensitivity (%)";
        refline 60 /axis=x;
        refline 75 /axis=x;
run;

/* 3.2 Second simulation : NNS to find a case of CHD per FE according to U/S sensitivity */
proc sgplot data = _sim noautolegend;
        where us_sens_perc>20;
        series x=us_sens_perc y=nns /curvelabel="Best" curvelabelpos=start lineattrs=(pattern=mediumdash
color=blue);
        series x=us_sens_perc y=nns2 /curvelabel="Worse" curvelabelpos=start
lineattrs=(pattern=mediumdash color=red);
        series x=us_sens_perc y=nns3 /curvelabel="Realistic" curvelabelpos=start
lineattrs=(pattern=solid color=green);
        scatter x=us_sens_perc y=nns_point / datalabel=nns_label;
        scatter x=us_sens_perc y=nns2_point / datalabel=nns2_label;
        scatter x=us_sens_perc y=nns3_point / datalabel=nns3_label;
        refline 60 /axis=x;
        refline 75 /axis=x;
        xaxis minor label="U/S sensitivity (%)";
        yaxis max=2000 minor label="Number needed to screen";
run;

/* 3.3 Third simulation: NNS to increase the sensitivity of the system by 1 percent */
proc sgplot data = _sim noautolegend;
        where us_sens_perc>20;
        series x=us_sens_perc y=nns_to_increase_sens_by_one /curvelabel="Best" curvelabelpos=start
lineattrs=(pattern=mediumdash color=blue);;
```

```
        series x=us_sens_perc y=nns2_to_increase_sens_by_one /curvelabel="Worse" curvelabelpos=start
lineattrs=(pattern=mediumdash color=red);;
        series x=us_sens_perc y=nns3_to_increase_sens_by_one /curvelabel="Realistic" curvelabelpos=start
lineattrs=(pattern=solid color=green);;
        scatter x=us_sens_perc y=nns_to_increase_point / datalabel=nns_to_increase_label;
        scatter x=us_sens_perc y=nns2_to_increase_point / datalabel=nns2_to_increase_label;
        scatter x=us_sens_perc y=nns3_to_increase_point / datalabel=nns3_to_increase_label;
        refline 60 /axis=x;
        refline 75 /axis=x;
        xaxis minor label="U/S sensitivity (%)";
        yaxis max=3000 minor min=0 label="NNS to increase sensitivity by 1%";
run;

/* 3.4 Fourth simulation : New detected CHD by FE */
proc sgplot data = _sim noautolegend;
        Where us_sens_perc>20;
        series x=us_sens_perc y=new_chd_detected_by_fe  /curvelabel="Best" curvelabelpos=start
lineattrs=(pattern=mediumdash color=blue);
        series x=us_sens_perc y=new2_chd_detected_by_fe  /curvelabel="Worse" curvelabelpos=start
lineattrs=(pattern=mediumdash color=red);
        series x=us_sens_perc y=new3_chd_detected_by_fe  /curvelabel="Realistic" curvelabelpos=start
lineattrs=(pattern=solid color=green);
        scatter x=us_sens_perc y=new_chd_point / datalabel=new_chd_label;
        scatter x=us_sens_perc y=new2_chd_point / datalabel=new2_chd_label;
        scatter x=us_sens_perc y=new3_chd_point / datalabel=new3_chd_label;
        refline 60 /axis=x;
        refline 75 /axis=x;
        xaxis minor label="U/S sensitivity (%)";
        yaxis type=log logbase=10 min=0.1 minor label="New CHD detected by FE per 100,000 pregnancies";
run;

/* 4. Creating summary table */
data _table1; set _sim1;
        if (_n_-1) / 5 ne round ((_n_-1)/5) then delete;
        keep us_sens_perc nns us_fe_sens_perc nns_to_increase_sens_by_one new_chd_detected_by_fe
CHD_in_not_at_risk CHD_in_at_risk;
run;
data _table2; set _sim2;
        if (_n_-1) / 5 ne round ((_n_-1)/5) then delete;
        keep us_sens_perc nns2 us2_fe_sens_perc nns2_to_increase_sens_by_one new2_chd_detected_by_fe
CHD_in_not_at_risk2 CHD_in_at_risk2;
run;
data _table3; set _sim3;
        if (_n_-1) / 5 ne round ((_n_-1)/5) then delete;
        keep us_sens_perc nns3 us3_fe_sens_perc nns3_to_increase_sens_by_one new3_chd_detected_by_fe
CHD_in_not_at_risk3 CHD_in_at_risk3;
run;

data _table;
        retain us_sens_perc;
        merge _table1 _table2 _table3;
        by us_sens_perc;
        fe_sens_inc = us_fe_sens_perc - us_sens_perc;
        fe_sens_inc2 = us2_fe_sens_perc - us_sens_perc;
        fe_sens_inc3 = us3_fe_sens_perc - us_sens_perc;
run;


/* 5. Simulation for NNS with increasing RR */
/* 5.1 creating data for simulaton */
data _sim5;

        /* baseline pamateters */
        chd_prev = 0.0018; /* severe CHD prevalence */
        FE_sens = 0.95;  /* FE sensitivity */
        us_sens = 0.60; /* US sensitivity (scenario #1) */
        us_sens2 = 0.75; /* US sensitivity (scenario #2) */

        do i=1 to 20 by 0.2;
                at_risk_RR = i;
```

```
                /* scenario #1 --> US sensitivity = 60% */
                prev_at_risk = chd_prev * at_risk_RR; /* prevalence of severe CHD in at risk population*/
                prev_undetected_at_risk = prev_at_risk * (1 - us_sens);
                prev_detected_by_fe_at_risk =  prev_undetected_at_risk * FE_sens ; /* prevalence detected
by FE */
                nns = 1/prev_detected_by_fe_at_risk; /* NNS */

                /* scenario #21 --> US sensitivity = 75% */
                prev_undetected_at_risk2 = prev_at_risk * (1 - us_sens2);
                prev_detected_by_fe_at_risk2 =  prev_undetected_at_risk2 * FE_sens ;
                nns2 = 1/prev_detected_by_fe_at_risk2;

                output;
        end;
        drop i;
run;

/* 5.2 Graph */
proc sort data=_sim5; by at_risk_RR; run;
proc sgplot data = _sim5 noautolegend;

        series y=nns x=at_risk_RR /curvelabel="US sens. = 60%" curvelabelpos=start
lineattrs=(pattern=solid color=red);
        series y=nns2 x=at_risk_RR /curvelabel="US sens. = 75%" curvelabelpos=start
lineattrs=(pattern=solid color=green);

        xaxis type=log logbase=10 label="Risk ratio";
        yaxis min=0 label="Number needed to screen";
run;
```