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, the increase in CHD detection rates by second-trimester ultrasound (U/S), and the high proportion of severe CHD in low-risk pregnancies. We aimed to determine situations in which additional screening by fetal echocardiography (FE) would result in a significant increase in sensitivity and a sizable decrease in the false-negative rate of detection of severe CHD.

Methods: We simulated the change in the numbers of detected severe CHD cases when FE is offered to women with a normal second-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 and the reduction in the rate of missed cases.

Results: For an U/S sensitivity of 60%, the addition of 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 number needed to screen to detect one additional case of severe CHD was 436 (156 to 952).

In 2004, the American Society of Echocardiography recommended performing fetal echocardiography (FE) in addition to the second-trimester obstetrical ultrasound (U/S) for fetuses with an increased risk of congenital heart disease (CHD), such as those with 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.”

The rationale for recommending FE for these pregnancies is based on the assumptions that (i) the prevalence of CHD is increased in these fetuses, (ii) a proportion of these extra CHD cases may be missed by the second-trimester U/S, and (iii) the necessary FE resources would be balanced by a significant increase in detection rates. Evidence supporting the effectiveness of referring women with these higher-risk pregnancies with a normal second-trimester U/S for 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 second trimester U/S in the past 2 decades,3-6 by a possible overestimation of the risk of severe CHD in high-risk pregnancies,7-9 and by the fact that > 90% of severe fetal
CHDs occur in pregnancies without risk factors. 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 fetal echocardiograms 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 by FE of pregnancies at high risk of CHD would result in a significant increase in sensitivity and 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 second-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 FE is offered to women with a higher risk of bearing a child with CHD, compared to using the second-trimester U/S alone. We defined “high-risk pregnancies” as pregnancies with a normal second-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 second-trimester U/S performed by an obstetrician or a radiologist. In accordance with the scientific statement from the American Heart Association, pregnancies with maternal, familial, or fetal risk factors for CHD are also referred for FE in a tertiary care centre, even if the second-trimester U/S is normal. In Canada, the cost of all pregnancy follow-ups and imaging is covered by the government universal healthcare insurance.

Contingency tables and outcomes were calculated with and without this additional FE in high-risk pregnancies. This approach 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 to whom FE was not offered. Outcomes were calculated when the theoretical sensitivity of the second-trimester U/S varied from 20% to 100%, and for 3 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 second-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 tract obstructions, common arterial trunk, double-outlet right ventricles, and tetralogy of Fallot.

The secondary outcomes were as follows: (i) the NNS (ie, the number of fetal echocardiograms needed to detect one additional severe CHD); (ii) the NNS to increase the sensitivity by 1 percentage point, and (iii) 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 Supplemental Table S1).

**Definition of the simulation scenarios**

Mathematically, the yield of FE used 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 scenario, a worst-case scenario, and a realistic scenario. The 3 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 Fetal Cardiac Registry of Quebec to Improve Resource Utilization in Fetal Cardiology (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. We used the preliminary results 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.

The worst-case and best-case scenarios were based on data available in the 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 in which FE is used as a screening tool in high-risk pregnancies.

### NNS 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 of 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%. All calculations were performed using SAS for Windows, version 9.4. The SAS programs used are available in Supplemental 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). Results are presented for the realistic scenario, with the worst-case and best-case scenarios shown in parentheses. We report outcomes for U/S sensitivities of 60% and 75%, which represent the range of observed sensitivities in the past decade.

Outcomes for the full spectrum of U/S sensitivities are presented in Figure 1, 2, 3 and 4 and Table 2.
of 1.5 percentage points (0.7 to 4.9) if the U/S sensitivity is 75%.

**NNS and number of missed CHD cases**

Figure 2 shows the NNS, that is, the number of fetal echocardiograms 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 fetal echocardiograms that would need to be performed to increase the sensitivity of detecting severe CHD cases by one percentage point. We found that for a U/S sensitivity of 60%, as many as 785 fetal echocardiograms (625 to 1333) were needed to increase the combined sensitivity from 60% to 61%. For a U/S sensitivity of 75%, the number needed would be 1255 (998 to 2132).

Figure 4 shows the number of severe CHD cases missed 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 CHD cases 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 CHD cases by 12.5%. For a population of 100,000 pregnancies, 3920 fetal echocardiograms would be needed to produce the same results. This number is twice as high as the theoretical number of 1904 high-risk pregnancies in the same population.

**Influence of relative risk on the number needed to screen**

To help determine in which situations the NNS would be low enough to justify performing 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 1000 pregnancies. If the U/S sensitivity is 75%, we found that a relative risk of ~10 is needed to yield an NNS of <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 of ~15 is needed to obtain an NNS of <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 second-trimester U/S. We found that in the usual environment in which screening FE is performed, there was a very modest
increase in sensitivity to detect severe CHD cases, at the expense of a high utilization of specialized medical resources. This finding was mostly driven by the low prevalence of severe CHD cases and by the low absolute number of severe CHD cases in higher-risk pregnancies, compared to the number in low-risk pregnancies. We also showed that to identify FE indications with an 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 purely a mathematical exercise, and that the usefulness of FE is much broader than just 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 second-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 observation, we initiated 2 parallel research projects. First, we undertook the FREQUENCY study, a population-based retrospective cohort study 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 second-trimester obstetrical U/S. Prenatal detection rates have been found to be quite variable. Detection rates of $<50\%$ have been reported for some critical CHDs requiring immediate specialized care at birth, such as transposition of the great arteries, although more recent experience points toward increasing detection rates with time. 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, even in the setting of a normal second-trimester U/S performed by the obstetrician or the radiologist.

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 U/S 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 are limited in most settings. This study highlights the fact that these limitations are due to the low prevalence of severe CHD, even in high-risk pregnancies, the very high proportion of missed CHD cases in the low-risk group, and the increasing detection rate at the second-trimester U/S.

Evidence supporting the effectiveness of referring high-risk pregnancies with normal second-trimester U/S for FE is scarce. In 2015, an interrogation of the Danish birth registry showed that only a minority of CHD cases were identified by adding FE in high-risk pregnancies. 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. In that study, 92% of CHD cases occurred in the low-risk group, a percentage similar to that in our simulations. Others have also observed that most CHD cases are identified during the second-trimester U/S, and that referring high-risk pregnancies for FE did little to increase overall detection rates.

Our model suggests that improving the overall sensitivity of the second-trimester U/S has much greater potential to reduce the number of undiagnosed severe CHD cases. A recent study in Canada highlighted the important regional variability of the second-trimester U/S, with sensitivities ranging from 14% to 72% for the prenatal detection of the transposition of the great arteries. In our realistic scenario, it was mathematically impossible to increase the sensitivity by $>5\%$ by adding FE in high-risk pregnancies, even with a second-trimester U/S 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. 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 among regions would outperform the entire high-risk pregnancy FE screening strategy. We fully recognize that FE has

| 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 [355–712] | 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 | 4.8 [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 [0.9–6.9] |
| 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 in brackets are the ranges obtained using the worse-case and the best-case scenarios. CHD, congenital heart disease; FE, fetal echocardiography.
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 second-trimester U/S, combined with a more focused strategy to refer these higher-risk pregnancies, are likely to bear fruit.

Although 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 in which screening by FE would be valuable, although such a combination of favourable parameters is not probable. Additional screening has a better yield in situations in which 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 results12 and those of other published studies7, 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 among regions, countries, and healthcare settings. We believe that most populations in which 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 recognize 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 focuses strictly on detection rates. The financial and clinical impacts 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 epidemiologic parameters are such that the benefit of referring women with high-risk pregnancies who have a normal second-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 economic, logistical, and psychological impact of the use of FE as a screening tool.

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Supplementary Material
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