UNIVERSITY OF MEDICINE AND PHARMACY CRAIOVA

DOCTORAL SCHOOL

PHD THESIS

FIRST TRIMESTER SONOGRAPHIC ASSESSMENT OF THE FETAL HEART

ACHIEVEMENTS, REALITIES AND CONTROVERSIES

SUMMARY

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Congenital heart diseases (CHD) are the most common of congenital anomalies, representing a major public health problem. This research is devoted to ultrasound evaluation of the fetal heart at the end of the first trimester (FT) of pregnancy. I chose this particular topic considering that the congenital cardiac anomalies detection field is one in which the two disciplines - Public Health and Prenatal Diagnosis - most closely intertwine and are most influencing each other.

THE GENERAL PART of the thesis, which reflects the stage of knowledge, was structured in four chapters. In the first chapter, named **"The importance of prenatal detection of cardiac anomalies. Early versus late screening",** I reviewed current data regarding the frequency of congenital heart anomalies in the population, the classification of these abnormalities and the main risk factors. I also comparatively presented the benefits and disadvantages of early vs. late CHD screening, in terms of social, economic and emotional costs for both the couple and the health care system.

In the second chapter**, "The methods of detection in high risk group vs in the general population"**, I described the main controversies in the literature related to the necessity of screening for major congenital heart anomalies (MCHD), depending on the populational risk: low risk population/unselected, respectively, high risk population for this pathology.

The third chapter **"Screening protocols for congenital heart anomalies"**, contains a summary of the recommendations of the Ultrasound Societies for FT and second trimester (ST) evaluation of the fetal heart, as well as guidelines and requirements for the training and competence in cardiac scanning. I presented the potential of early CHD ultrasound diagnostic, highlighting the extremely wide differences in detection rates, and leading causes for these variations (extension of the protocol, populational risk, the approach, operator's experience, the routinely use of color Doppler). I pointed out that a normal result of the cardiac examination, at any moment in pregnancy, cannot exclude the CHD since some cardiac lesions are evolving in utero and they may acquire ultrasound semiology only later in pregnancy or even after birth.

The last chapter of the general part **"Volumetric Ultrasound in fetal heart evaluation"** presents the advantages and limitations of using this technique, including the efficiency in CHD detection. This technique has emerged as a new, complementary strategy of the fetal heart scan with special benefits in the spatial evaluation of the cardio-vascular system, lowering the dependency on the operator abilities and experience, but requiring accessibility to specific ultrasound equipment and to those for telemedicine.

In the **SPECIAL PART** of the thesis are given my own contributions as achieved in the study.

OBJECTIVES. The main objective of the study was to assess the accuracy of 2D and 4D morphological examination of the fetal heart at the end of the first trimester of pregnancy.

Secondary objectives of the study consisted in investigating ***the visualisation rates of fetal cardiac parameters***, studying the ***intra-and inter-observer agreement*** for the evaluation of cardiac structures in normal fetuses, analysing the ***potential benefits of adding color Doppler method*** in each of the two ultrasound techniques, investigating the ***efficiency and acceptability of the transvaginal (TV) route*** used to complete the non-informative transabdominal approach (TA), comparing ***the diagnostic accuracy of the two methods (2D and 4D-STIC)*** in MCHD screening, proposing ***a standardized and simplified study protocol*** for the FT ultrasound evaluation of fetal heart in unselected population, and studying ***the learning curve*** of the protocol.

METHOD AND ALGORITHM have been staged, in order to address all of the proposed goals. All scans have been carried out by **certified and experienced examiners**, using **modern ultrasound equipment**, equipped with probes and software dedicated to fetal morphology study, including cardiac assessment.

The study group consisted of all singleton pregnancies, unselected, consecutively enrolled, at 11 + 0 to 13 +6 weeks of gestation according to crown rump length (CRL), and low risk based on medical history. The final calculations included only those cases with known pregnancy outcome and at least one method for confirmation of the diagnosis documented.

We used 2D technique, both Gray scale and color Doppler, and in some selected cases, we acquired volumetric ultrasound data. The ultrasound examination was scheduled as close to the 12th week of gestation as possible. Choosing the classical cardiac acquisition planes, we targeted to achieve optimal images of the fetal heart, using a lateral or an apical approach.

During the first stage of the study, between 2011 and 2014, using an extended cardiac scanning protocol, I intended to demonstrate 11 FT cardiac parameters, six parameters in the Gray scale and five parameters in color Doppler mode: abdominal situs, four chambered heart, intact crux, at least one pulmonary vein entering the left atrium, left ventricular outflow tract and septo-aortic continuity, confluence of the arterial arches on the left of the spine, equal atrioventricular flow, no flows between ventricles, aortic flow, crossover of the great arteries and confluence of the arterial arches with normal direction and equal flow in both arches.

In the second stage of the study, after 2014, I attempted to simplify the standardized fetal heart scanning protocol. Normality has been documented up to 4 cardiac parameters and one extracardiac: in Gray scale – transversal abdominal plane and the four chambered heart image, and using color Doppler – the equal atrioventricular flow, the crossing of the great arteries and equal flow in both arches, or "V" sign.

We used transabdominal (TA) approach, but in cases where fetal anatomy could not be fully evaluated, the transvaginal (TV) route was proposed to pregnant women. Later, they were invited to respond to a questionnaire concerning their perception of the TV techniques.

When using color Doppler, safety ultrasound guidelines were followed.

Later, I was interested in the characteristics of the simplified protocol learning curve for inexperienced examiners.

All women were offered a complete follow up program (but customised as rhythmicity) of the pregnancy. The FT scan results have been reported to the data obtained through the following methods, which are considered the standard tests: re-examination by a multidisciplinary team, morphological evaluation in the second trimester of pregnancy, autopsy (for deceased fetuses or for ones from interrupted pregnancies) and postnatal diagnosis (in cases of live births).

RESULTS During the study period we evaluated at the end of the first trimester 3240 cases by means of 2D ultrasound (Gray-scale and color Doppler). Confirmation was obtained in 2908 cases (lost to follow up rate 10.24%).

The accuracy of the standardized 2D ultrasound (simplified protocol) in FT detection of CHD take into account in the period of the research 38 congenital heart anomalies, 26 (8.94‰) being major defects and 12 (4.13‰) minor ones. All major anomalies of the heart and large vessels were diagnosed prenatal, but there were two false-negative cases of minor anomalies identified later.

First trimester ultrasound identified correctly 21/26 (80.77%) of the major CHD and 4/12 (33.33%) of the minor fetal heart defects. The 2D method specificity was 99.9%, equal for both major and minor anomalies detection. Sensitivity was lower for minor defects than for the major CHD (33.3% vs. 80.8%), with discrepancies between positive predictive values (57.14% 87.5%).

FT 2D ultrasound method missed 13 cases of cardiac anomalies, of which 5 were major defects: 2 cases of Tetralogy of Fallot and three evolving disease cases (critical aortic stenosis, cardiomegaly and major pericardial effusion).

The false-positive rate (0.1%) was identical for both major and minor defects. The false-negative rate was higher for minor anomalies (66.67%) than for the major CHD (19.23%).

The efficiency of the FT extended protocol for the evaluation of normal fetal heart using in 2D method (Gray-scale and color Doppler) and 4D (Gray-scale and color Doppler) has been assessed primarily by **investigating the visualisation rates of cardiac parameters** in 100 normal fetuses.

The visualization rate on Gray-scale imaging for both 2D and 4D methods was good (≥80%) for most cardiac structures, the exceptions being the visualization rate of at least one pulmonary vein entering the left atrium, the crux and confluence of the arterial arches on the left of the spine. On color flow mapping, the visualization rate was excellent (≥85%) for all parameters.

Evaluation of reproducibility and repeatability of each 2D and 4D techniques showed for all the 11 cardiac parameters, an good or excellent intra-observer agreement for both operators and for each of the two methods (kappa > 0.6), with an overall intraobserver agreement > 95% for all cardiac features.

For all the 11 cardiac parameters, both 2D and 4D methods, it has obtained a good, excellent or perfect inter-observer agreement (kappa > 0.6), with an overall inter-observer agreement > 96%.

All parameters were better assessed using 2D method, but I have not found statistically significant differences between the two techniques ($p > 0.05$, McNemar test)

The importance of the application of color Doppler in FT examination of the fetal heart was demonstrated by using pairs of correspondent parameters. Comparing Gray scale with color Doppler imaging in both 2D and 4D techniques, for both observers, we found statistically significant differences between results for two pairs of features (1) left ventricular outflow tract and septo-aortic continuity/aortic flow and (2) confluence of arterial arches on left of the spine/equal flow in both arches, with visualisation on color Doppler being significantly better than that on Gray Scale ($p < 0.05$, McNemar test).

The acceptability and usefulness of transvaginal approach were quantified. The transvaginal route was proposed for completing the FT transabdominal ultrasound examination of the heart in 8.52% (124/1456) of cases due to the persistent unfavourable fetal position (3.36%) and unfriendly maternal conditions (5.14%).

As a result of proper counselling provided by the sonographer, the acceptability of transvaginal method was 100%.

All patients who had the TV re-affirmed that they would definitely agree upon such ultrasound monitoring for a future pregnancy if necessary. Women appreciated that the inconvenience caused by the TV method was significantly less discomforting than having a cervical smear (Wilcoxon as Z =-21.34, P< 0.001) or having a digital clinical evaluation (Wilcoxon as Z =-15.03, P< 0.001).

The learning curve for the newly simplified protocol for cardiac evaluation at the end of first trimester was studied for the first 100 examinations, for each of the four obstetricians (resident doctors) in the training program. The failure rate (the number of unsuccessful examinations) had a decreasing tendency by the end of the training programme: 12.12% - 48.49% (32.65% of 132 of the fetal heart scans) for the first third of the examinations, 0%-17.65% (8.09% of 136 of ultrasound scans) for the second third and 0% for the last third of the examinations.

The overall operating time decreased from an average of 9.17 minutes (at the beginning of learning process) to an average of 3.80 minutes (in the last part of the training programme).

For better assessing of the learning trend I used the moving average method. I noticed an initial plateau-like region having the operating time of 9 minutes, followed by a steep slope between the 30^{th} and the 40^{th} scan, then a descending trend until the 70^{th} scan, subsequently stabilized in a plateau after the 80^{th} scan around the value of 3.5 minutes at the end of learning.

Multivariate ANOVA test results showed that the trainee (p = 0,686) or the trainee's dependence of the number of repetitions (p = 0,311) did not have a statistically significant influence on the observed variation, and only repeating the manoeuvre of imaging influenced the process of learning (= 1.82×10^{-90}).

DISCUSSION In this research I have initially targeted the ultrasound evaluation of normal fetal heart.

Our results showed a high intra- and interobserver agreement in the assessment of all cardiac anatomical structures at 12 + 0 - 13 + 6 weeks of gestation for both ultrasound techniques (2D and 4D - STIC). In the same time, during this stage targeted at the normal fetal heart, I have documented higher visualization rates of certain cardiac structures after the application of color

Doppler mapping, both in 2D and in 4D methods. These “coloured” parameters are the most important in early diagnosis of the MCHD.

Ultrasound examinations are considered to have a high dependence on the observer’s experience, but, by using a standardized protocol, there is a good chance to solve this problem. The implementation of this homogeneous protocol, similar to second trimester assessment of the heart, was relatively easy to perform and it allowed the confirmation of normality in a large series of fetuses.

This stage of my study has a high degree of originality. Prior to the publication of our results, only few have compared 2D with 4D - US method for first trimester cardiac assessment. There have been no studies comparing the Gray scale imaging and the color Doppler technique for visualisation of the normal heart in the first trimester of pregnancy. I found that fetal heart parameters were better visualised using 2D rather than using 4D method, although the statistical significance has not been reached. Therefore, the 2D ultrasound, being the conventional approach, should remain the first intention method. Furthermore, it is a cheaper and easier method compared to 4D-US.

Regarding the acceptability and benefits of transvaginal examination approach used to complete the non-informative transabdominal (TA) cardiac scan, although necessary in only 8.5% of the cases, based on our findings, we believe that the TV can be an important complementary source of information. In our study, the acceptance of the TV route was 100%, which reflects the opening of our patients to a new approach, if that is necessary for the proper evolution of the pregnancy.

After the "maturation" of the standard technique proposed at the beginning of our research, I decided to simplify it by reducing the number of anatomical features targeted.

The sensitivity of the first trimester ultrasound examination in detection of CHD in low risk populations, calculated with respect to the findings of second trimester scan and to the autopsy results, has wide variations in the literature, between 36.8% and 84.2%. We also report a high sensitivity, slightly lower than that of another study conducted on a high risk population, based on increased nuchal translucency values.

Our research is the first study addressing the accuracy in the detection of minor cardiac defects. Our results highlight the difference between the early detection of major and minor defects, showing an increased number of false-negative cases for the latter. This reinforces the opinion of our research group that the FT cardiac assessment should not be dedicated to establishing a specific, detailed or complete diagnosis, but rather it should remain a screening method strictly addressed to the detection of major congenital heart anomalies.

We believe that the strength of our research is the use of a homogeneous, standardized protocol in the first trimester evaluation of the fetal heart, for all women participanting in the study. Because our research has been done on unselected population, with a minimal contextual influence, using a standardized scanning protocol, we can reasonably argue that we have lowered the dependency on the operator and that we have almost eliminated the dependency on the fetal position, two of the most important reasons for delaying diagnosis of major CHD.

After we have demonstrated that our scanning protocol proved excellent detection rates in MCHD at the end of FT, in the last stage of the research I have been concerned about the potential for disseminating this protocol. Thus, we have dedicated the last study interval to evaluate the characteristics of the learning curve of the first trimester (FT) fetal heart scan. The outcome indicated good results, for all our trainees, in the ability of demonstrating the normal cardiac features at the end of first trimester of pregnancy. Our findings showed that, for a sonographer without experience in FT fetal cardiac scanning, the minimum number of scans required to achieve competence in examining the fetal heart is of 50 cases. The operating time stabilizes at an acceptable value after 80 cases in moving average analysis. At the end of the learning period, all four trainees had 100% success rate in identification of normality in required time less than 10 minutes.

Up to date there are no other publications on the fetal heart scan learning curve in the first trimester for examiners without previous experience.

Previous research has shown that, for an experienced operator, it was required a minimum of 75 scans up to a complete evaluation of the heart. This difference in relation to our results can be explained by a slightly more extended protocol than the one proposed by us. It should be borne in mind, however, the small number of participants in the training programme and the lack in stratification for other confounders that could affect the quality of the cardiac sweep.

The majority of published studies in this area does not meet the criteria of an accuracy study, in which it is absolutely mandatory to use a standard test for confirmation. In general, for congenital anomalies, perinatal autopsy or post-natal examination were used as standard tests. However, previous research argues that early diagnosis of CHD is feasible and that it is associated with lowering neonatal morbidity and mortality. Therefore, efforts should be made to establish workplace-based training programs for all obstetricians, that would ideally incorporate educational strategies pertinent to young ultrasonographers.

CONCLUSIONS Early evaluation of the fetal heart (at the end of the first trimester of pregnancy) has not the goal to provide a complete specific diagnosis, but to detect or at least suspect major cardiac anomalies. This statement might have an important consequence: the teams that assume this technique and the patients that request it must accept the fact that, based on this evaluation, the process of counselling may be inaccurate or incomplete.

With all its limitations, our research team mitigates for generalizing the technique for several reasons: prospective researches, on very large populations, will be able to determine the real accuracy of the method; false-positive rates are extremely small, making the situations in which operators face the risk of producing unnecessarily anxiety very rare; and, to certain couples, obtaining early favourable results are very important from a psychological point of view.

FT fetal heart ultrasound evaluation should no longer to be regarded as a superior technique which requires expertise and practice. I pointed out that, if one uses a standard protocol, the sonographers involved in screening could obtain, for each case, the most important parameters of cardiac morphology, with a minimum of additional examination time. The learning curve is relatively fast when running a simple and standardized protocol. As a result, we can appreciate that, after wide implementation of this scanning protocol, there will be lower variations in FT detection rates of CHD between a specialized examiner and a less experienced one. These rates will have smaller variations among different prenatal diagnostic centres and among different countries.

In my opinion, this research makes a valuable contribution in improving knowledge related to the FT evaluation of fetal heart and proposes a simple and efficient standard protocol, based on conventional 2D ultrasound, a cheap and accessible technique.

The usage of color Doppler technique improves the visualization rates of cardiac morphology parameters, resulting in an increase in accuracy (both in 2D and 4D technique), specially for conotruncale anomalies. Color Doppler is the most effective way to gather important data about heart and large vessels at the end of FT. As a result, our findings require the organization of future studies to carefully and systematically assess the safety of FT use of color Doppler.

Even if in this prospective research we have reached high detection rates for MCHD, the FT fetal heart screening protocol must remain complementary to the second trimester fetal heart scanning, at least for the near future. Under no circumstances it can become a substitute.

The CHD spectrum is extremely vast. Therefore, it is not to be expected that a particular screening method (in our case the FT sonographic evaluation of the fetal heart) has the same efficiency in all types of cardiac anomalies.

During the process of counselling parents regarding the early detection of CHD, it should be highlighted that the full spectrum of fetal heart defects may be clarified/completed but only later in pregnancy. The evolution and the management of a specific cardiac anomaly could be accurately described only after performing second trimester echocardiography. Furthermore, it should be explained in detail the evolutionary/progressive character of certain cardiac abnormalities.

If using high-performance ultrasound system and standard scanning protocols, both ultrasound methods (2D and 4D) are perfectly reproducible and repeatable, reaching high detection rates for CHD.

When the transabdominal approach is not informative, the transvaginal route may increase the visualization rates of cardiac parameters. However, the results of the TV is highly dependent on the examination conditions, especially on the fetal position. Furthermore, even if TV ultrasound is easily accepted by Romanian pregnant women, its acceptance rate may greatly vary worldwide, according to cultural and religious customs.

I appreciate that the results of my research can be easily replicated in other institutions, and may be the basis for future public health policies.

Considering the fact that most cases of congenital heart abnormalities are detected in low-risk patients, ultrasound screening for MCHD should be offered routinely in all centres at the nuchal screening time. The only restriction morally acceptable is the refusal of the parents, after being well-informed of the advantages and disadvantages of the method, and the limited access to high-resolution equipment.

Keywords: first trimester, congenital cardiac anomalies, 2D ultrasound, accuracy, standard protocol, color Doppler, screening.