ORIGINAL PAPER

RJME
Romanian Journal of Morphology & Embryology
http://www.rjme.ro/

Cardiac axis evaluation as a screening method for detecting cardiac abnormalities in the first trimester of pregnancy

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Abstract

Congenital cardiac abnormalities refer to especially anatomic malformations of the heart that normally occur during fetal heart development, before eight weeks after conception. *Aim*: The aim is to investigate the association between cardiac axis and congenital heart abnormalities for a potential underline clinical application of cardiac axis evaluation during detection by abnormalities at the time of first trimester ultrasound. It is known that aneuploids can be associated in almost half of cases with cardiac abnormalities, so the angle of the cardiac axis could be a potential indirect marker for the detection of aneuploids in the first trimester of pregnancy. Being easy to obtain, from the cross-section at the chest level with the visualization of the four chambers, does not require additional sections to those provided in the current guides, we aim to prove its usefulness in diagnosing aneuploids and congenital cardiac abnormalities along with the translucent nuchal flow, at the level of the venous duct and the presence of tricuspid regurgitation. *Conclusions*: Cardiac axis has a higher value for the detection of congenital cardiac abnormalities with respect to the nuchal translucency, tricuspid regurgitation and inverted A wave at the level of the venous duct.

Keywords: congenital heart abnormalities, aneuploids detection, angle of the cardiac axis.

Introduction

Diagnosis of early prenatal cardiac congenital abnormalities can predict the postnatal prognosis of these children, offers the possibility of adequate counseling, provides time for a genetic evaluation to know if this structural abnormality is isolated or is within a genetic syndrome, offers the possibility of planned birth in a tertiary center with interventional cardiology and/or cardiac surgery to be able to intervene early, especially in the case of duct-dependent cardiac malformations [1, 2].

Currently, the first trimester screening provides for the evaluation of indirect markers that may suggest the presence of cardiac abnormalities, such as nuchal translucency, the presence of tricuspid regurgitation and the abnormal flow in the venous duct [3]. The angle of the fetal cardiac axis to first trimester ultrasound (US) has been poorly studied and there are relatively few studies published in the literature regarding its potential utility for early detection of cardiac abnormalities. This diagnostic element, on the other hand, was studied extensively in the second and third trimester of pregnancy, being a very good indicator for the existence of cardiac abnormalities, especially of the conotruncal ones [4, 5].

It was assumed that the value of the cardiac axis varies very little during pregnancy and therefore the values could be extrapolated in the first trimester of pregnancy. Thus, deviations from normal values could be suggestive for the presence of cardiac abnormalities and at the time of first trimester screening [6]. More than half of the fetuses with Down syndrome, as well as those with Edwards & Patau syndrome have associated cardiac abnormalities, so an additional marker for detecting these cardiac abnormalities would increase the accuracy of detecting these cases with numerical chromosomal abnormalities [7].

Even if cardiac axis deviation is not a parameter included in the *Fetal Medicine Foundation* (FMF) algorithm for individual risk assessment of Down, Edwards & Patau syndrome, the presence of this marker may be an indication for genetic testing even in the presence of a low *FMF* adjusted risk that would otherwise not. It would even constitute an indication for a noninvasive prenatal test [8, 9].

In addition, the presence of this marker might require the indication of extended cardiac evaluation in the first trimester screening US, where current guidelines provide optional recommendations for cardiac evaluation, as well as later echocardiography in pregnancy to detect undetectable abnormalities in the first trimester or they have an evolutionary character, which can only be seen US late, in the third trimester [10–12].

Aim

The aim of this paper is to find if the presence of cardiac axis deviation may be an indication for genetic testing and might require the indication of extended cardiac evaluation in the first trimester screening US.

Patients, Materials and Methods

We conducted a prospective study on a batch of 3000 single-pregnancy pregnancies highlighted in the first

trimester of pregnancy. The study was carried out for a period of three years (2015–2018) within the III[rd] Stationary of the Emergency County Hospital, Oradea and the Department of Obstetrics and Gynecology, Municipal Emergency Hospital, Timişoara, Romania.

Patients who referred for pregnancy monitoring in the first trimester or were sent for evaluation were screened for screening for fetal abnormalities. Two screening methods were proposed, and depending on their choice, they were divided into two study groups.

Within the study group of pregnant women, which included 3000 cases, during the evaluation of fetal anatomy, according to the guide developed by the Romanian Society of Ultrasonography in Obstetrics and Gynecology, the angle of the fetal cardiac axis was measured prospectively.

Cardiac axis evaluation was performed according to the following protocol:

- cranial length (CRL) was between 45 mm and 84 mm, according to the *FMF* screening standards;
- transabdominal evaluation, in case of difficult visualization the transvaginal examination was continued;
- thoracic cross-section with visualization of the ribs on both sides of the lateral thoracic wall and highlighting of the four cardiac chambers;
- the cardiac axis was measured as the angle between the line that crosses the long axis of the heart, through the interventricular septum and the anteroposterior line passed at the level of the chest on the midline;
- the normal value of the heart axis angle was considered between 30º and 60º;
- the other constituents of the screening were also evaluated: presence of tricuspid regurgitation, blood flow to the venous duct and nuchal translucency;
- because the studied group is similar to the one in which the accuracy of the screening for the aneuploids was evaluated, the cases with multiple pregnancies were excluded.

All cases were monitored until birth. US was performed to assess fetal morphology in the second trimester of pregnancy between 18–22 weeks.

At 32 weeks of age, an US evaluation of the fetal heart was performed to detect any abnormalities known to be evolutionary and could have been detected at this age of pregnancy.

All newborn observation sheets were reviewed to document the existence of major or minor cardiac congenital aneuploids or abnormalities that were not diagnosed antenatally.

In case the pregnancy stopped evolving intrauterine or the patients aborted a fetus, autopsy was performed to document the US diagnosed cardiac anomaly.

Major cardiac abnormalities refer to those fetal heart malformations that require cardiac surgery or other procedures during the first year of life.

We compared the measurements of the cardiac axis between the group with cardiac abnormalities and the rest of the cases that did not present cardiac abnormalities to observe if the deviation of the cardiac axis appears more frequently in the fetuses with major cardiac abnormalities.

Also, the association of cardiac axis deviation with increased nuchal translucency, tricuspid regurgitation and venous duct with abnormal flow were compared in order to evaluate the differences between them regarding the detection rate of congenital cardiac abnormalities. Nuchal translucency, tricuspid regurgitation and inverted wave on the venous duct are already consecrated indirect markers for the diagnosis of cardiac malformations, being considered as "gold standard", makes this comparison of the cardiac axis with mentioned parameters to provide valuable information on its usefulness in diagnosis of cardiac abnormalities in the first trimester of pregnancy.

Results

Within the studied group that included a total number of 3000 pregnancies with gestational ages between 11 weeks and 13+6 weeks, we identified a number of 21 (0.7%) fetuses with major cardiac abnormalities (Figure 1).

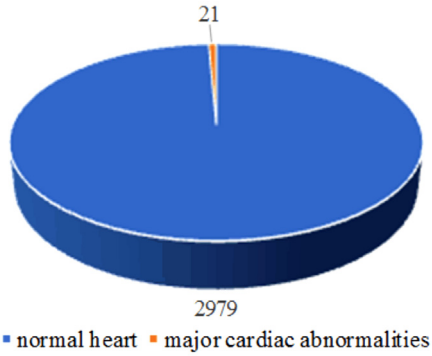

Figure 1 – ***The share of fetuses with major cardiac abnormalities in the studied group.***

Within the studied group, we evaluated the cardiac axis in all the first trimester US; we found an abnormal angle value in 14 (0.46%) cases (Figure 2).

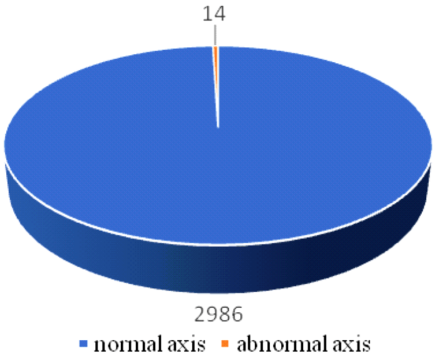

Figure 2 – ***The weight of the fetuses with cardiac axis deviated in the studied group.***

In the group with abnormal cardiac axis, 1/14 (7.14%) cases had no associated cardiac abnormality, the axis being deviated due to the presence of a congenital diaphragmatic hernia and 13/14 (92.85%) cases had the axis deviated in the context of the presence of an anomaly congenital heart (Figure 3).

Of the 21 fetuses, six (28.57%) had trisomy 21, three (14.28%) had trisomy 13, and five (23.8%) had trisomy 18. Seven (33.3%) cases with major cardiac abnormalities had normal karyotype (Figure 4).

In the group with cardiac abnormalities, eight (38.09%) cases had the cardiac axis within normal limits, between 35º and 55º, the other 13 (61.9%) cases being with changes in the cardiac axis (Figure 5).

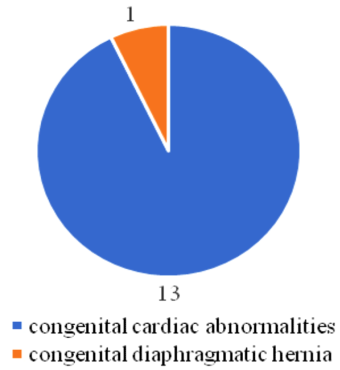

Figure 3 – ***Distribution of cases with deviated cardiac axis according to pathology.***

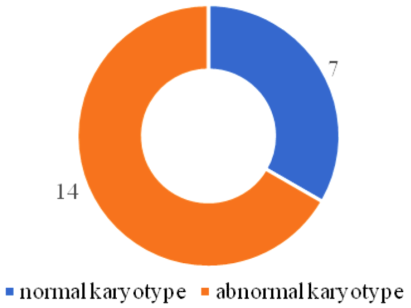

Figure 4 – ***Distribution of cases according to genetic testing.***

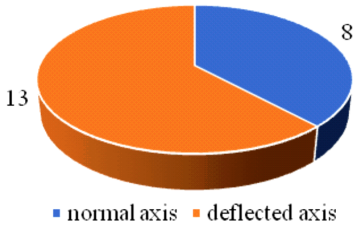

Figure 5 – ***Cases with deviated heart axis in the group with cardiac abnormalities.***

If we evaluate the accuracy of the method for detecting cardiac abnormalities, taking into account the false positive diagnosis of congenital diaphragmatic hernia, we obtain a method sensitivity of 72.41%, 95% confidence interval (CI) 52.76–87.27, a specificity of 50%, 95% CI 1.26–98.74, with a positive predictive value of 83.76%, 95% CI 83.76–98.84 and a negative predictive value of 11.11%, 95% CI 2.7–36.05, accuracy being 70.97%, 95% CI 51.96–85.78 (Table 1).

Table 1 – ***Accuracy of cardiac axis assessment in the diagnosis of congenital cardiac abnormalities***

Accuracy	Sensitivity	Specificity	Positive predictive value	Negative predictive value
70.97%	72.41%	50%	83.76%	11.11%
95% CI 51.96–85.78	95% CI 52.76–87.27	95% CI 1.26–98.74	95% CI 83.76–98.84	95% CI 2.7–36.05

CI: Confidence interval.

We obtained the following values of the angles of the cardiac axis in the fetuses with cardiac abnormalities, the average 61.62º and 33.22º (range 5–110º) (Table 2), of these nine (69.23%) presented the left axis deviation and four (30.76%) the right axis deviation.

Table 2 – ***Cardiac axis in fetuses with major cardiac abnormalities***

Left turn	Right turn
No. (%)	*No (%)*
9 (69.23%)	4 (30.76%)

Further, the association between the cardiac deflected axis and the nuclear translucency has been increased with regard to the diagnosis with congenital cardiac abnormalities, following the analysis, it can be found that in the case of my subgroup there is an abnormal cardiac axis (71%) at that time, when translating an enlarged walnut (28%) (Table 3).

Table 3 – ***Association between deviated cardiac axis and nuchal translucency in fetuses with cardiac abnormalities***

No. of cases in the group with cardiac abnormalities	Nuchal translucency >95th percentile	Cardiac axis deviated	*p*-value
	No. (%)	*No. (%)*	
21	6 (28.56%)	13 (61.9%)	0.0046

From this data analysis, it is shown that cardiac axis measurement is a better method for detecting cardiac abnormalities than the measurement of nuchal translucency (Figure 6).

Comparative evaluation of data on tricuspid regurgitation and cardiac axis deviated reveals a percentage of 19% (4/21) of fetuses who had tricuspid regurgitation, compared to 13/21 (62%) who had an abnormal cardiac axis (Table 4).

Table 4 – ***Association between deviated cardiac axis and tricuspid regurgitation in fetuses with cardiac abnormalities***

No. of cases in the group with cardiac abnormalities	Tricuspid regurgitation	Cardiac axis deviated	*p*-value
	No. (%)	*No. (%)*	
21	4 (19.04%)	13 (61.9%)	0.0003

Thus, cardiac axis assessment is a more reliable measure for detecting major cardiac abnormalities compared to evaluating the existence of tricuspid regurgitation (Figure 7).

We analyzed and compared the association between congenital cardiac abnormalities and the presence of abnormal flow at the level of the venous duct with the frequency of occurrence of deviation of the fetal cardiac axis, in the studied group being observed three cases with wave A reversed on the venous duct (14.28%), compared with 13 cases with shaft deflected (Table 5).

Table 5 – ***Association between deviated cardiac axis and abnormal flow on the venous duct in fetuses with cardiac abnormalities***

No. of cases in the group with cardiac abnormalities	A negative wave on venous duct	Cardiac axis deviated	*p*-value
	No. (%)	*No. (%)*	
21	3 (14.28%)	13 (61.9%)	0.0001

From the analysis performed, the wave A reversed in the venous duct is less reliable than the measurement of the cardiac axis for the detection of congenital heart malformations (Figure 8).

The presence of abnormal flow in the fetal venous duct is less specific for the existence of a congenital cardiac anomaly than the measurement of the cardiac axis.

From the analyzed data, it is found that the measurement of the cardiac axis angle is much more reliable for the detection of fetal cardiac abnormalities than the measurement of the nuchal translucency, the evaluation of tricuspid regurgitation and the flow in the venous duct.

There were 13 cases of cardiac abnormalities that showed deviation of the cardiac axis, the types of abnormalities were: complete atrioventricular septal defect, tetralogy of Fallot, common arterial trunk, right ventricle with double exit pathway, aortic arch interrupted, hypoplastic left heart syndrome, tricuspid atresia, double aortic arch (Table 6).

Table 6 – ***Types of cardiac abnormalities associated with abnormal cardiac axis***

Cardiac anomaly type	Abnormal cardiac axis (No. of cases)
Complete atrioventricular septal defect	1
Tetralogy of Fallot	2
Common arterial trunk	2
Right ventricle with double exit pathway	1
Aortic arch interrupt	2
Hypoplastic left heart syndrome	2
Tricuspid atresia	1
Aortic stenosis	1
Double aortic arch	1
Total	13

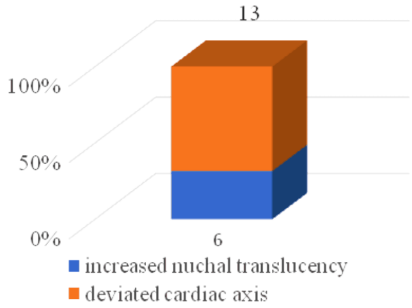

Figure 6 – ***Increased nuchal translucency distribution and deviated cardiac axis in the group with cardiac abnormalities.***

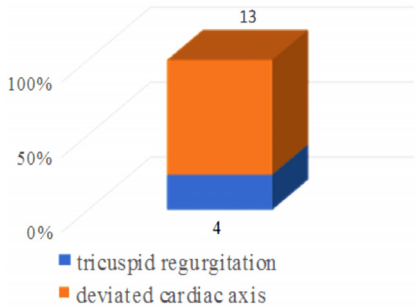

Figure 7 – ***Distribution of tricuspid regurgitation and deviated cardiac axis in the group with cardiac abnormalities.***

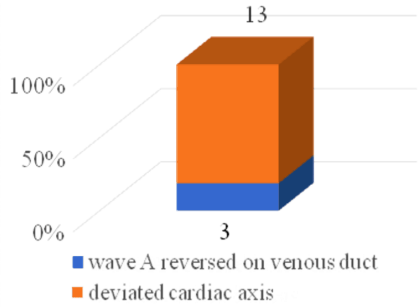

Figure 8 – ***Distribution of abnormal flow on venous duct and deviated cardiac axis in the group with cardiac abnormalities.***

Discussions

With the advancement of technology and the emergence of high-resolution US, prenatal diagnosis of most congenital cardiac abnormalities with high accuracy becomes possible. The four-chamber section has long been included in US screening in both the second trimester.

According to data from published studies, only assessing the heart in the four-chamber section can detect 60% of major cardiac abnormalities, and viewing an abnormal four-chamber section requires later echocardiography during pregnancy [13, 14].

Recently, this section was introduced as a method of cardiac screening in the first trimester of pregnancy [15, 16].

Also, the cardiac axis, has been intensively studied in the past as a method of detecting cardiac abnormalities in the second trimester, but has lost value with the new possibilities of US [17–20].

The current trend is to make a diagnosis with the highest accuracy in the first trimester of pregnancy, which is why some studies have appeared [21, 22], which have published data on the usefulness of measuring the angle of the heart axis in the first trimester US.

The values of the cardiac axis obtained from the measurements made in our study are in accordance with those published in the previous studies, the normal values being considered to be between 30º and 60º.

We obtained values indicating the deviation of the cardiac axis in the case of complete atrioventricular septal defects, tetralogy of Fallot, common arterial trunk, right ventricle with double exit pathway, interrupted aortic arch, left hypoplastic heart syndrome, tricuspid atresia, double aortic arch, abnormalities that have also been reported in studies published in the literature that state that they may be associated with deviations of the cardiac axis [17, 18].

According to the study published by Wiechec *et al.* [15], in 2015, we can detect 47.71% of the major cardiac anomalies using the four-chamber section in the first trimester of pregnancy and if we add the three-vessel and trachea section, we can increase the detection rate to 88.57%. But, the section of three vessels and trachea requires an examiner with experience in the first trimester US, a fact confirmed and considered in the practice guides adopted by most countries, where this incidence is mentioned as optional and not obligatory, as is the one four rooms.

Thus, these sections will be evaluated mainly by those with an over-specialization of maternal–fetal medicine and not by all those who carry out first-trimester screening, which are in fact the first line in the detection of fetal and cardiac abnormalities in particular, after which the cases considered abnormal are sent to specialized maternal and fetal medicine centers.

Because of this, we actually need markers that can be quantitatively quantified, can be easily highlighted and do not require the evaluation of additional sections than those recommended by the good practice guides, so not evaluating them will not significantly extend the examination time.

Published studies, as well as a meta-analysis, show that increased nuchal translucency in fetuses with normal karyotype is associated with an increased risk of structural

abnormalities, most commonly major cardiac abnormalities [19]. In our study, we obtained a prediction rate for cardiac abnormalities of the nuchal translucency increased over the 95th percentile of 28.5%, a value well below that published in studies 63.3%, but this is because the studies reported the rate of prediction only in fetuses with normal karyotype and we evaluated data on fetuses diagnosed with congenital heart abnormalities.

In recent years, studies have also been published regarding the detection rate of cardiac abnormalities using indirect markers, tricuspid regurgitation and inverted wave at the level of the venous duct, these having a reported prediction rate of 32.9% and 28.2% respectively, with a false positive rate of 1.3% and 2.1% [23–28].

The data obtained show a prediction rate for cardiac malformations of the presence of tricuspid regurgitation of 19.04%, and for the wave reversed at the level of the venous duct, we had a prediction rate of 14.28%.

Assessing the contribution of cardiac axis measurement to the prediction of congenital cardiac abnormalities, we obtained an accuracy of 70.97%, 95% CI 51.96–85.78, a method sensitivity of 72.41%, 95% CI 52.76–87.27, a specificity of 50%, 95% CI 1.26–98.74, with a positive predictive value of 83.76%, 95% CI 83.76–98.84 and a negative predictive value of 11.11%, 95% CI 2.7–36.05.

After comparing the data obtained by calculating the prediction rate for cardiac abnormalities using separately the increased nuchal translucency, above the 95th percentile, the presence of tricuspid regurgitation and the inverted wave at the venous duct interrogation, with the rate prediction of the fetal cardiac axis angle: we obtained the following results: (*i*) cardiac axis measurement is a better method for detecting cardiac abnormalities than measuring nuchal translucency; (*ii*) cardiac axis evaluation is a better measure for detecting major cardiac abnormalities compared to evaluating the existence of tricuspid regurgitation; (*iii*) a wave reversed in the venous duct is less reliable than the measurement of the cardiac axis for the detection of congenital heart malformations.

The occurrence of cardiac axis deviation has been reported to be dependent on the type of congenital cardiac abnormality, being more commonly encountered in fetuses with conotruncal abnormalities or complex cardiac malformations and in our study, the conotruncal anomalies predominated, being in accordance with the studies published in the literature [18].

Conclusions

Cardiac axis angle measurement is a reliable marker for the detection of congenital cardiac abnormalities in the first trimester of pregnancy. The cardiac axis is easy to measure, from the standard section and does not imply an increase in the duration of the examination, as no additional sections are required in comparison with the present guidelines. The cardiac axis has a higher value for the detection of congenital cardiac abnormalities with respect to the nuchal translucency, tricuspid regurgitation and wave A reversed at the level of the venous duct. This evaluation can be used as an indirect marker valuable for the detection of numerical chromosomal abnormalities, because almost half of the aneuploids also associate cardiac abnormalities.

Conflict of interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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Received: January 17, 2020

Accepted: May 19, 2020