ORIGINAL ARTICLE

BRAZILIAN JOURNAL OF ULTRASONOGRAPHY 2022; 32: 14-19 - DOI - 10.29327/261922-2

PRENATAL DIAGNOSIS OF CONGENITAL HEART DEFECT IN TWINS - EXPERIENCE OF A FETAL MEDICINE REFERENCE SERVICE

LUCIANE RAMOS VIEIRA[1], JORGE ALBERTO BIANCHI TELLES[2], ANDRÉ CAMPOS DA CUNHA[2], BIBIANA DE BORBA TELLES[1], RODRIGO DA SILVA BATISTI[1], RAFAEL FABIANO MACHADO ROSA[1]

ABSTRACT

OBJECTIVE: Congenital heart defects represent the most frequent malformation at birth. In twin pregnancies, specific findings increase the risk of cardiac complications for the fetus. Due to the scarcity of data on Brazilian patients, the objective was to determine the incidence of cardiac alterations and their associations in this sample.

METHODS: Observational, cross-sectional and retrospective study in a public hospital. Multiple pregnancies were evaluated through the application of a clinical protocol with data collection from the medical records of patients treated at a reference Fetal Medicine Service in southern Brazil from November 2008 to September 2019

RESULTS: 225 multiple pregnancies were included, of which 221 (98.2%) occurred spontaneously. Maternal mean age 27.5 (+or- 6.5) years. Median of 2 previous pregnancies. Most pregnancies were two fetuses (96.4%), dichorionic (64%) and diamniotic (93.3%). In 157 pregnancies (69.8%), the diagnosis of twins was made in the first trimester. Fetal echocardiography was performed in 56.9% of pregnancies. Heart defects were classified according to Botto et al. Cardiac alterations occurred in nine pregnancies (7%). Most pregnancies ended preterm (65%)

CONCLUSIONS: It is necessary to recognize multiple pregnancy as a high-risk situation for fetal cardiac compromise and, from there, to increase the awareness of the general population and health professionals about the importance of prenatal diagnosis of congenital heart disease in these situations.

KEYWORDS: TWINS, FETAL HEART, PREGNANCY, CONGENITAL HEART DEFECTS, PRENATAL CARE

INTRODUCTION

Congenital heart diseases represent the most frequent malformation at birth and are the main cause of death from a congenital defect in childhood [1-3].

In twin pregnancies, in addition to the occurrence of structural heart diseases, other particularities are observed that increase the risk of cardiac involvement, such as: diagnosis of heart disease in one of the conceptuses increasing the risk of the other twin, functional alterations secondary to monochorionic pregnancy and imperfect twinning with cardiac involvement [4,5].

While non-cardiac congenital malformations can be suspected on obstetric ultrasound, most congenital heart defects are diagnosed after birth. Newborns with critical heart disease, characterized by ductus arteriosus dependence, present early decompensation, with cyanosis, metabolic acidosis and death within a few hours [1-3].

These alterations have high morbidity and mortality which, associated with the difficulty in accessing specialized services, characterizes a serious public health problem, both in Brazil and in other less developed countries [3,6].

The association between twins and congenital heart disease is established, as well as the variation in the incidence of twins among different ethnicities [7,8]. However, Brazilian studies are needed to demonstrate the correlation between twins and cardiac involvement in this population.

OBJECTIVE

The association between twins and cardiac involvement results in high morbidity and mortality for the conceptuses. Due to the scarcity of data in the Brazilian population, the objective was to evaluate the incidence of cardiac alterations and their associations in the prenatal period in twin pregnancies in southern Brazil, as well as to evaluate the indication for fetal echocardiography.

METHODS

This is an observational, cross-sectional and retrospective study carried out in a public fetal medicine service.

Patients with twin pregnancies referred by the munici-

1. Universidade Federal de Ciências da Saúde de Porto Alegre (UFCSPA), Porto Alegre, RS
2. Medicina Fetal do Hospital Materno Infantil Presidente Vargas (HMIPV), Porto Alegre, RS

MAILING ADDRESS
JORGE ALBERTO BIANCHI TELLES
Rua Desembargador Moreno Loureiro Lima, 195 / 1201,
Bairro Bela Vista, CEP 90450-130, Porto Alegre-RS
E-mail: jorge@telles.med.br

palities of Rio Grande do Sul and attended in the prenatal period at Hospital Materno Infantil Presidente Vargas, a reference public service of Fetal Medicine in southern Brazil. Clinical protocols were applied with data collection from the pregnant women's medical records. The inclusion of cases followed the following criteria: Multiple pregnancies attended at this service from November 2008 to September 2019. Patients who presented incomplete medical records were excluded from the study.

This study was approved by the Ethics Committee of Hospital Materno-Infantil Presidente Vargas and Universidade Federal de Ciências da Saúde de Porto Alegre under protocol number 2.465.950. All procedures involved in this study are in accordance with the Declaration of Helsinki of 1975, updated in 2013.

The clinical protocol considered the following variables: maternal age at pregnancy, number of previous pregnancies, number of fetuses, spontaneous twin pregnancy or use of "in vitro fertilization" (IVF), chorionicity, amnionicity, obstetrical gestational age at the time of the diagnosis of twins, obstetric gestational age at delivery, fetal echocardiography, diagnosis of heart disease, preterm delivery and fetal death.

STATISTICAL ANALYSIS

Data was entered into the Excel program and later exported to the IBM SPSS version 20.0 program for statistical analysis. Categorical variables were described by frequencies and percentages. The normality of quantitative variables was evaluated using the Kolmogorov-Smirnov test. Quantitative variables with normal distribution were described by the mean and standard deviation and those with asymmetric distribution by the median and the interquartile range (25th and 75th percentiles)

RESULTS

Data were collected from 225 patients, with a mean age of approximately 28 years. The median number of previous pregnancies was two pregnancies. Table 1 presents the characteristics of the sample.

Characteristics	Evaluated number	Descriptive measures
Pregnant woman's age in years, mean±SD	225	27.5±6.5
Number of pregnancies, median (IQR)	225	2 (1-3)
Diagnosis age of twin pregnancy, median (IQR)	225	11 (8-15)
Absolute gestational age at birth, median (IQR)	225	36 (34-37)
Preterm		145 (65.0)
Term		78 (35.0)
Death Absolute gestational age, mean±SD	22	23.2±8.4

SD: standard deviation; IIQ: interquartile range (25th and 75th percentiles)

Tabela 1 - Características das pacientes.

Regarding the characteristics of pregnancy, most were two fetuses, dichorionic and diamniotic. In eight cases, spontaneous triplet pregnancy occurred. In 221 of the 225 pregnancies, spontaneous multiple pregnancy occurred. In the four cases in which pregnancy occurred through "in vitro" fertilization, these were paid for by the Unified Health System (SUS) in the following situations: after tubal ligation, after bilateral oophorectomy, female homosexual relationship, HIV serodiscordant couple (seropositive man) and resulted in diamniotic dichorionic pregnancies.

In this study, two cases of imperfect twins and two pregnancies with an acardiac fetus were recorded.

In more than two thirds of the sample, the diagnosis of twins was made in the first trimester.

Other characteristics are presented in Table 2.

Characteristic	Evaluated	n(%)
Absolute number of fetuses in the current pregnancy	225	
2 fetuses		217 (96,4)
3 fetuses		8 (3,6)
Chorionicity	225	
Monochorionic		77 (34,2)
Dichorionic		144 (64,0)
Trichorionic		4 (1,8)
Amnionicity	225	
Monoamniotic		7 (3,1)
Diamniotic		210 (93,3)
Triamniotic		8 (3,6)
Acardiac fetus twinning	225	2 (0,9)
Imperfect twinning	225	2 (0,9)
Gestational age at diagnosis of twin pregnancy	225	
First trimester		157 (69,8)
Second trimester		66 (29,3)
Third trimester		2 (0,9)

Table 2 - Table of pregnancy characteristics.

FREQUENCY OF PERFORMANCE OF ECHOCARDIOGRAM

More than 50% of patients underwent a fetal echocardiogram in the second trimester and most were normal. In cases where more than one echocardiogram was performed, the diagnosis remained unchanged in subsequent examinations.

Most pregnancies ended preterm (65% of cases).

One of the fetuses died in 18 pregnancies (8%) and two fetuses died in four pregnancies (1.8%). Deaths occurred in 14 dichorionic and eight monochorionic pregnancies. In the four pregnancies in which both twins died, two were dichorionic-diamniotic and two were monochorionic dichorionic.

Table 3 A and B detail these results.

Echocardiograms	Evaluated number	n(%)
Number of fetal echocardiograms	225	
0 fetal echocardiograms		97 (43,1)
1 fetal echocardiogram		122 (54,2)
2 fetal echocardiograms		4 (1,8)
3 fetal echocardiograms		2 (0,9)
Echocardio fetus 1	128	
Normal fetal echocardio		122 (95,3)
Altered fetal 1 echocardio		4 (3,1)
Imperfect twins		1 (0,8)
Acardiac fetus		1 (0,8)
Echocardio fetus 2	128	
Normal fetal echocardio		121 (94,5)
Altered fetal 2 echocardio		4 (3,1)
Imperfect twins		1 (0,8)
Acardiac fetus		1 (0,8)
Death fetus 2		1 (0,8)
Echocardio fetus 3	128	
Normal fetal echocardio		4 (3,2)
There is no fetus 3		124 (96,8)
Trimester of performance of the first echocardiogram	128	
Second trimester		71 (55,5)
Third trimester		57 (44,5)

Table 3A - Descriptive table of gestational echocardiograms.

Echocardiograms and evolution	Evaluated number	n(%)
Prenatal congenital heart disease	128	9 (7)
Group classification according to Botto		9 (7)
Heterotaxis		1 (11,1)
Right-sided obstructive defects		1 (11,1)
Left-sided obstructive defects		1 (11,1)
Septal Defects		5 (55,6)
Other major heart defects		1 (11,1)
Classification Type according to Botto		9 (7)
Heterotaxis		1 (11,1)
Tricuspid atresia		1 (11,1)
Left heart hypoplasia		1 (11,1)
Ventricular Septal Defect		5 (55,6)
Other Major Heart Defects		1 (11,1)
Fetal death	225	
Yes		22 (9,8)
No		201 (89,3)
Acardiac fetus		2 (0,9)

Table 3B.- Table of altered fetal echocardiograms and deaths.

In the evaluation of fetal echocardiograms, the following findings were observed:

Nine pregnancies (7%) had fetal heart disease, and in seven only one fetus was affected. In two pregnancies, both fetuses had heart disease (one with concordant and one discordant congenital heart disease), totaling 11 affected fetuses.

In two pregnancies (0.9%) there was twin reversed arterial perfusion (TRAP) / acardiac fetus with a viable twin without signs of cardiac involvement.

Figure 1 illustrates the case of feto-fetal transfusion syndrome in which the recipient fetus presented pathological tricuspid regurgitation (-90cm/s) on pulsed Doppler, evidencing fetal heart failure.

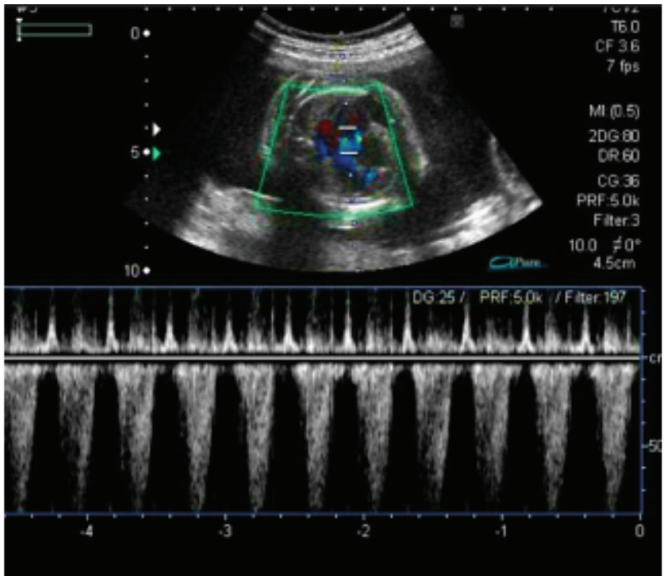

Figure 1. Recipient fetus presents pathological tricuspid valve regurgitation.

In cases of imperfect twinning, thoracopagus twins had complex heart disease, sharing pericardium and atrial wall. Imperfect pygopagus twins did not show cardiac involvement. Figure 2 shows a fetal echocardiogram performed on thoracopagus twins which on color Doppler examination demonstrates flow through the four atrioventricular valves of both fetuses.

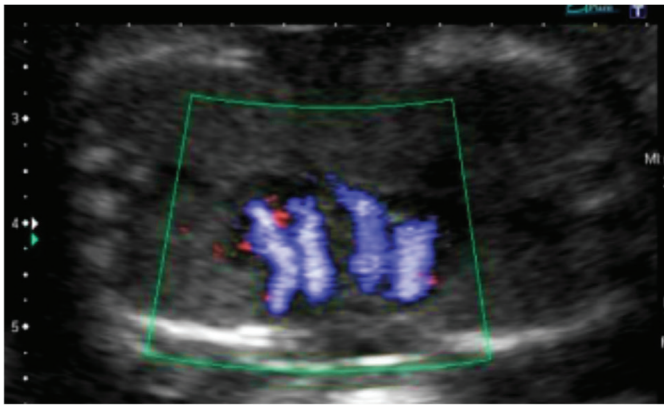

Figure 2. Color Doppler on atrioventricular valves in thoracopagus twins.

As for chorionicity and amnionicity among fetuses with heart disease, we had the following distribution: one monochorionic-monoamniotic pregnancy, four monochorionic-diamniotic pregnancies and four dichorionic-diamniotic pregnancies

DISCUSSION

In the last two decades, there has been an increase in the

frequency of multiple pregnancies associated with advanced maternal age and the use of assisted reproduction techniques. Factors such as ethnicity, frequency variation over time, parity, nutritional status and use of ovulation inducers, have also been associated, as reported in countries such as the United States, Austria, Finland, Norway, Sweden, Canada, Australia, Hong Kong. , Israel, Japan and Singapore [9].

The Brazilian medical literature is scarce regarding the characteristics of twin pregnancies.

Initially, there is a need to know the epidemiological profile of twin pregnancies in the public service in our country, as well as the characteristics of prenatal care offered. In this study, the mean maternal age was 27.5 years and most twin pregnancies occurred spontaneously, without reproductive techniques, unlike international studies.

The performance of obstetric ultrasound before thirteen weeks and six days is of great value in twin pregnancies. Through this test, it is possible to reliably calculate the gestational age and identify chorionicity and amnionicity, significantly impacting the follow-up of twin pregnancy[10].

In our work, we evaluated structural congenital heart diseases.

In singleton pregnancies, these same heart diseases are six times more frequent than chromosomal disorders and four times more frequent than neural tube alterations. Its incidence varies between 0.8% in developed countries and 1.2% in underdeveloped countries[11]. In our study, an incidence of 7% of congenital heart disease (CHD) was recorded in multiple pregnancies.

In Belgium, there was an incidence of 8.3% of CHD in live births and stillbirths with a gestational age equal to or greater than 26 weeks without chromosomal alterations[12]. The fetal incidence of CHD varies between different studies and ethnicities. This has led to different guidelines regarding the forms of diagnosis and policies to improve access to treatment, especially in less developed countries. In population studies, the frequency of diagnosis of CHD ranges from 8.5% to 25%. Due to the complexity and cost of the fetal echocardiogram exam, the identification of risk factors is crucial for its indication[13]. According to Donofrio et al, in a study published in 2014, the risk of heart disease among siblings is greater than the risk of incidence when one of the parents is affected. This study reinforces the indication of fetal echocardiography in twin pregnancies.

In our study, nine pregnancies (7%) had congenital heart disease, and in seven they affected a fetus. In two pregnancies, both fetuses had congenital heart disease, one pregnancy with concordant and one discordant congenital heart disease, totaling 11 fetuses with congenital heart disease. As for chorionicity and amnionicity among fetuses with heart disease, we had the following distribution: one monochorionic-monoamniotic pregnancy (imperfect twinning), four monochorionic-diamniotic pregnancies and four dichorionic-diamniotic pregnancies.

According to Herskind, in a study published in 2013, evaluating a sample of 41,525 twins in Denmark, there was an increase in the incidence of congenital heart disease in both monozygotic and dizygotic twins compared to single twins [14].

In Brazil, most of the population with congenital heart disease is assisted by the Unified Health System (Sistema Único de Saúde - SUS). It is estimated that 20-30% of patients with congenital heart disease have complex heart disease and of these, 2-3% die in the neonatal period. Approximately 30% of newborns with critical heart disease are discharged from the hospital without a diagnosis and progress to shock, hypoxia and early death, before receiving adequate treatment[15].

Patients with acyanotic heart disease with increased pulmonary blood flow undergo definitive surgical correction in the first years of life. Patients with critical heart disease, after palliative procedures in the first month of life, need staged, palliative or corrective surgical correction. These corrections eventually present residual defects, which lead to the need for new procedures throughout life, with indication for heart transplantation in some cases[15].

When evaluating the association between congenital heart disease and twins, it is recognized that structural heart diseases are more common in monochorionic pregnancies, with a prevalence of 7.5%, increasing to 25% risk when a twin is affected. Although controversial, there are studies suggesting that twins conceived by assisted fertilization have an increased risk of heart disease, regardless of chorionicity. In our study, the incidence of structural heart disease was equal between monochorionic and dichorionic pregnancies. In in vitro fertilization pregnancies, no heart disease was recorded. In monochorionic, diamniotic pregnancies, the most frequent lesion is ventricular septal defect, although all lesions are present with agreement in 25-46% of cases. In monoamniotic monochorionic pregnancies, the risk is even greater for all types of heart disease, including changes in laterality and heterotaxis[5]. In the same case series study, published by Weber and Sebire in 2010, one third of the cases presented heterotaxy[5]. In imperfect twins, thoracopagus are the most common type, occurring in 40% of cases and cardiac involvement is more common, with 90% sharing the pericardium and 75% having structural heart disease. Heart disease is also present in other forms of imperfect twins, which influences the feasibility of postnatal separation. Laterality is altered in thoracopagus and parapagus (side by side). Imperfect twins mainly affect girls at a ratio of 3:1 [5,16]. In our study, we observed two cases of imperfect twins (0.9%), being one case of pygopagus, without cardiac involvement and one case of thoracopagus with complex heart disease, characterized by sharing the pericardium and atrial wall.

As for the typical alterations of twin pregnancies, it is important to emphasize that all monochorionic conceptuses have transamnionic connections. These anastomosis can be of three types: arteriovenous, venovenous and arterioarterial. The imbalance between these communications results in the feto-fetal transfusion syndrome and, in extreme cases, culminates in the reversed arterial fetal perfusion sequence,

also called TRAP (Twin reversed arterial perfusion) or fetal acardia. In our sample, there were two cases of TRAP (0.9%), and the viable fetuses did not present heart disease in any of the cases[4].

Twin pregnancies have an increase in maternal complications when compared to singleton pregnancies: increased risk of pulmonary edema, hypertensive diseases, preeclampsia and eclampsia, altered liver function and platelet count, uterine overdistention with urinary tract compression, diabetes mellitus, kidney and heart failure, infection, respiratory distress, placental abruption, premature rupture of membranes, preterm labor and preterm delivery. In relation to the fetus, there is a greater risk of prematurity, intrauterine growth restriction, feto-fetal transfusion syndrome and extra-cardiac malformations, with low birth weight and prematurity being largely responsible for morbidity and mortality [9,10,17]. In the indication of the mode of delivery, the predominance of cesarean sections is observed. In the postpartum period, there is an increase in the incidence of uterine atony and hemorrhage. The occurrence of maternal death is 2.5 times more frequent in twin pregnancies when compared to singleton pregnancies[18].

According to Beiguelman and Franchi-Pinto, in a study carried out in Campinas, São Paulo, involving 116,699 deliveries, published in 2000, despite the incidence of twins of 0.9%, 10.7% of early neonatal deaths and 3.5% of all stillbirths were twins [19].

The postnatal evolution of twins presents particularities in relation to single fetuses, due to the increased risk of prematurity and its consequences, such as increased morbidity and mortality[20]. Premature or preterm births are defined as births that occur before 37 weeks of gestation. Worldwide, around 15 million children are born with this condition each year, accounting for 11.1% of births according to the World Health Organization (WHO). Preterm labor, premature rupture of membranes, induction of labor due to maternal or fetal causes are some of the related causes [21,22]. The WHO considers prematurity as a global problem and Brazil is among the 10 countries with the highest rates, which are responsible for 60% of premature births in the world. In 2018, prematurity remained the leading cause of death for children under five. In Brazil, neonatal mortality accounts for almost 70% of deaths in the first year of life, and newborn care remains challenging [23].

When performing the fetal echocardiogram, the time and place for termination of pregnancy in fetuses affected by cardiac alteration can be more securely defined. The diagnosis of cardiovascular alterations in twin pregnancies can be performed even in the intrauterine period, and its identification allows these patients to be referred during pregnancy to reference services, thus receiving adequate follow-up and treatment, avoiding neonatal complications and improving the prognosis. .

In this study, we recorded a 65% incidence of premature births. In pregnancies with fetuses with critical heart disease, in our country, elective cesarean section is indicated, allowing the team, including neonatologists, pediatric cardiologists and pediatric hemodynamicists, to prepare to receive the newborn.

In this study, we emphasize the association between prematurity, twins and heart disease in the population of southern Brazil.

In Brazil, in 2016, Salim et al, published a population-based study evaluating mortality from malformations of the circulatory system in children and adolescents in the state of Rio de Janeiro. Among the 115,728 deaths that occurred between 1996 and 2012, mortality from malformation of the circulatory system was 7.5/100,000 in males and 6.6/100,000 in females. In this study, acquired diseases of the circulatory system and malformations of the circulatory system were evaluated separately. Regarding the higher mortality rate from malformations of the circulatory system, these are described as unspecified malformations of the circulatory system in all ages and sex. It was concluded that these are more marked in the first years of life, while diseases of the circulatory system are more relevant in adolescents. Limited access to prenatal care and adequate birth conditions probably make it impossible to adequately treat these pathologies [24].

According to Gomes et al, in 2013, the deficit of pediatric cardiac surgery in Brazil was 65%, which reinforces the need for early diagnosis for adequate and timely treatment[6]. In 2017, the Ministry of Health, through the publication of the "Synthesis of evidence for health policies: Early diagnosis of congenital heart diseases" reviews actions that allow the early diagnosis of critical heart diseases, emphasizing the importance of performing obstetric ultrasound, fetal echocardiography, neonatal pulse oximetry and neonatal echocardiogram[25].

CONCLUSION

We are aware of possible biases related to retrospective studies and the sample of a reference service. However, we believe that, based on these data, it is possible to outline strategies that favor the early diagnosis of congenital heart diseases in multiple pregnancies, leading to adequate clinical management and referral to specific services in situations that require interventional treatments available in the Brazilian reality. Such measures allow greater effectiveness, reducing morbidity and mortality.

We believe that it is necessary to recognize multiple pregnancy as a risk situation for fetal cardiac involvement and, from there, to raise the awareness of health professionals about the importance of prenatal diagnosis of congenital heart disease in this situation.

REFERENCES

01. Silva JN, Trevisan V, Zen TD, Rosa EB, Silveira DB, Varella-Garcia M, et al. Congenital heart disease in Southern Brazil: potential impact and prevention. Int J Cardiol 2015; 179:9-10.

02. Lopes SAV, Costa SFO, et al. Mortalidade para cardiopatias congênitas e fatores de risco associados em recém-nascidos. um estudo de coorte. Arq Bras Cardiol 2018; 111(5):666-673.

03. Cucu IA, Chifiriuc MC. Congenital heart disease: global burden and challenges to eliminate health disparities. Ann Public Health Reports 2018; 2(1):26-29.
04. Manning N. The influence of twinning on cardiac development. Early Hum Dev 2008; 84(3):173-179.
05. Weber MA, Sebire NJ. Genetics and developmental pathology of twinning. Semin Fetal Neonatal Med 2010; 15(6):313-318.
06. Gomes WJ, Nogueira AJS, Jatene FB, Wanderley Neto J, Mulinari LA, Caneo LF, et al. A dívida com a saúde da nação: o caso das cardiopatias congênitas. Revista Brasileira de Cirurgia Cardiovascular 2013; 28(2):VI
07. Tong S, Short RV. Dizygotic twinning as a measure of human fertility. Human Reproduction 1998; 13 (1):95-98.
08. Mahle WT. What we can learn from twins congenital heart disease in the Danish twin registry. Circulation 2013; 128:1173-1174.
09. Chauhan SP, Scardo JA, Hayes E, Abuhamad AZ, Berghella V. Twins: prevalence, problems, and preterm births. Am J Obstet Gynecol. 2010; 203(4):305-315.
10. Khalil A, Rodgers M, Baschat A, et al. ISUOG Practice Guidelines: role of ultrasound in twin pregnancy. Ultrasound Obstet Gynecol. 2016; 47(2):247-263.
11. Rocha LA, Júnior EA, Rolo LC, Barros FSB, Silva KP, Stochero ATF. Prenatal detection of congenital heart diseases: one-year survey performing a screening protocol in a single reference center in Brazil. Cardiology Research and Practice 2014; Article ID 175635:5 pages.
12. Donofrio MT, Moon-Grady AJ, Hornberger LK, Joshua A Copel, Mark S Sklansky, Alfred Abuhamad, et al. Diagnosis and treatment of fetal cardiac disease: a scientific statement from the American Heart Association. Circulation 2014; 27;129(21):2183-2242
13. Bahtiyar MO, Dulay AT, Weeks BP, Friedman AH, Copel JA. Congenital heart defects in monochorionic/diamniotic twin gestations. J Ultrasound Med 2007; 26:1491-1498.
14. Herskind AM, Pedersen DA, Christensen K. Increased prevalence of congenital heart defects in monozygotic and dizygotic twins. Circulation 2013; 128:1182-1188.
15. Pavão TCA, Souza JCB, Frias LP, Silva LDC. Early diagnosis of congenital heart disease: an integrative review. J Manag Prim Health Care 2018; 9:e10.
16. Tannuri AC, Batatinha JAP, Velhote MCP, Tannuri U. Conjoined twins – twenty years' experience at a reference center in Brazil. Clinics 2013; 68(3):371.
17. Diretriz Associação Médica Brasileira. Via de parto na gestação gemelar. https://amb.org.br/files/_DIRETRIZES/via-de-parto-em-gestacao-gemelarfilesassets/common/downloads/publication.pdf, acessado dia 28 Fevereiro de 2022.
18. Santana D, Surita F, Cecatti J. Multiple pregnancy: epidemiology and association with maternal and perinatal morbidity. Rev. Bras. Ginecol. Obstet. 2018; 40(9):554-562.
19. Beiguelman B, Franchi-Pinto C. Perinatal mortality among twins and singletons in a city in southeastern Brazil, 1984-1996. Genetics and Molecular Biology 2000; 23(1):15-23.
20. Miyague NI. Persistência do canal arterial em recém-nascidos prematuros. Jornal de Pediatria 2005; 81(6):429-430.
21. Souza RT, Cecatti JG, Passini R Jr, et al. Brazilian multicenter study on preterm birth study group. the burden of provider-initiated preterm birth and associated factors: evidence from the Brazilian Multicenter Study on Preterm Birth (EMIP). PLoS One. 2016; 5;11(2).
22. Atenção à saúde do recém-nascido: Guia para profissionais de saúde. https://bvsms.saude.gov.br/bvs/publicacoes/atencao_saude_recem_nascido_profissionais_v1.pdf, acessado dia 28 Fevereiro de 2022.
23. Oliveira LL, Gonçalves AC, Costa JS, Bonilha AL. Maternal and neonatal factors related to prematurity. Rev Esc Enferm USP. 2016; 50(3):382-389
24. Salim TR, Soares GP, Klein CH, Oliveira GMM. Mortalidade por doenças e malformações do aparelho circulatório em crianças no Estado do Rio de Janeiro. Arq Bras Cardiol 2016; 106(6):464-473.
25. Ministério da Saúde. Síntese de evidências para políticas de saúde. Diagnóstico precoce de cardiopatias congênitas. http://bvsms.saude.gov.br/bvs/publicacoes/sintese_evidencias_politicas_cardiopatias_congenitas.pdf, acessado 8 de Março de 2021.