ORIGINAL

Placenta morphology and biomarkers in pregnancies with congenital heart disease. A systematic review

Morfología de la placenta y biomarcadores en embarazos con cardiopatías congénitas. Una revisión sistemática

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Abstract

Background: Congenital heart defect (CHD) is an influential factor that restricts intrauterine growth. One of the most critical complications in children with CHD is delayed nerve growth, which appears to begin from the fetal period. Delayed fetal neurodevelopment can be associated with or even explained by the impaired placenta in cases of CHD. This systematic study presents a literature review on placental growth with CHD.

Methods: We performed a regular search and used the Newcastle-Ottawa measure to evaluate data quality. Outcomes included size and weight of the placenta, vascular structure, immuno-histo-chemistry, expression of placental genes, and angiogenic biomarkers.

Results: 1308 studies were evaluated, and 21 articles were included. Studies with a genetic abnormality or multiple pregnancies were excluded. CHD cases had a lower weight of the placenta and an increased insertion rate in the umbilical cord. Further, microscopic characteristics of the abnormal placenta showed decreasing and increasing in angiogenic and anti-angiogenic biomarkers, respectively, in maternal serum and umbilical cord blood. The results showed Altered expression of genes affects placental and fetal growth pathways in placental and maternal serum tissues.

Conclusion: placental impairments were found in CHD cases. More researches are required to clarify the role of the abnormal placenta in delayed neurodevelopment.

Key words: Placenta morphology, placenta biomarkers, congenital heart disease, congenital heart defect.

Resumen

Antecedentes: La cardiopatía congénita (CC) es un factor influyente que restringe el crecimiento intrauterino. Una de las complicaciones más críticas en los niños con CC es el retraso en el crecimiento nervioso, que parece comenzar desde el periodo fetal. El retraso del neurodesarrollo fetal puede estar asociado o incluso explicarse por la alteración de la placenta en los casos de CC. Este estudio sistemático presenta una revisión de la literatura sobre el crecimiento de la placenta con la CC.

Métodos: Se realizó una búsqueda periódica y se utilizó la medida Newcastle-Ottawa para evaluar la calidad de los datos. Los resultados incluyeron el tamaño y el peso de la placenta, la estructura vascular, la inmunohistoquímica, la expresión de los genes placentarios y los biomarcadores angiogénicos.

Resultados: Se evaluaron 1308 estudios y se incluyeron 21 artículos. Se excluyeron los estudios con una anomalía genética o con embarazos múltiples. Los casos de CHD presentaban un menor peso de la placenta y una mayor tasa de inserción en el cordón umbilical. Además, las características microscópicas de la placenta anormal mostraron una disminución y un aumento de los biomarcadores angiogénicos y antiangiogénicos, respectivamente, en el suero materno y en la sangre del cordón umbilical. Los resultados mostraron que la expresión alterada de los genes afecta a las vías de crecimiento de la placenta y del feto en los tejidos de la placenta y del suero materno.

Conclusión: se encontraron alteraciones de la placenta en los casos de cardiopatía isquémica. Se requieren más investigaciones para aclarar el papel de la placenta anormal en el retraso del neurodesarrollo.

Palabras clave: Morfología de la placenta, biomarcadores de la placenta, cardiopatía congénita, defecto cardíaco congénito.

Introduction

As a common congenital aberration, congenital heart deficiency (CHD) affects five to eight per thousand infants[1]. CHDs are a significant cause of newborn mortality worldwide, and approximately half of the cases are severe1. However, survival rates of affected infants have improved Due to the continuous growth of ICU-care and cardiothoracic operation. For that purpose, the focus of discovery has turned from improving survival rates to increasing long-term developmental consequences[2]. The neurodevelopmental break has been announced in a significant number of children and adolescents affected with CHD, which is a considerable part of the CHD morbidity[3,4]. Much earlier literature associated this morbidity with the complicated cardiothoracic operation in early life and its adverse effects[3,4]. But more recently, fetal ultrasound and MRI technologies were discovered several impairments in CHDs fetuses and infants before the operation, such as decreasing fetal and newborn head circumference and delaying cortical maturation[3,4]. In addition, intrauterine growth restriction, pre-eclampsia, and pregnancy-induced hypertension have been detected in pregnancies with prenatal CHD[5-7]. Impairment signs in placental growth are detected by increased umbilical artery resistance and decreased global placental perfusion[8]. In prenatal CHD, the increased umbilical artery resistance may correlate with neurodevelopmental consequences and proposes whether this is a potential contributor to damaged neurodevelopment in these pregnancies[9]. The association of placenta features, placental biomarkers, and placental neurodevelopment in CHD remains unclear and has not been investigated accurately. In this systematic and meta-analysis review, a survey of the literature on CHD and placenta biomarkers is presented, intending to examine the use of the placenta biomarkers in the association with CHD and fetal neurodevelopment.

Materials and methods

Search strategy
We conducted a regular search in PubMed, Embase, Google Scholar, and Cochrane on Nov 15th, 2021. The search terms included "congenital heart deficiency," "placenta," "biomarkers," "fetus," "neurodevelopment," "genetic," "angiogenic. We admitted Papers from all years. The entire research sequence was: "Heart Defects", "Placenta"," Fetus"," English".

Study selection
Two independent researchers (MS, MA) screened the title/abstracts and consequently read the full text of selected articles. A third researcher (MH) was helping if there was disagreement. Eligibility criteria for inclusion were: 1) infants with CHD 2) placenta features concerning macroscopic analyses, immunohistochemistry, vascular and villous structure, immunoreactivity, angiogenic

biomarkers, 3) description of placenta characteristics compared with evidence values or a control group. exclusion criteria for studies were: 1) articles associated with CHD and a genetic or syndrome disorder 2) articles associated with CHD and multiple pregnancies 3) articles with less than ten participants.

Assessment of data Quality and extraction
Quality assessment was evaluated utilizing the Newcastle Ottawa Scale (NOS) for estimating the degree of non-randomized studies Quality. Placenta features concerning macroscopic analyses, immunohistochemistry, vascular and villous structure, immunoreactivity, angiogenic biomarkers were extracted and investigated.

Results

Study screening
The performed search find1308 studies. Following title/abstract screening, 125 studies were read the full text, and finally, 18 studies were entered (**Figure 1**)[10-27].

The characteristics of included studies are presented in **table I**. There were differences in the categorization of CHDs types and comparing study groups within included studies (**Table I**).

According to cardiac intervention requirements, CHDs were categorized as full CHD, significant CHD (intervention in the first breath year), or only one specific congenital heart defect. Of the included articles, ten represented macroscopic placenta features, six represented microscopic placenta features, four expressed maternal/umbilical cord angiogenic biomarkers in serum samples, and five described gene expressions in placental tissue/maternal serum.

Assessment of data Quality
Assessing the Quality is presented in **table II**. In this systematic review, the quality ranking of Most included studies was satisfactory. Consistent with the quality grading of studies according to NOS, thirteen studies received five to six stars. However, one study received just one star because of the low cases and inadequate cohort/controls selections. Further, three studies received three stars due to not having a control group for comparing the measurements.

Results of included studies
At the birth time, a decrease in weight and percentiles of the Placenta was seen associated with ventricular septal defect (VSD), Tetralogy of Fallot (ToF), double-outlet right ventricle28, and hypoplastic left heart syndrome (HLHS) (**Table I**)[14]. At 18 and 39 weeks of pregnancy, the smaller volume of the Placenta was associated with CHD cases, but these changes were not statistically significant[13]. It is essential to distinguish

the placenta-to-birthweight rate because placenta weight does not differ between cases with and without intrauterine growth restriction. Five studies that reported conflicting data described the ratio of the placenta to the birth weight as an estimate of placental weight by adjusting for birth weight. Although, four studies detected No significant difference in the placenta-to birthweight rate[16,20,21,27], implying that smaller placentas in CHD only exist in subjects with low birth weight. According to the birth weight of CHD, three studies[19,24,25] reported that the placentas were smaller than anticipated, and there was a significantly lower ratio of placenta-to-birth weight. When CHD placentas are smaller than birthweight, the fetus can attain its growth potential; therefore, the placental preserves the function. Adverse outcomes have been detected for Abnormal umbilical cord insertion, such as intrauterine growth restriction and demise. In one study, 200 CHD cases were evaluated16 that were reported Significantly high percentages of abnormal umbilical cord insertion. However, in two studies that had analyzed, the HLHS

(16 patients) and other types of CHD (32 cases)[14,21], probably due to the small number of inclusions, no high percentages of abnormal umbilical cord insertions were reported. In addition, placental disorders were found less than other macroscopic disorders in major CHD types26. defects in fetal-maternal relations are commonly observed in Histological reports of CHD gestations. Some studies reported the impaired microscopic in HLHS types, which described fibrin deposition and hypoplasia of distal villous, lower vascular area, and membrane counts of vascular-syncytial[14,25]. Subsequently, researchers detected other defects in CHD subjects that were not found in healthy placentae, like thrombosis, choriangiosis, infarction, and impaired maturation of villous[19,21,24,27]. However, the rate of microscopic abnormality in the placental did not show a significant difference between subjects PE, PIH, and IUGR[24]. Placental trophoblasts are responsible for the production of angiogenic biomarkers such as placental growth factor (PlGF) and pregnancy-associated plasma protein-A (PAPP-A)[29,30]. The concentrations of PlGF and

Figure 1: Flow charts for the studies were identified, displayed, and included in the study.
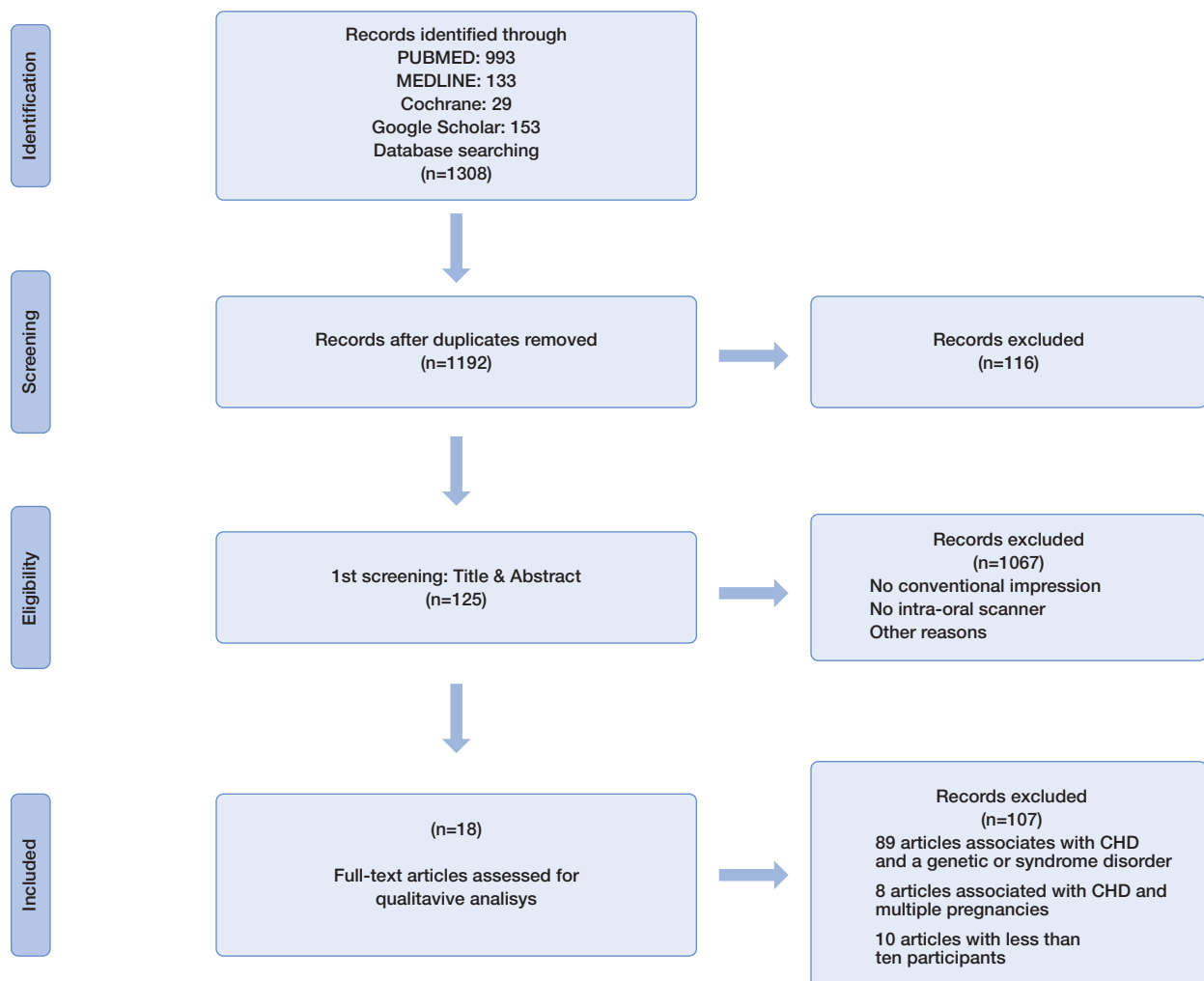
PAPP-A in maternal serum were significantly lower in CHD cases, so the decreased expression of angiogenic biomarkers may cause changes in placental vascular pathways in CHD[11,12,15]. In contrast, the concentrations of anti-angiogenic biomarkers such as fms-like soluble tyrosine kinase-1 (sFlt-1) and soluble endoglin (sEng) in maternal serum and umbilical cord blood were significantly higher in CHD[12]. These findings could explain dysfunction, perfusion, and placental weight loss in CHD cases due to alterations in the expression of these biomarkers. In CHD cases, placental tissue and maternal serum altered functional and developmental gene expression in mRNA levels. Altered expression of developmental genes of trophoblast, placental, and embryonic may indicate a correlation between CHD and genetic expression[10,15,17,22,25].

Table I: Study characteristics of included studies.

Author/year	Study design	Follow up time	Total	Case	Control	CHD type	Conclusion
			Participants (N)				
Ozcan et al, (2021)	R	Post-partum	139	47	92	MCCD	The highest risk is seen in fetal CHD with maternal risk factors
Giorgione et al, (2020)	R	Post-partum	936	480	456	MCCD	Major CHD are significantly associated with the risk of PE, SGA and PTB
Courtney et al, (2020)	R	Post-partum	42	24	18	HLHS	Despite common vascular disturbances in placentas from HLHAs
Schlatterer et al, (2019)	P	Post-partum	51	51	0	All type	These data suggest that placental abnormalities are common in CHD and may have a compounding effect on brain lesions in this high-risk population
Russell et al, (2019)	P	Post-partum	133	133	0	CHD requiring surgery	Damaging variants in proangiogenic genes may impact placental function and are associated with impaired fetal growth in pregnancies involving a fetus with congenital heart defect
Radhakrishna et al, (2019)	P	Post-partum	18	8	10	VSD	This is the first report in which placental analysis has been used for determining the pathogenesis of and predicting VSD
Miremberg et al, (2019)	R	Post-partum	66	32	34	Severe CHD	Placental vascular malperfusion lesions are more common in pregnancies complicated with CHD as compared with CNS malformations
Takemoto et al, (2018)	P	Post-partum	663	37	626	All type	Major anomalies may tend to aggregate in the 90th percentile of the BW/PW ratio
Rychik et al, (2018)	P	Post-partum	120	120	0	All type	Studies investigating the relationship between placental abnormalities and postnatal outcomes may offer insight into the fetal origins of outcome variability in CHD
Morano et al, (2018)	R	Second trimester	40	10	30	VSD	These data confirm previous studies on the specific association of mRNA species and type of congenital heart defect and confirm that ventricular septal defects are associated with abnormal mRNA for the tenascin-X gene
Contro et al, (2017)	R	Second trimester	78	36	42	LVOT	These data suggested that molecular screening of CNTRA and LVOT obstruction in the second trimester is feasible
Curti et al, (2016)	P	Second trimester	70	39	31	All type	These data represent a step forward in the screening of CHDs
Albalawi et al, (2016)	R	Post-partum	400	200	200	CHD requiring surgery	t cord insertion should be evaluated at routine obstetric sonography
Jones et al, (2015)	R	Post-partum	34	16	18	HLHS	Placentas from pregnancies complicated by fetal HLHS are characterized by abnormal parenchymal morphology, suggesting immature structure may be due to vascular abnormalities
Llurba et al, (2014)	P	Post-partum	269	65	204	MCCD	Data suggest that ani imbalance angiogenic-antiangiogenic factors is associated with developmental defects of the human heart
Andescavage et al, (2014)	P	Second trimester	135	41	94	All type	Abnormalities in placental development may contribute to the significant morbidity in this high-risk population. Assessment of placental volume by MRI allows for in vivo assessments of placental development
Llurba et al, (2013)	P	First trimester	408	68	340	MCCD	In pregnancies with isolated fetal heart defects there is evidence of impaired placental angiogenesis in the absence of impaired placental perfusion and function
Arcelli et al, (2010)	R	Second trimester	88	40	48	All type	Altered placental genetic expression was found at term delivery in affected fetuses. The aberration was also confirmed in maternal blood at the second trimester of women bearing a fetus with congenital heart disease

R: Retrospective; MCCD: Major congenital cardiac defects; HLHS: hypoplastic left heart syndrome; P: Prospective; VSD: ventricular septal defects; LVOT: Left Ventricular Outflow Tract

Table II: Quality of included studies based on the Newcastle-Ottawa assessment scale.

	Selection		Comparability	Outcome		
	Representativeness of exposed cohort	Selection of non-exposed cohort	Comparability of cohorts	Assessment of outcome	Adequacy of follow-up	Total score (0-6)
Ozcan (2021)	★	★	★	★	★	5
Giorgione (2020)	★	★	★	★	★	6
Courtney (2020)	★	★	★★		★	5
Schlatterer (2019)	★			★	★	3
Russell (2019)	★			★	★	3
Radhakrishna (2019)	★	★	★★	★	★	6
Miremberg (2019)				★		1
Takemoto (2018)	★	★	★★	★	★	6
Rychik (2018)	★			★	★	3
Morano (2018)	★	★	★★	★	★	6
Contro (2017)	★	★	★★	★	★	6
Curti (2016)	★	★	★★	★	★	6
Albalawi (2016)	★	★	★★	★	★	6
Jones (2015)		★	★★	★	★	5
Llurba (2014)	★	★	★★	★	★	6
Andescavage (2014)	★	★	★★	★		5
Llurba (2013)	★	★	★★	★	★	6
Arcelli (2010)	★	★	★★	★	★	6

Discussion

This systematic study showed an association between CHD disorder and the incidence of weight loss, abnormalities, and altered genes expression in the placenta. Comparable properties were seen in IUGR, PE, and PIH, all of which had abnormal trophoblast invasion and insufficiency in the placenta[25]. Subsequently, in CHD cases, placental defects could reduce oxygen and nutrients between the fetus and mother. Further, In CHD without PE and IUGR, the altered and insufficient placenta was also found. The probable reason for these results could be associated with the altered expression of genes involved in CHD development. In addition, insufficient trophoblast invasion may be responsible for pathological placenta alterations related to the classical defective phenotype.

Altered expression of molecules that affect vascular development can induce vascular changes in the placenta and fetus. Alteration of gene expression at the protein level was reported as having a local or systemic effect on cardiac tissue of the placenta and maternal serum. These findings indicate that alterations in gene expression and affecting cardiac and placental tissue also affect vascular growth pathways in other fetal tissues. Since environmental and genetic predisposition performs a significant function in developing CHD, this disorder is known to have multifactorial features. Epigenetic effects or hypoxic stress on early embryogenesis can explain angiogenic imbalance and vascular formation changes in CHD cases[19,25]. On the other hand, epigenetic changes in CHD may be due to the hemodynamic influences, which affect developmental pathways of vascular and causes alteration in angiogenesis and abnormalities in placental. The results show that the CHD pathogenesis factors can have epigenetic effects on placental tissue[23,25]. Typically, more placental weight loss is seen in CHD cases, so changes in the expression level of angiogenic biomarkers may be associated with the placental size. Further researches are needed to understand better the correlation between angiogenic biomarkers and placental weight in CHD cases. Since placental changes are also observed in cases of CHD without PE and IUGR, it can assume that vascular alterations delay the maturation of the fetal brain and growth in childhood[4]. Therefore, comparing the placental perfusion disorder, vascular genetic pathways, and angiogenic expression in CHD with PE and IUGR. Fetal tissue perfusion and hypoxia can be caused by placental dysfunction and alterations in vascular expression. There were so many issues in the veterinary and public health[31-45], which need additional studies.

Conclusion

The findings of this systematic study reveal an association between CHD cases with lower weight of placenta, macroscopic and microscopic abnormalities of the placenta, altered expression of genetic and angiogenic biomarkers in placental tissue, and maternal serum. These findings indicate defective development of vascular in the placenta and fetus. The neurodevelopmental disorder is also an essential complication of CHD. Thus, more research on impaired placental effects on consequences of these cases is needed in the future. Furthermore, there should be a correlation between morphology and placental function with neurodevelopmental results in the fetus, childhood and adulthood, and hemodynamic consequences of different types of CHD. Finally, the benefits of this information for CHD cases can help develop preventive measures in the entire lifespan.

Conflict of interest
Authors do not have any conflict of interest to declare.

References

1. Hoffman JI, Kaplan S. The incidence of congenital heart disease. Journal of the American college of cardiology. 2002 Jun 19;39(12):1890-900.

2. Tennant PW, Pearce MS, Bythell M, Rankin J. 20-year survival of children born with congenital anomalies: a population-based study. The lancet. 2010 Feb 20;375(9715):649-56.

3. Everwijn SM, Namburete AI, van Geloven N, Jansen FA, Papageorghiou AT, Noble AJ, et al. Cortical development in fetuses with congenital heart defects using an automated brain-age prediction algorithm. Acta obstetricia et gynecologica Scandinavica. 2019 Dec;98(12):1595-602.

4. van Nisselrooij AE, Jansen FA, van Geloven N, Linskens IH, Pajkrt E, Clur SA, et al. Impact of extracardiac pathology on head growth in fetuses with congenital heart defect. Ultrasound in Obstetrics & Gynecology. 2020 Feb;55(2):217-25.

5. Gumusoglu SB, Chilukuri AS, Santillan DA, Santillan MK, Stevens HE. Neurodevelopmental outcomes of prenatal preeclampsia exposure. Trends in neurosciences. 2020 Apr 1;43(4):253-68.

6. Binder J, Carta S, Carvalho JS, Kalafat E, Khalil A, Thilaganathan B. Evidence for uteroplacental malperfusion in fetuses with major congenital heart defects. Plos one. 2020 Feb 5;15(2):e0226741.

7. Sun BZ, Moster D, Harmon QE, Wilcox AJ. Association of preeclampsia in term births with neurodevelopmental disorders in offspring. JAMA psychiatry. 2020 Aug 1;77(8):823-9.

8. Gol S, Pena RN, Rothschild MF, Tor M, Estany J. A polymorphism in the fatty acid desaturase-2 gene is associated with the arachidonic acid metabolism in pigs. Scientific reports. 2018 Sep 25;8(1):1-9.

9. Abeysekera JB, Gyenes DL, Atallah J, Robertson CM, Bond GY, Rebeyka IM, et al. Fetal Umbilical Arterial Pulsatility Correlates With 2-Year Growth and Neurodevelopmental Outcomes in Congenital Heart Disease. Canadian Journal of Cardiology. 2021 Mar 1;37(3):425-32.

10. Arcelli D, Farina A, Cappuzzello C, Bresin A, De Sanctis P, Perolo A, et al. Identification of circulating placental mRNA in maternal blood of pregnancies affected with fetal congenital heart diseases at the second trimester of pregnancy: implications for early molecular screening. Prenatal Diagnosis: Published in Affiliation With the International Society for Prenatal Diagnosis. 2010 Mar;30(3):229-34.

11. Llurba E, Syngelaki A, Sánchez O, Carreras E, Cabero L, Nicolaides KH. Maternal serum placental growth factor at 11–13 weeks' gestation and fetal cardiac defects. Ultrasound in Obstetrics & Gynecology. 2013 Aug;42(2):169-74.

12. Llurba E, Sanchez O, Ferrer Q, Nicolaides KH, Ruíz A, Domínguez C, et al. Maternal and foetal angiogenic imbalance in congenital heart defects. European heart journal. 2014 Mar 14;35(11):701-7.

13. Andescavage N, Yarish A, Donofrio M, Bulas D, Evangelou I, Vezina G, et al. 3-D volumetric MRI evaluation of the placenta in fetuses with complex congenital heart disease. Placenta. 2015 Sep 1;36(9):1024-30.

14. Jones HN, Olbrych SK, Smith KL, Cnota JF, Habli M, Ramos-Gonzales O, et al. Hypoplastic left heart syndrome is associated with structural and vascular placental abnormalities and leptin dysregulation. Placenta. 2015 Oct 1;36(10):1078-86.

15. Curti A, Lapucci C, Berto S, Prandstraller D, Perolo A, Rizzo N, et al. Maternal plasma mRNA species in fetal heart defects: a potential for molecular screening. Prenatal diagnosis. 2016 Aug;36(8):738-43.

16. Albalawi A, Brancusi F, Askin F, Ehsanipoor R, Wang J, Burd I, et al. Placental characteristics of fetuses with congenital heart disease. Journal of Ultrasound in Medicine. 2017 May;36(5):965-72.

17. Contro E, Stefani L, Berto S, Lapucci C, Arcelli D, Prandstraller D, et al. Circulating mRNA in maternal plasma at the second trimester of pregnancy: a possible screening tool for cardiac conotruncal and left ventricular outflow tract abnormalities. Molecular diagnosis & therapy. 2017 Dec;21(6):653-61.

18. Morano D, Berto S, Lapucci C, Baldinazzo LW, Prandstraller D, Farina A. Levels of circulating mRNA for the Tenascin-X (TNXB) gene in maternal plasma at the second trimester in pregnancies with isolated congenital ventricular septal defects. Molecular diagnosis & therapy. 2018 Apr;22(2):235-40.

19. Rychik J, Goff D, McKay E, Mott A, Tian Z, Licht DJ, et al. Characterization of the placenta in the newborn with congenital heart disease: distinctions based on type of cardiac malformation. Pediatric cardiology. 2018 Aug;39(6):1165-71.

20. Takemoto R, Anami A, Koga H. Relationship between birth weight to placental weight ratio and major congenital anomalies in Japan. Plos one. 2018 Oct 22;13(10):e0206002.

21. Miremberg H, Gindes L, Schreiber L, Raucher Sternfeld A, Bar J, Kovo M. The association between severe fetal congenital heart defects and placental vascular malperfusion lesions. Prenatal diagnosis. 2019 Oct;39(11):962-7.

22. Radhakrishna U, Albayrak S, Zafra R, Baraa A, Vishweswaraiah S, Veerappa AM, et al. Placental epigenetics for evaluation of fetal congenital heart defects: Ventricular Septal Defect (VSD). PloS one. 2019 Mar 21;14(3):e0200229.

23. Russell MW, Moldenhauer JS, Rychik J, Burnham NB, Zullo E, Parry SI, et al. Damaging variants in proangiogenic genes impair growth in fetuses with cardiac defects. The Journal of pediatrics. 2019 Oct 1;213:103-9.

24. Schlatterer SD, Murnick J, Jacobs M, White L, Donofrio MT, Limperopoulos C. Placental pathology and neuroimaging correlates in neonates with congenital heart disease. Scientific reports. 2019 Mar 11;9(1):1-1.

25. Courtney J, Troja W, Owens KJ, Brockway HM, Hinton AC, Hinton RB, et al. Abnormalities of placental development and function are associated with the different fetal growth patterns of hypoplastic left heart syndrome and transposition of the great arteries. Placenta. 2020 Nov 1;101:57-65.

26. Giorgione V, Fesslova V, Boveri S, Candiani M, Khalil A, Cavoretto P. Adverse perinatal outcome and placental abnormalities in pregnancies with major fetal congenital heart defects: A retrospective case-control study. Prenatal Diagnosis. 2020 Oct;40(11):1390-7.

27. Ozcan T, Kikano S, Plummer S, Strainic J, Ravishankar S. The association of fetal congenital cardiac defects and placental vascular malperfusion. Pediatric and Developmental Pathology. 2021 Jun;24(3):187-92.

28. Matthiesen NB, Henriksen TB, Agergaard P, Gaynor JW, Bach CC, Hjortdal VE, et al. Congenital heart defects and indices of placental and fetal growth in a nationwide study of 924 422 liveborn infants. Circulation. 2016 Nov 15;134(20):1546-56.

29. Sun IY, Overgaard MT, Oxvig C, Giudice LC. Pregnancy-associated plasma protein A proteolytic activity is associated with the human placental trophoblast cell membrane. The Journal of Clinical Endocrinology & Metabolism. 2002 Nov 1;87(11):5235-40.

30. Arroyo J, Torry RJ, Torry DS. Deferential regulation of placenta growth factor (PlGF)-mediated signal transduction in human primary term trophoblast and endothelial cells. Placenta. 2004 May 1;25(5):379-86.

31. Dehkordi FS, Saberian S, Momtaz H. Detection and segregation of Brucella abortus and Brucella melitensis in aborted bovine, ovine, caprine, buffaloes and camelid fetuses by application of conventional and real-time polymerase chain reaction. The Thai Journal of Veterinary Medicine. 2012;42(1):13.

32. Dehkordi FS, Momtaz H, Doosti A. Application of Real-Time PCR for detection of Aspergillus species in aborted ruminant foetuses. Bulgarian Journal of Veterinary Medicine. 2012;15(1):30-6.

33. Dehkordi FS. Prevalence study of Coxiella burnetii in aborted ovine and caprine fetuses by evaluation of nested and real-time PCR assays. American Journal of Animal and Veterinary Sciences. 2011;6(4):180-6.

34. Dehkordi FS, Tavakoli-Far B, Jafariaskari S, Momtaz H, Esmaeilzadeh S, Ranjbar R, et al. Uropathogenic Escherichia coli in the high vaginal swab samples of fertile and infertile women: virulence factors, O-serogroups, and phenotyping and genotyping characterization of antibiotic resistance. New Microbes and New Infections. 2020;38:100824.

35. Dehkordi FS, Haghighi N, Momtaz H, Rafsanjani MS, Momeni M. Conventional vs real-time PCR for detection of bovine herpes virus type 1 in aborted bovine, buffalo and camel foetuses. Bulgarian Journal of Veterinary Medicine. 2013;16(2):102-12.

36. Dehkordi FS, Yazdani F, Mozafari J, Valizadeh Y. Virulence factors, serogroups and antimicrobial resistance properties of Escherichia coli strains in fermented dairy products. BMC Research Notes. 2014c;7(1):1-8.

37. Dehkordi FS, Barati S, Momtaz H, Ahari SN, Dehkordi SN. Comparison of shedding, and antibiotic resistance properties of Listeria monocytogenes isolated from milk, feces, urine, and vaginal secretion of bovine, ovine, caprine, buffalo, and camel species in Iran. Jundishapur Journal of Microbiology. 2013a;6(3):284.

38. Ghorbani F, Gheisari E, Dehkordi FS. Genotyping of vacA alleles of Helicobacter pylori strains recovered from some Iranian food items. Tropical Journal of Pharmaceutical Research. 2016;15(8):1631-6.

39. Dehkordi FS, Gandomi H, Basti AA, Misaghi A, Rahimi E. Phenotypic and genotypic characterization of antibiotic resistance of methicillin-resistant Staphylococcus aureus isolated from hospital food. Antimicrobial Resistance & Infection Control. 2017;6(1):1-1.

40. Dehkordi FS. Prevalence study of Bovine viral diarrhea virus by evaluation of antigen capture ELISA and RT-PCR assay in Bovine, Ovine, Caprine, Buffalo and Camel aborted fetuses in Iran. AMB Express. 2011;1(1):1-6.

41. Dehkordi FS, Parsaei P, Saberian S, Moshkelani S, Hajshafiei P, Hoseini SR, et al. Prevalence study of Theileria annulata by comparison of four diagnostic Techniques in shouthwest Iran. Bulgarian Journal of Veterinary Medicine. 2012;15(2): 123-30.

42. Dehkordi FS, Haghighi Borujeni MR, Rahimi E, Abdizadeh R. Detection of Toxoplasma gondii in raw caprine, ovine, buffalo, bovine, and camel milk using cell cultivation, cat bioassay, capture ELISA, and PCR methods in Iran. Foodborne Pathogens and Disease. 2013;10(2):120-5.

43. Dehkordi FS, Khamesipour F, Momeni M. Brucella abortus and Brucella melitensis in Iranian bovine and buffalo semen samples: The first clinical trial on seasonal, Senile and geographical distribution using culture, conventional and real-time polymerase chain reaction assays. Kafkas Univ Vet Fak Dergisi. 2014;20(6):821-8.

44. Dehkordi FS, Valizadeh Y, Birgani TA, Dehkordi KG. Prevalence study of Brucella melitensis and Brucella abortus in cow's milk using dot enzyme linked immuno sorbent assay and duplex polymerase chain reaction. Journal of Pure and Applied Microbiology. 2014b;8(2):1065-9.

45. Dehkordi FS, Tirgir F, Valizadeh Y. Effects of Guajol® ointment synthesized from medicinal smoke condensate of jennet feces on burn wound healing on Wistar rat. Veterinary Research Forum. 2017; 8(3):215.