Literature Review

Neurodevelopment and Fetal Growth in Fetuses with Congenital Heart Disease

Perkembangan Saraf dan Pertumbuhan Janin dengan Penyakit Jantung Bawaan

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Abstract

Objective: To determine mechanisms underlying fetal growth abnormalities, particularly intrauterine neurodevelopment, in congenital heart defects.

Method: Literature Review.

Results: Since intrauterine, smart mechanisms have ensured that blood flow to the central nervous system remains smooth to maintain Neurodevelopment. The mechanism fluctuates to keep oxygen flowing to the brain. Blood with the highest oxygen content should always be pumped to upper body and the head via the heart and the aorta. Aortic arch region contains three major blood vessels, a.Brachiocephalic, a.Carotid communis, and a.Subclavia that bleed the upper body and head, including the brain. So, blood flow from the left heart through the aortic arch is critical for fetal brain growth. If the heart cannot drain blood to the head, brain growth will be jeopardized because hypoxia will interfere with brain growth so will be influence to Neurodevelopment. Impaired blood flow can occur as early as intrauterine, particularly if the fetus has congenital heart disease. Blood flow in the Middle Cerebral Artery (MCA) can be used to measure blood flow in the fetus head. The pulsatility index value can be used to measure blood flow in the MCA, and another parameter is the cardioplacental ratio. There is a decrease in flow to the head in congenital heart disease, which results in a decrease in the Pulsatily index of the MCA and a decrease in the cardioplacental ratio.

Conclusions: Prolonged reduction in cardiac-derived blood flow leads to compromised neurodevelopment. Consequently, timely correction of postpartum heart defects becomes paramount to prevent protracted impairments in brain growth. Failing to address this promptly could also diminish the overall quality of life for children afflicted by congenital heart disease.

Keyword: cardioplacental ratio, cerebral media artery, congenital heart disease, fetal neurodevelopment.

Abstrak

Tujuan: *Untuk menentukan mekanisme kelainan pertumbuhan janin terutama perkembangan saraf intrauterin pada cacat jantung bawaan.*

Metode: *Kajian Pustaka.*

Hasil: Pada kehidupan intrauterin, mekanisme yang baik telah memastikan bahwa aliran darah ke sistem saraf pusat tetap lancar untuk mempertahankan perkembangan saraf. Mekanisme ini berfluktuasi untuk menjaga oksigen tetap mengalir ke otak. Darah dengan kandungan oksigen tertinggi harus selalu dipompa ke otak melalui jantung dan arteri utama ke kepala melalui a.Brachiocephalic, a.Carotid communis, dan a.Subclavia. Pada daerah arkus aorta terdapat tiga pembuluh darah utama yang memperdarahi tubuh bagian atas dan kepala, termasuk otak. Aliran darah ini dipompa melalui jantung kiri melalui arkus aorta. Bila jantung tidak dapat mengalirkan darah ke kepala, maka akan menyebabkan pertumbuhan otak terancam karena hipoksia akan mengganggu pertumbuhan otak, sehingga secara jangka panjang akan berpengaruh terhadap perkembangan saraf fetus. Gangguan aliran darah dapat terjadi sejak dini terutama jika janin memiliki penyakit jantung bawaan. Aliran darah di Arteri Serebri Media (MCA) dapat digunakan untuk mengukur aliran darah pada bagian kepala. Nilai indeks pulsatilitas dapat digunakan untuk mengukur aliran darah di MCA, dan parameter lain adalah rasio kardioplasental. Terdapat penurunan aliran ke kepala pada penyakit jantung bawaan, yang mengakibatkan penurunan indeks Pulsatily pada MCA serta terdapat penurunan rasio kardioplasental.

Kesimpulan: *Penurunan perkembangan saraf terjadi ketika aliran darah dari jantung berkurang secara kronis ke daerah kepala janin, sehingga bila terdapat kelainan jantung bawaan pasca persalinan harus diperbaiki segera agar penurunan pertumbuhan otak pada periode pascasalin tidak berlangsung terlalu lama. Bila hal ini terjadi akan menurunkan pula kualitas hidup anak dengan penyakit jantung bawaan.*

Kata kunci: *arteri serebri media, penyakit jantung bawaan, perkembangan saraf janin, rasio kardioplasenta.*

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INTRODUCTION

The fetal brain is highly malleable and relies on environmental cues for proper development; therefore, an unsupportive environment can impede its progress.[1] Elevated intrauterine pressure has both short- and long-term impacts on fetal neurological development, with lasting consequences for mental health disorders throughout childhood and adulthood, as supported by existing empirical evidence.[2] The principal pathways implicated in programming brain development involve endocrine and inflammatory stress mediators.[3] These mediators respond to various intrauterine disorders and modify crucial signaling pathways essential for optimal brain development.[4]

In addition, the maintained blood flow to the head is very important. The flow towards the head in the intrauterine period is supplied mainly by the left heart, while the right heart predominantly pumps clean blood towards the rest of the body through ductus arteriosus. Failure of the left heart to pump blood towards the aortic arch results in a lack of blood supply and oxygen to the upper body and head. So if there is a heart defect in the fetus, especially those that affect the heart pump, it will have a bad effect on brain growth. Indirectly, if the fetal brain is not developed, it will affect fetal weight during intrauterine or the baby's weight during labor has a small for gestational age category (SGA).

There exist two potential mechanisms: Firstly, the brain development in infants with congenital heart defects (CHD) might diverge due to genetic or environmental influences. Secondly, both the heart and brain undergo simultaneous development within the human fetus, guided by a genetic pathway.[5] Disruptions in either of these pathways can lead to anomalous development of both organs, consequently giving rise to neurological developmental disorders.[6] Heart defects cause changes in blood flow, which affects the supply of oxygen and nutrients to the brain and, as a result, can interfere with normal brain development.[7]

The plasticity of the brain is very high, with the possibility of disruption in the event of hypoxia or when there is a relatively short period of hypoxemic state, which causes partial neuron loss and brain white matter damage.[8] Smooth brain injury, for example, can occur, and this can have a significant effect on certain system functions, so that postnatal abnormalities are highly dependent on which region experiences pathology.[9] Hypoxic brain injury may not affect survival rate and can survive until delivery, but brain development is not optimal and may even appear disturbed in subsequent developments.[10] This can be seen in autism syndrome, hyperactivity, lack of intelligence and other conditions.[11]

Mild and chronic placental insufficiency can result in long-term deficits in neuronal connectivity, affecting postnatal function, as seen in the auditory and visual systems.[12] Repeated acute inflammatory agent exposure causes diffuse white matter damage and, in some cases, periventricular necrosis.[13] As a result, the duration and severity of this prenatal disorder are long-term predictors of functional outcome.[14] Doppler examination of MCA can be used to detect the presence of disturbances in blood flow to the brain or systemic conditions that result in fetal hypoxia.[15]

The examination of the Middle Cerebral Artery involves assessment within the Willis circle (Figure 1A), followed by the identification of the MCA itself, and the placement of a sample volume at its proximal third (Figure 1B). A standard MCA Doppler spectral pattern displays minimal diastolic waves (Figure 1C), corresponding to a high Pulsatility Index (PI) value. Conversely, instances of chronic hypoxia, such as Fetal Growth Restriction, lead to an elevation in the peak of diastolic waves, resulting in a decrease in the PI value (Figure 1D).

The Doppler parameter analysis indicated that the Pulsatility Index (PI) of the Middle Cerebral Artery (MCA) exhibited lower values across all study groups, including cases of congenital heart defects (CHD) diagnosis.[16] When contrasting with healthy controls, fetuses diagnosed with left hypoplastic heart syndrome (HLHS) or heart anomalies linked with compromised brain oxygen supply demonstrated a diminished Pulsatility Index in the middle cerebral artery (MCA-PI).[17,18] Conversely, when comparing to HLHS, fetuses afflicted with right-sided obstructive lesions often displayed elevated MCA-PI values.[19] None of the studies on Doppler parameters in CHD fetuses found higher MCA when compared to healthy controls.[20] Very low MCA-PI levels begin in the second trimester and continue into the third trimester, and they tend to decline faster than expected for gestational age.[20,21]

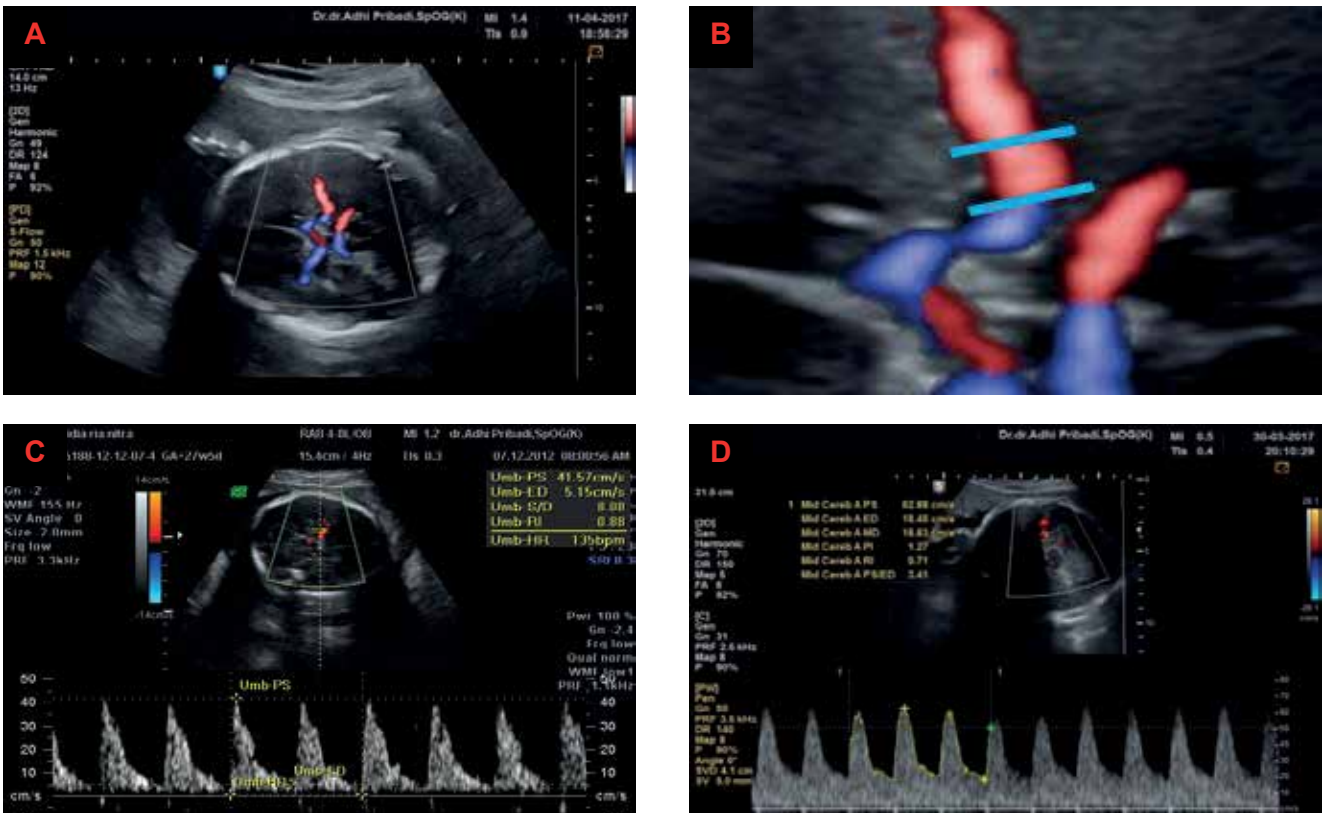

Figure 1. Middle Cerebri Artery (MCA). A.Circle of willis, B. Proximal one third to place volume samples, C. Normal MCA, D. Increase end diastolic waves results in a decrease PI value

The CPR appears to be an important predictor of adverse pregnancy outcomes which has implications for assessing fetal well-being in women of small gestational age.[22] Calculated as a simple ratio of the middle cerebral artery pulsatility index (MCA-PI) and the umbilical artery pulsatility index (UA-PI).[23] This ratio is associated with placental insufficiency and adverse effects on the fetus, and it is almost certainly associated with postnatal neurological outcomes.[24] If there is a heart abnormality that affects head growth and overall fetal growth, it will affect CPR and neurodevelopmental as a whole.

METHODS

In this review, a search was conducted across five electronic databases—Scopus, Cochrane Library, Science Direct, PubMed, and Google Scholar. Data extraction was carried out from original articles written in English.

RESULTS

Study found childbirth with a SGA incidence of 26% in CHD cases.[25] Wallenstein's study found patients with a prenatal diagnosis of fetal CHD had a threefold increased risk of becoming fetal growth restriction (FGR); patients with isolated fetal CHD were twice as likely to develop FGR.[26] In the CHD subtypes associated with lower mean HC, these percentages ranged from simple transposition of the great arteries (3%) and Hypoplastic Left Heart Syndrom (8%) to higher in subgroups associated with lower placental weight, that is, in anomalous pulmonary vein return (13%), Tetralogy of fallot as much as 36%, and Ventricle Septal Defect as much 66%.[27] Fetal CHD is associated with uteroplacental dysfunction, secondary to maternal uteroplacental perfusion disorders resulting in hypoxemia and reduced fetal growth.[28] Below is shown (table 1) the results of the search for stunted growth events affected by the size of the fetal head (head circumference) with the results of SGA delivery. the variation in the incidence of stunted fetal growth in the incidence of CHD, which is in the range of 15.2% at the lowest to the highest as much as 26% of all CHD cases, which of course is influenced by the size of the fetal head. [25-31] The limitation of this study is that not all search results from articles found display the incidence of fetal growth restriction or SGA in pregnancy without CHD as the results of the study so comparisons cannot be made.

Table 1. Incidence of Small for Gestational Age (postpartum) in CHD

Method	CHD (N)	SGA (N/%)	Country	Reference No
Meta-analysis	1789	470/26	France	25
Retrospective Cohort study	175	28/16	US	26
Retrospective study	7569	1589/21	Danish	27
Retrospective Case control	153	37/24	UK	28
Retrospective	6863	1722/25.1	US	29
Retrospective	3395	516/15.2	US	30
Retrospective	303	56/18.5	Japan	31

Note: SGA: small for gestational age, CHD: congenital heart disease

DISCUSSION

When compared to a fetus with normal CPR, fetuses with abnormal CPR that is suitable for gestational age or has a late-onset small for gestational age (≥ 34 weeks of gestation) have a higher incidence of fetal distress in labor that requires emergency caesarean delivery, lower cord pH, and an increased level of admission to the intensive care unit.[32] Fetuses with early-onset small for gestational age (≤ 34 weeks of gestation) and abnormal CPR have a higher risk of worsening and are linked to the following; preterm birth, small for gestational age, increased cesarean section rates, an increase in Apgar score of less than 7 in 5 minutes, an increase in neonatal acidosis, an increase in intensive care, and an increase in perinatal death.[33] CPR also predicts adverse outcomes earlier than the biophysical, umbilical artery, or media cerebral artery profiles.[34,35] Finally, CPR should be considered as an assessment tool for fetuses undergoing third trimester ultrasound examination.[35]

Cerebroplacental ratio was also found to be lower in the majority of CHD fetuses.[36] Flow from the left heart through the aortic arc is critical for fetal brain growth because the arcus region contains three major blood vessels that bleed the upper body and head, including the brain.[37] The three blood vessels are; a.Inominata or a.Brachiocephalic, a.Left Carotid comunnis, and a. Left Subclavia (figure 2). If the flow into these three blood vessels is obstructed (particularly the carotid), there will be a lack of blood supply to the brain and a decrease in brain oxygenation (figure 3).[38] Long-term effects will include chronic hypoxia and widespread brain damage.[10] Types of heart defects that affect fetal brain development, especially when there are abnormalities in the left heart, for example, Hypoplastic left heart syndrom, Aortic stenosis or atresia, and aortic coarctasio. Decreased neurodevelopment due to inadequate blood flow to the head results in a lower HC,[27] which practically affects the growth chart in general, and makes it easier for the fetus to be included in the category of fetal growth restriction or SGA after delivery.

If blood flow to the brain decreases, resulting in hypoxia, the body will respond by dilating blood vessels and increasing blood flow to these organs, particularly the brain which will be reflected by changes in the appearance of MCA [39] The MCA pulsatility index, which tends to decrease in hypoxia to a certain point is said to be the brain sparring effect.[40] The description of the brain sparring effect in obstetrics occurs frequently in cases of intrauterine growth retardation, with the same principle (hypoxia) in the CHD state.[41]

The limitation of this study is that not all search results from articles found display the incidence of fetal growth restriction or SGA after delivery without CHD as the results of the study, so comparisons cannot be made. When looking at the incidence of FGR in the entire population ranges from 2.3% to 10.3%,[42] so that the overall incidence of FGR in CHD (table 1) is higher when compared to the general population.

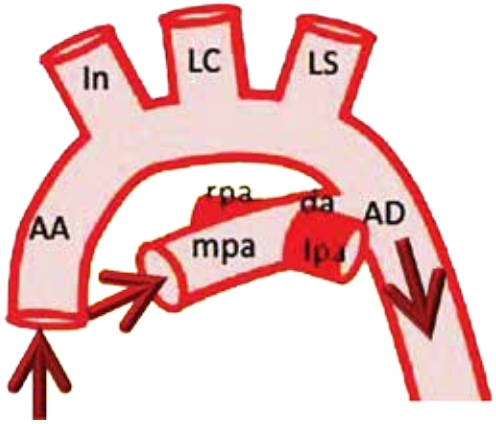

Figure 2. Normal flow in the aorta arch and ductus arteriosus. The amount of blood pumped from the right and left hearts is equal. AA:Ascendent Aorta, In:Inominate (Brachiocephalic), LC:Left Carotid, LS: Left Subclavia, mpa:main Pulmonary artery, rpa:right pulmonary artery, lpa:left pulmonary artery, da: ductus arteriosus,AD:Descendent Aorta.

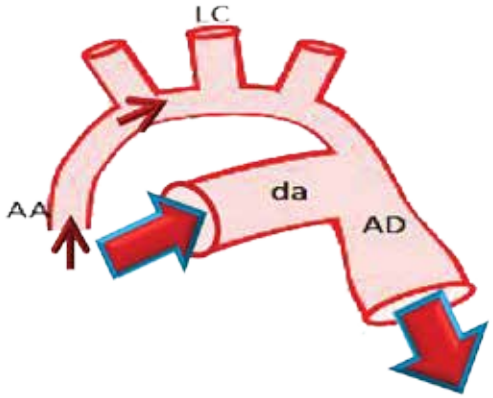

Figure 3. Abnormal flow in the aortic arch and ductus arteriosus. The amount of blood pumped from the right and left heart is anequal. Blood flow to the carotid artery decreases or less blood is pumped into the head area, while blood flow to the ductus arteriosus increases (does not flow into the head area directly to the entire body).AA: Ascendent aorta, LC: Left Carotid, da:ductus arteriosus, AD: Descendent Aorta.

CONCLUSIONS

In conclusion, the incidence of lower head circumference (HD) in CHD is higher when compared to the general population. This contributes to a rise in occurences of infants classified as small for gestational age (SGA). As a result, the prompt correction of postpartum heart defects becomes imperative.

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