Title Successful Prenatal Treatment with Continuous Chronic Maternal Hyperoxygenation Therapy in Hypoplastic Left Heart in Two Pregnancies: Case report

Ali Gedikbasi[1], Gokhan Bolluk[2], Aylin Oztarhan[3], Cagdas Vural[4], and Kazim Oztarhan[5]

[1]Private Center
[2]Basaksehir Cam ve Sakura Sehir Hastanesi
[3]Istanbul Sisli Hamidiye Etfal Egitim ve Arastirma Hastanesi Kardiyoloji Klinigi
[4]Eskisehir Sehir Hastanesi
[5]İstanbul Medical School Division of Pediatric Cardiology

July 7, 2023

Abstract

ABSTRACT Maternal hyperoxygenation (MH) has been studied as a diagnostic tool to evaluate pulmonary vasculature and as a treatment option to improve the growth of fetal left heart in fetuses with left-sided cardiac defects. Chronic maternal hyperoxygenation (CMH) therapy leads to an improvement in fetal pulmonary blood flow resulting in an enhanced venous return to the left heart with increased gestational age. With this manipulation it is anticipated to augment blood flow directed remodeling of the left heart structures and to improve left heart growth spanning from the mitral valve to the aortic isthmus. However, there are concerns about CMH therapy with regard to fetal complications with growth restriction and fetal brain development. Now, with two successful cases we try to discuss this fetal treatment option and related concerns.

INTRODUCTION

Investigators have observed a fetal cardiovascular response to maternal hyperoxygenation (MH) therapy, which leads to an improvement in fetal pulmonary blood flow and an enhanced venous return to the left heart as gestational age increases (1). Investigators have therefore studied chronic maternal hyperoxygenation (CMH) therapy as a fetal initial and/or corrective treatment opportunity, especially for left-sided obstructed congenital heart diseases and hypoplastic left heart lesions (2-7).

The principle of MH is based on the oxygen-induced decrease in fetal pulmonary vascular resistance. The response of the fetal pulmonary vasculature to additional oxygen has been shown to occur by the completion of 26 gestational weeks (8). The reduction in fetal pulmonary resistance should increase pulmonary arterial blood flow and pulmonary venous return. In addition, the improved left atrial volume should stimulate growth of the following cardiac structures growth: mitral valve; left ventricle; and aortic valve.

There have been concerns, however, about CMH therapy with respect to fetal complications (growth restriction) and fetal brain and placental development (9).

We present herein two patients diagnosed antenatally, one with mitral valve and aortic hypoplasia (AH), and another with isthmic hypoplasia. Both patients developed hypoplastic left heart syndrome (HLHS), and were successfully treated with CMH therapy in the third trimester without requiring any further surgical procedures.

CASE REPORT

Case 1

A 28-year-old gravida 1 para 0 at 27 weeks gestation was referred for evaluation of antenatally-diagnosed AH + HLHS. Fetal echocardiography was performed by AG (Voluson E8, GE Healthcare Ultrasound, Milwaukee, WI, USA), and confirmed the diagnosis of left ventricular hypoplasia due to mitral valve hypoplasia, left ventricular outflow tract obstruction, a small peri-membranous ventricular septal defect (VSD), and reverse flow at the aortic isthmus and duct without other extracardiac pathologic findings. The family had been informed of the prognosis at two other maternal-fetal clinics; however, she declined karyotyping and/or termination of the pregnancy (TOP). Following information on MH therapy, the family accepted this management option.

At 28 + 0 gestational weeks, CMH therapy was initiated in accordance with previously described protocols (2, 5). The fetus was monitored biweekly via echocardiography to assess ductus arteriosus constriction and cardiovascular status, and daily cardiotocography in the outpatient clinic during subsequent therapy days. Additionally, fetal growth, cranial measurements, and umbilical and middle cerebral artery (MCA) Doppler measurements were determined during follow-up evaluations.

Left ventricle length and width z-scores progressively increased during CMH therapy, especially during the first 3 weeks. Left cardiac measurements were near normal levels at the end of therapy (Figures 1 and 2; Videos 1 and 2). The bidirectional Doppler flow pattern in the aortic isthmus, in which the retrograde flow portion was greater, changed at the end of therapy and antegrade flow was established during fetal therapy. Similarly, reverse flow in the foramen ovale from left-to-right also changed during therapy with appropriate intracardiac flow from right-to-left.

CMH therapy was continued for 46 days, but due to spontaneous rupture of membranes at 35 + 4 gestational weeks, a cesarean section was performed and a 2,980 g male newborn with Apgar scores of 6 and 9 at 1 and 5 min, respectively, was delivered. The left ventricle measurements were within normal limits, but a restrictive peri-membranous ventricular septal defect, mild mitral stenosis, and mild aortic stenosis were diagnosed postnatally (by KO). The newborn was followed in the NICU during the first week of life and was discharged home without surgery on day 10. No ocular, respiratory, neurologic, glucose metabolism, or growth anomalies were detected during the neonatology examination. Postnatal karyotyping and chromosomal microarray were normal.

During the first year of life, a subaortic ridge with minimal aortic regurgitation developed in addition to the initial diagnoses. Routine follow-up evaluations continue at 2 years of age.

Case 2

A 35-year-old gravida 2 para 0 at 25 weeks gestation underwent fetal echocardiography as a second opinion for an isthmic hypoplasia + HLHS diagnosis. The family had been informed about the prognosis based on a normal karyotype and chromosomal microarray results in her country of residence, and declined a TOP. The family was offered and accepted CMH therapy after all questions were answered.

At 28 + 0 gestational weeks, CMH therapy was initiated and performed as described above and below. Because the patient resided in a neighboring country, subsequent antenatal examinations could only performed at 30 and 34 gestational weeks after the first week of therapy. Although isthmic hypoplasia persisted and was visible during the entire duration of pregnancy with aliasing Doppler flow (2.7 mm at 28 weeks, z-score -2.04; 3.1 mm at 30 weeks, z-score -1.69; 3.8 mm at 34 weeks, z-score -1.29) (10), the left ventricle length and width z-scores increased throughout CMH therapy (Figures 1 and 2, Video 3).

After 51 days of CMH therapy, a Cesarean section was performed at 36+2 weeks gestation and a 3,800 g male newborn with Apgar scores of 7 and 9 at 1 and 5 min, respectively, was delivered in own country of residence. The newborn was followed in the NICU during the first week and the initial cardiac examinations were unremarkable, according to reports. Discharge to home occurred without intervention on day 7. The baseline postnatal examination was performed in the first month (by KO) and showed normal left ventricle and aortic arch sizes during the first postnatal month [isthmus, 4.9 mm (z-score -0.70)]. No ocular, respiratory,

neurologic, glucose metabolism, or growth defects were detected during examination at the 6^{th} and 12^{th} months (Figure 3). Routine follow-up evaluations continue at 16 months of age.

Management Protocol

Fetal therapy was approved by the Institutional Review Board (reference number: 2020/377). Written informed consent was obtained from both families.

At 28 + 0 weeks gestation, CMH therapy was initiated in accordance with previously described protocols (2, 5). On the first day, oxygen was provided for 6 h, One hour after administration of oxygen, the pulmonary circulation response and improved venous return loading effect to the left ventricle was demonstrated by Doppler sonography. Fetal pulmonary venous blood flow velocity and quantitative changes in color Doppler of lung vessels were compared to document pulmonary vasodilation, as described by Kohl (3). From the second day forward, the patient received daily MH therapy for 8 h (50% FiO_2 at 6 L/min via face mask until delivery) in a continuous fashion. The fetus was monitored with biweekly echocardiography to monitor ductus arteriosus constriction and cardiovascular status, and daily cardiotocography in the outpatient clinic. Doppler evaluation of the umbilical artery (UA) and MCA was performed. All Doppler values, including the MCA pulsatility index (PI), UA PI, and UA systolic-to-diastolic (S:D) ratio, were measured using the average values of three consecutive cycles. The cerebroplacental ratio (CPR) was calculated as the MCA PI-to-UA PI.

Measurements of the long and short ventricular axes, and the mitral (MV) and tricuspid valves (TV) were obtained from the four-chamber view from the inner edge-to-the inner edge at end-diastole. The aortic valve (AV), ascending aorta (AAo), descending aorta (DAo), pulmonary valve (PV), and main pulmonary artery (MPA) measurements were obtained during ventricular ejection in the longitudinal view. The aortic isthmus was closely measured proximal to the insertion of the arterial duct with ductal diameter measurement in the three-vessel trachea (3VT) section. Additionally, the flow pattern at the isthmus was followed on the 3VT or sagittal view with a Doppler angle $< 10°$. Evaluation of fetal cardiovascular structures was carried out several times. The first two measurements were obtained immediately before treatment and in the first week of MH therapy. Moreover, documentation was performed in a 2- or 4-week period during pregnancy follow-up.

Postnatal cardiac evaluation and follow-up was performed by our pediatric cardiologist (KO) blinded to prenatal measurements several times in the 1^{st} week, and at 6 and 20 months of age in the first case, and in the 1^{st} month (because she delivered in her country of residence), in the 6th and 12th months in the second case (Figures 1 and 2).

Each measurement was used to obtain antenatal and postnatal z-scores using previously published normative data. The data were expressed as gestational age–related and postnatal z-scores-based data (Detroit data) provided by a Web site calculator available at http://www.parameterz.com (10-14).

Maternal arterial PO_2 was measured via maternal femoral artery puncture on the first and final days of MH therapy. A postnatal ocular examination of the neonate and a chest x-ray of the mother were performed. Additionally, neurologic examinations were performed and routine glucose and biochemical laboratory results were obtained during every visit in the first year of life.

DISCUSSION

CMH therapy in the third trimester results in fetal pulmonary vasodilation following larger venous return to the left fetal heart and increased left ventricle filling with significantly increasing anterograde flow in the aortic isthmus. With this manipulation it is anticipated to augment blood flow-directed remodeling of the left heart structures and improve left heart growth spanning from the mitral valve to the aortic isthmus (8). It has been shown in animals that increased ventricular preload was followed by myocyte proliferation in hypoplastic left ventricles due to an increase in cardiac preload from pulmonary vasodilation, which may also increase hypoplastic fetal cardiovascular dimensions in humans (15). To date, there have been a limited number of studies published on intrauterine fetal treatment of HLHS in humans with CMH (2-7).

Kohl (2) was the first to demonstrate the effects of CMH on cardiac dimensions, which suggested therapy after 28–29 weeks of gestation in 15 fetuses with various grades of hypoplastic cardiovascular structure. Kohl (2) reported that CMH therapy improved ventricular volume, atrioventricular valve diameter, semilunar valve diameter, and great artery and aortic isthmus diameters in most fetuses.

In a related case study, Kohl (3) also reported that additional cardiac defects, such as ventricular septal defects (VSDs) and obstruction in ventricular filling or emptying neutralized the effect of CMH therapy. In the current study VSD and mitral stenosis had no deleterious effect on fetal therapy.

Zeng et al. (5, 6) used a similar fetal oxygenation protocol several hours each day in cases with coarctation of the aorta (CoA) during the third trimester until delivery. Zeng et al. (5, 6) found an association between the CMH therapy time interval and cardiac measurements; specifically, the longer the hyperoxygenation period, the better the increase in left heart size. The same group also reported (6) an increase in the strain and strain rate of both ventricles in fetuses treated with CMH compared to untreated fetuses with CoA, suggesting that CMH leads to an improvement in ventricular function.

Finally, Lara et al. (7) examined the effects of CMH on fetuses with HLHS and showed progression in AV and MV dimensions, although the difference was not statistically significant because of the small sample size. Lara et al. (7) concluded that CMH $>$ 9 h/d was related to better aortic annular development.

There is growing evidence of brain dysmaturation in fetuses with congenital heart disease (CHD) originating during the fetal period (16). The decrease in fetal brain oxygenation has been demonstrated in fetuses with CHD, which has been related to smaller fetal brain volumes (17, 18). The fetal brain has a protective autoregulatory mechanism to avoid the difference between cerebral metabolic demand and supply by increasing cerebral blood flow with a decrease in cerebrovascular resistance (CVR). Better hemodynamic status may be achieved with MH administration to augment global oxygen saturation and increase aortic flow; however, only one study described the practice of CMH in the third trimester as a possible treatment method to improve fetal brain growth (9). Edwards et al. (9) reported nine fetuses with left heart hypoplasia (LHH) treated with CMH that resulted in a significant decrease in fetal biparietal diameter (BPD) development during pregnancy and a smaller head circumference (HC) Z-score 6 months postpartum. Although umbilical artery resistance and placental growth were not significantly different between groups and there was no apparent change in the MCA CVR, Edwards et al. (9) hypothesized that CMH may have a negative effect on placental function and growth. MH administration for greater than 9 h/d had a positive effect on MCA CVR, suggesting an improvement in cerebral oxygenation. Furthermore, a higher duration of weeks and hours on CMH were related to a superior increase in BPD. Based on these findings, Edwards et al. (9) hypothesized that the dosing and timing of CMH may be important. In a fetal lamb study conducted by Accurso et al. (19), MH caused a peak in pulmonary blood flow at 45 min, which returned to baseline within 2 h. Such temporary peaks and normalizations in blood flow with intermittent periods of increased oxygen may have consequences, resulting in numerous periods of pulmonary and systemic vascular fluctuations, which may disturb cerebral blood flow and impact BPD and HC growth. Compared to the Kohl (3) and Zeng et al. (5,6) studies, another difference in the current cases was starting CMH at 26 gestational weeks instead of [?]28-29 gestational weeks. Finally, Edwards et al. (9) modified the CMH protocol to longer daily exposure with fewer interruptions and a lower FiO_2 for corollary studies.

In addition, Hogan et al. (20) reported that the affected structural anatomy and related cardiovascular physiology differed from the cerebrovascular autoregulatory responses in CHD. Fetuses with left-sided obstructive lesions (LSOLs) had the lowest CR compared to right-sided obstructive lesions (RSOLs) and transposition of the great arteries (TGAs). The reason for the lower CR pattern in LSOLs was due to both intracardiac mixing and reduced aortic output.

Furthermore, You et al. (21) demonstrated differences in single- and two-ventricle fetuses brain oxygen autoregulation during AMH. While single-ventricle and aorta-obstructed fetuses had a blood oxygen level dependent magnetic resonance imaging (MRI), two-ventricle CHD and healthy fetuses had no change in brain oxygenation with progressing gestation. They concluded that single-ventricle and aorta obstructed

fetuses had lower baseline cerebral oxygen delivery, whereas the absence of increased brain oxygenation during AMH in two-ventricle CHD and healthy fetuses reflected the existence of a stable cerebrovascular regulatory system, which proved that essential oxygen delivery to the brain was preserved in these fetuses.

The possibility of adverse impulse on brain development in CMH was also discussed by Rudolph (22) in a fetal lamb study. With a reduction in cerebral blood flow, even though the cerebral oxygen supply was maintained, cerebral glucose delivery and consumption was significantly reduced. These metabolic changes did not occur in our cases.

Finally, Lee et al. (23) and Co-Vu et al. (24) both concluded in their reviews of MH therapy that current evidence suggests an increase in pulmonary blood flow, pulmonary venous return, ductal flow, and left heart dimensions in fetuses and that it has the potential to be used as a diagnostic tool, as well as therapeutic tool in fetuses with CHD. Lee et al. (23) and Co-Vu et al. (24) also highlighted that well-designed randomized controlled trials are needed and that it is difficult to ascertain whether CMH therapy provides improved outcomes on fetuses with CHD to baseline.

CONCLUSION

Zeng et al. (5) confirmed that the recovery of cardiac structure was time-dependent. Additionally, the need for postnatal surgery in neonates with CMH therapy was lower (53% in the Kohl study (2) and 20.8% in the Zeng et al study (5)) in contrast to the control group with (75% in the Zeng et al. study (5)), which resulted in an important decrease in cardiac surgery, which was not noted in the two cases reported herein.

References

1. Szwast A, Tian Z, McCann M, Donaghue D, Rychik J. Vasoreactive response to maternal hyperoxygenation in the fetus with hypoplastic left heart syndrome. Circ Cardiovasc Imaging. 2010;3:172–178.
2. Kohl T. Chronic intermittent materno-fetal hyperoxygenation in late gestation may improve on hypoplastic cardiovascular structures associated with cardiac malformations in human fetuses. Pediatr Cardiol. 2010;31:250–263.
3. Kohl T. Effects of maternal-fetal hyperoxygenation on aortic arch flow in a late-gestation human fetus with closed oval foramen at risk for coarctation. J Thorac Cardiovasc Surg. 2011;142:e67–e69.
4. Borik S, Macgowan CK, Seed M. Maternal hyperoxygenation and foetal cardiac MRI in the assessment of the borderline left ventricle. Cardiol Young. 2015;25:1214–1217
5. Zeng S, Zhou J, Peng Q, et al. Sustained maternal hyperoxygenation improves aortic arch dimensions in fetuses with coarctation. Sci Rep. 2016;6:39304
6. Zeng S, Zhou J, Peng Q, et al. Sustained chronic maternal hyperoxygenation increases myocardial deformation in fetuses with a small aortic isthmus at risk for coarctation. J Am Soc Echocardiogr 2017;30:992-1000
7. Lara DA, Morris SA, Maskatia SA, Challman M, Nguyen M, Feagin DK, et al. Pilot study of chronic maternal hyperoxygenation and effect on aortic and mitral valve annular dimensions in fetuses with left heart hypoplasia. Ultrasound Obstet Gynecol. 2016;48:365–372
8. Rasanen J, Wood DC, Debbs RH, Cohen J, Weiner S, Huhta JC. Reactivity of the human fetal pulmonary circulation to maternal hyperoxygenation increases during the second half of pregnancy: a randomized study. Circulation. 1998;97:257–262.
9. Edwards LA, Lara DA, Sanz Cortes M, Hunter JV, Andreas S, Nguyen MJ, et al. Chronic maternal hyperoxygenation and effect on cerebral and placental vasoregulation and neurodevelopment in fetuses with left heart hypoplasia. Fetal Diagn Ther. 2019;46:45–57.
10. Krishnan A, Pike JI, McCarter R, Fulgium AL, Wilson E, Donofrio MT, Sable CA. Predictive Models for Normal Fetal Cardiac Structures. J Am Soc Echocardiogr. 2016;29:1197-1206
11. Schneider C, McCrindle BW, Carvalho JS, Hornberger LK, McCarthy KP, Daubeney PE. Development of Z-scores for fetal cardiac dimensions from echocardiography. Ultrasound Obstet Gynecol. 2005;26:599–605.
12. McElhinney DB, Marshall AC, Wilkins-Haug LE, et al. Predictors of technical success and postnatal

biventricular outcome after in utero aortic valvuloplasty for aortic stenosis with evolving hypoplastic left heart syndrome. Circulation. 2009;120:1482–1490.
13. Pettersen MD, Du W, Skeens ME, Humes RA. Regression equations for calculation of z scores of cardiac structures in a large cohort of healthy infants, children, and adolescents: an echocardiographic study. J Am Soc Echocardiogr. 2008;21:922–934.
14. Cantinotti M, Scalese M, Murzi B, et al. Echocardiographic nomograms for chamber diameters and areas in caucasian children. J Am Soc Echocardiogr. 2014;27:1279–1292.
15. deAlmeida A, McQuinn T, Sedmera D. Increased ventricular preload is compensated by myocyte proliferation in normal and hypoplastic fetal chick left ventricle. Circ Res 2007;100:1363–1370
16. Ortinau CM, Rollins CK, Gholipour A, Yun HJ, Marshall M, Gagoski B, Afacan O, Friedman K, Tworetzky W, Warfield SK, Newburger JW, Inder TE, Grant PE, Im K. Early Emerging Sulcal Patterns Are Atypical in Fetuses with Congenital Heart Disease. Cereb Cortex 2019;29:3605-3616
17. Claessens NHP, Khalili N, Isgum I, Ter Heide H, Steenhuis TJ, Turk E, Jansen NJG, de Vries LS, Breur JMPJ, de Heus R, Benders MJNL. Brain and CSF Volumes in Fetuses and Neonates with Antenatal Diagnosis of Critical Congenital Heart Disease: A Longitudinal MRI Study. AJNR Am J Neuroradiol. 2019;40:885-891.
18. Sun L, Macgowan CK, Sled JG, Yoo SJ, Manlhiot C, Porayette P, Grosse-Wortmann L, Jaeggi E, McCrindle BW, Kingdom J, Hickey E, Miller S, Seed M. Reduced Fetal Cerebral Oxygen Consumption is Associated With Smaller Brain Size in Fetuses With Congenital Heart Disease. Circulation 2015;131:1313-1323
19. Accurso FJ, Alpert B, Wilkening RB, Petersen RG, Meschia G. Time dependent response of fetal pulmonary blood flow to an increase in fetal oxygen tension. Respir Physiol 1986;63:43-52
20. Hogan WJ, Moon-Grady AJ, Zhao Y, Cresalia NM, Nawaytou H, Quezada E, Brook M, McQuillen P, Peyvandi S. Fetal cerebral vascular response to maternal hyperoxia in congenital heart disease: effects of cardiac physiology. Ultrasound Obstet Gynecol 2021;57:769-775
21. You W, Andescavage NN, Kapse K, Donofrio MT, Jacobs M, Limperopoulos C. Hemodynamic responses of the placenta and brain to maternal hyperoxia in fetuses with congenital heart disease by using blood oxygen-level dependent MRI. Radiology 2020;294:141-148.
22. Rudolph AM. Maternal hyperoxygenation for the human fetus: should studies be curtailed? Pediatr Res 2020;87:630-633
23. Lee FT, Marini D, Seed M, Sun L. Maternal hyperoxygenation in congenital heart disease. Transl Pediatr 2021;10:2197-2209
24. Co-Vu J, Lopez-Colon D, Vyas HV, Weiner N, DeGroff C. Maternal hyperoxygenation: A potential therapy for congenital heart disease in the fetuses? A systematic review of the current literature. Echocardiography. 2017;34:1822-1833

ACKNOWLEDGMENTS

None

CONFLICTS OF INTEREST

None

ETHICAL APPROVAL

Fetal therapy approvement from institutional review board at İstanbul Sadi Konuk Research and Education Hospital, Health Science University (reference number: 2020/377).

CONSENT FOR PUBLICATION

Written informed consent was obtained from the pregnant mothers for publication of this case report and any accompanying images. The doctors who collected the images used in this paper have also provided their written informed consent.

Authors:

Gokhan Bolluk (1), ORCID ID: 0000-0002-3506-6806

Aylin Oztarhan (2), ORCID ID: 0000-0003-2599-4251

Cagdas Vural (3), ORCID: 0000-0003-2734-0972

Kazim Oztarhan (4), ORCID ID: 0000-0001-9919-1414

Ali Gedikbasi (5), ORCID ID: 0000-0002-04727-0310

- (1) Health Sciences University Istanbul Cam Sakura City Hospital Maternal-Fetal Medicine Division, İstanbul, Türkiye
- (2) Health Science University Istanbul Sisli Etfal Hospital Department of Obstetrics and Gynecology, İstanbul, Türkiye
- (3) Eskisehir City Hospital Division of Pediatric Cardiology, Eskisehir, Türkiye
- (4) İstanbul Medical School Division of Pediatric Cardiology, İstanbul, Türkiye
- (5) Private Center, İstanbul, Türkiye

Address for correspondence:

Ali Gedikbasi, M.D.

Atakoy 11. Kisim, Yasemin Apt. D.16, 34716 İstanbul / Türkiye

E-mail: alged_1971@yahoo.com

Telephone Number: +90 / 532 213 51 40

FIGURE 1. A. LV long axis measureme

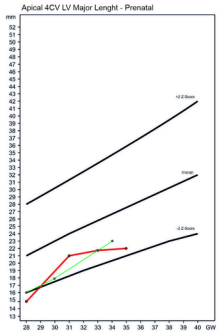
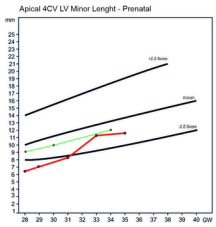


FIGURE 1. B. LV short axis measurement



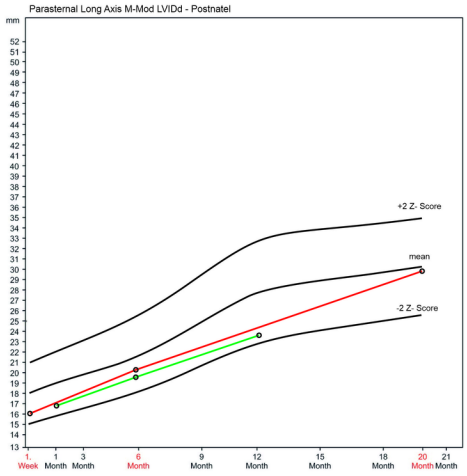


Figure 2. A. Mitral Valve Measurments

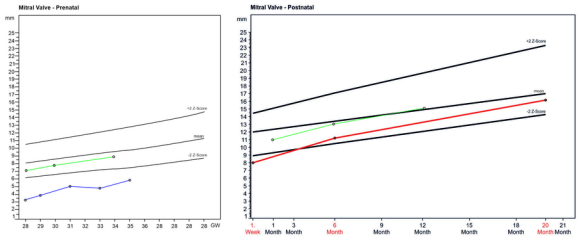
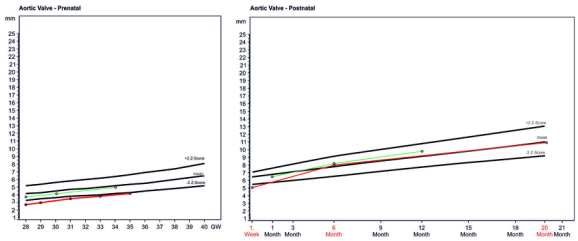
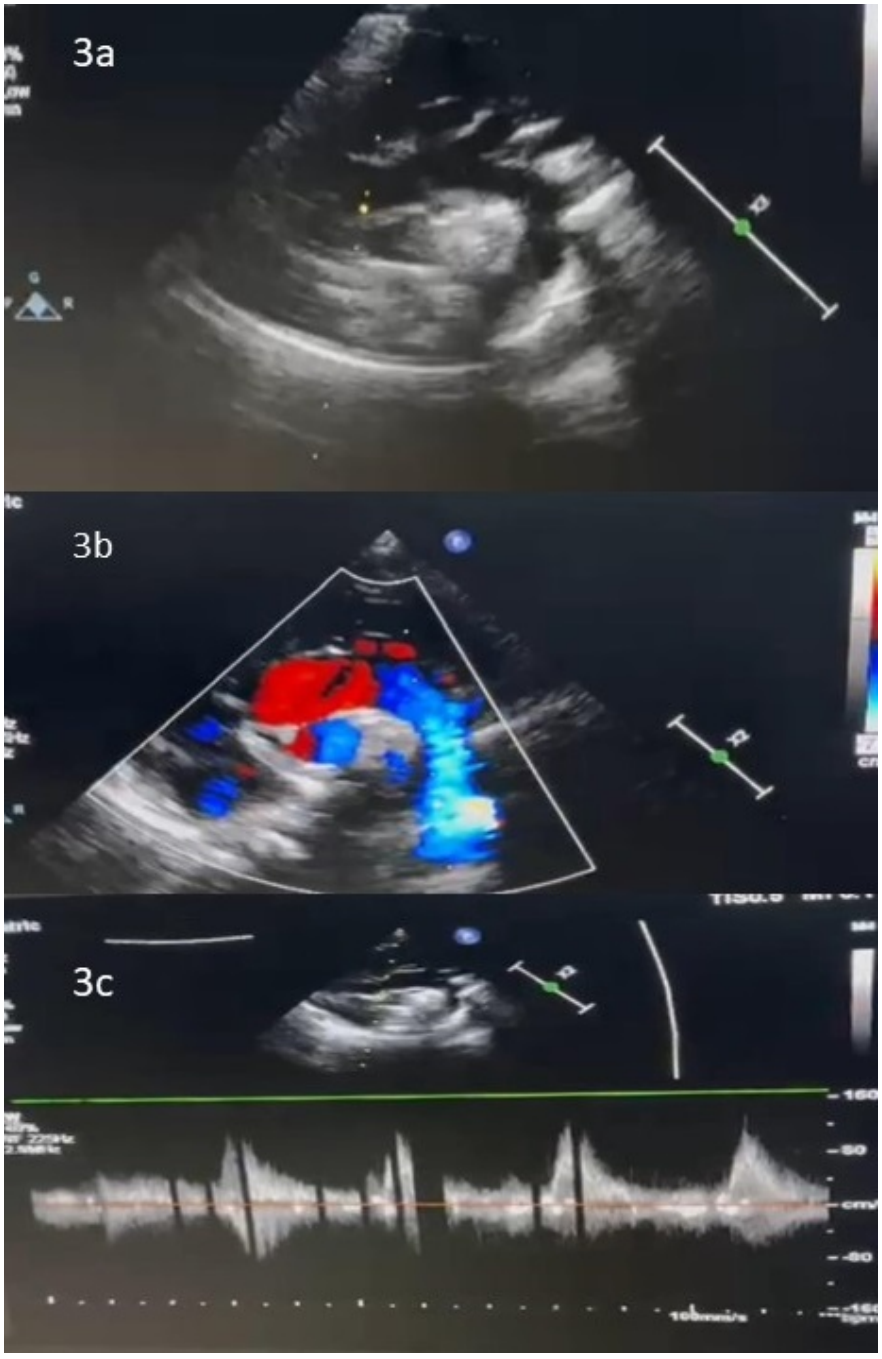


FIGURE 2. B. Aortic Valve measurements





Hosted file

Figure Desription.docx available at https://authorea.com/users/636572/articles/653364-title-successful-prenatal-treatment-with-continuous-chronic-maternal-hyperoxygenation-therapy-in-hypoplastic-left-heart-in-two-pregnancies-case-report