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Review paper

Maternal hyperoxygenation in prenatal ultrasound and fetal echocardiography – literature review 2020

Maria Respondek-Liberska[1,2], Mary Donofrio[3]

[1]Department of Fetal Malformation's Diagnoses and Prevention, Medical University of Lodz, Poland
[2]Department of Fetal Cardiology, Polish Mother's Memorial Hospital, Lodz, Poland
[3]Director of Fetal Heart Program, Children's National Hospital, George Washington University School of Medicine, United States

Abstract

Twenty-nine publications about maternal hyperoxygenation (MHO) were reviewed: 20 discussing MHO as a diagnostic test used by obstetricians (in SGA/IUGR, preeclampsia, fetuses with diaphragmatic hernia, healthy fetuses) and fetal cardiologists (in HLHS, Ebstein, lung hypoplasia, diaphragmatic hernia). Maternal hyperoxygenation was used for 8-20 min, and out of 13 obstetrical publications 8 provided positive effects for stratification of perinatal management. Seven of the fetal cardiology publications were positive. Nine publications dealing with MHO as a transplacental treatment presented positive results in 7, in 1 there was suggestion for necessity for postnatal follow-up with head circumference measurements during postnatal life, and 1 paper (review) suggested that MHO should be curtailed.

Based on the current literature, it can be concluded that MHO has no harmful effect when used in the short term for testing. Longer paediatric and neurological follow-up is needed when used chronically as a fetal therapy. Institutional Review Board approval is recommended as well as informed consent.

Maternal hyperoxygenation as a test might be a useful for testing the fetal circulation, and it gives insight into fetal CV physiology and during transition and might be helpful for the better stratification for perinatal care in fetuses with selected heart defects.

Assessment of blood flow and cardiovascular status during MHO by fetal echocardiography in the 3rd trimester is challenging and requires a high level of expertise. Optimally it should be performed in fetal cardiac centres.

Key words: prognosis, fetal echocardiography, prenatal, heart defect, perinatal treatment.

Corresponding author:
Prof. Maria Respondek-Liberska
Medical University of Lodz
Polish Mother's Memorial Hospital
Rzgowska 281/289
93-345 Lodz, Poland
e-mail: maria.respondek-liberska@uni.lodz.pl

Introduction

Maternal hyperoxygenation (MHO) is a test in which a pregnant woman is given, via a face mask, 100% oxygen or a 60% mixture, and using obstetrical ultrasound or fetal echocardiography, evaluation by comparing specific parameters before, during, and after oxygenation are analysed to provide insight into fetal well-being. Usually MHO is performed as a limited test; however, there are some publications presenting the effect of MHO used for much longer duration, even for weeks, as a method of transplacental treatment. So far, there are no recommendations on how and when to use MHO (Figures 1, 2).

The literature review about MHO can be divided into 2 categories: 1) MHO as diagnostic test (for usually 10-20 min) performed by: A) obstetricians or B) fetal cardiologists (Tables 1 and 2); 2) MHO as a therapy (for days or weeks) (Table 3).

Figure 1. Maternal hyperoxygenetion

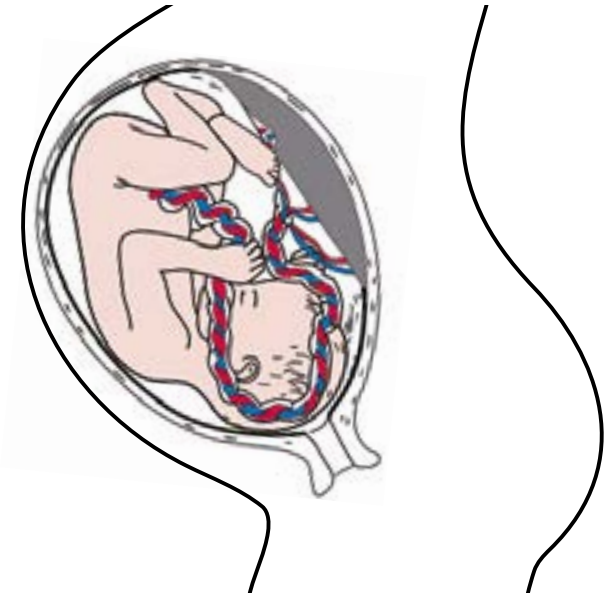

Figure 2. Fetus during maternal hyperoxygenetion

MHO as a diagnostic test performed by obstetricians

One of the very first publication related to maternal hyperoxygenation was published more than 30 years ago and comes from an obstetrician: Nicolaides at al. from 1987 [1]. Five pregnancies (4 singleton and 1 pair of twins) with severe intrauterine growth retardation, oligohydramnios, high blood-flow impedance in the fetal aorta and umbilical artery, and low mean blood-velocity in the fetal thoracic aorta were treated using MHO. It resulted in a sustained increase in the mean blood-velocity in the fetal thoracic aorta.

Table 1. Maternal hyperoxygenation as test in normal fetuses, FGR fetuses, and pregnancy with preeclampsia from an obstetrician's point of view – literature review

Author	Year	No. of fetuses	Duration of MHO	What was evaluated	Conclusions
Nicolaides [1]	1987	5		Fetal thoracic aorta and UMB A	Positive
Arduini [2]	1989	22	20 min test	UMB A PI, fetal thoracic Ao, internal carotid artery	Trend of a change in values towards normal after MHO proves maintained placental transfer
Rizzo *et al.* [3]	1990	38		Time to peak velocity in PA and Ao in SGA and normal fetuses	Positive for Ao
Arduini *et al* [4]	1990	45	Test	Internal carotid artery PI	Positive
Bilardo *et al.* [5]	1991	35	4 weeks, all day long in hospital (72 hours)	V max in Ao desc A, PI in fetal common carotid artery	Positive
Bataglia *et al.* [6]	1992	17 IUGR fetuses		UMB PI	Positive
Soregaroli *et al.* (Rizzo group) [7]	1993	12 healthy fetuses	15 min	DV	Positive
Caforio *at al.* [8]	1998	25 (27-38 weeks)		MCA, UMB, AoV max vel, PV max vel	Limited usefulness
Bratenberg and Sonesson [9]	1999	25 (27-38 weeks) IUGR		MCA, UMB Ao, Ao isthmus	Positive
Broth *et al.* [10]	2002	29 fetuses > 30 weeks with lung hypoplasia		Pulmonary artery PI	Positive
Chanthasenanont *et al.* [11]	2009	54 fetuses of preeclamptic pregnant women	(only based on abstract, Taiwan journal)	MCA, DV PI, UMB PI	Negative: MHO increased risk of low birth weight and admission to ICU
Done-Deprest group [12]	2011	38 fetuses with DH / FETO		Pulmonary vascular reactivity	±
DeKonnick-Deprest group [13]	2012	62 healthy fetuses		MPA and first branch of PA	±
Khatib *et al.* (Israel) [14]	2018	12 fetuses	10 min	MCA, UMB, MPA, RPA	±

Table 2. Maternal hyperoxygenation as a test performed by fetal cardiologists – literature review

Author	Year	No. of fetuses	Gest. age (weeks)	Inclusion	Details from US/ echocardiography	Conclusions
Rasanen *et al.* [15]	1998	20 + 20	20-26 31 – 36	Singleton healthy fetuses	RPA, LPA Fo flow DA flow Cardiac output	Positive
Szwast *et al.* [16]	2010	43 + 27		HLHS + NHA	RPA, LPA, PV, MCA	Positive
Żarkowska-Szaniawska *et al.* [17]	2011	40	32-37	Singleton fetuses with different cardiac or lungs problems	RPA, LPA, V max pulmonary arteries	Positive
Channing (CHOP) [18]	2015	12	Mean 35,3	ASA	ASE, SI	Positive
Enzensberger *et al.* [19]	2016	22	26	HLHS	Pulmonary veins	Positive to evaluate pulmonary vasculopathy
Szwast *et al.* [20]	2018	43	20-41, mean 28	HLHS	MCA	Positive
Schidlow and Donofrio [21]	2018	12		2 Ebstein 2 TAPVC 4 HLHS 4 d-TGA		Positive To help identify fetuses with CHD at risk for perinatal compromise

Five fetuses survived with minimum neonatal morbidity. It was concluded that MHO may prove to be a useful method of assessing placental function and guiding management (Table1).

Two years later in 1989 an Italian group published their results in SGA fetuses [2]: Abnormalities in fetal blood flow velocity wave forms (umbilical artery, thoracic aorta, and carotid artery) seemed to precede the appearance of pathological

Table 3. Maternal hyperoxygenation as a therapy in fetal cardiac problems: HLHS, CoA, and diaphragmatic hernia – literature review

Author	Year	No. of fetuses	Gest age (weeks)	Fetal pathology	What was evaluated	Per day	How long	Conclusions
Kohl [22]	2010	15	33-38	HLHS	13/15 – HLHS MV E,A, AoV (cm/ sec); pulmonary veins (mean), colour Doppler (lung flow)	1st day 6 hours 3 × 4 hours daily	8-33 days	Positive
Kohl [23]	2011	1	36	CoA	Ao isthmus Ao velocity PV	3-4 hours 3 × daily	2 weeks	Positive, no surgery
Zeng [24]	2016	48	26-41	CoA		3,9 – 14 weeks		Positive in CoA Neg. in case of bicuspid valve and or AS
Lara *et al.* Texas [25]	2016	9 + 9	26-34	Borderline Lv, Shone syndrome NO hlhs, NO as		8 hours/day	Median 48 days (33-84) Total hours on oxygen 542 h (292-1011)	Positive
Edwards [26]	2019	9		HLHS	HC at 6 and 12 months			Negative: diminished BPD fetal growth and diminished HC at 6 months
Ishii R *et al.* (Osaka) [27]	2014	1	35	Diaphragmatic hernia andCHF		3 h per day 4 times	2 weeks	Positive
Arunamata *et al.* [28]	2017	1	36	Ebstein		4 h 3 times per day	2 weeks	Positive outcome Surgery at 2 weeks and discharged home
Rydzewska *et al.* [29]	2020	3		Ebstein			2 weeks	0 morality

cardiotocographic findings, but the time interval between the 2 events was difficult to establish because of wide individual differences. In this study the baseline values of pulsatility index (PI) from the different vessels investigated did not aid the prediction of fetal outcome; although in contrast, monitoring fetal vascular responses to maternal oxygen administration clearly distinguished fetuses at high risk for fetal distress. These findings suggested that in non-responders either placental transfer of oxygen or fetal response to oxygen was severely impaired, and such fetuses might require early delivery. On the other hand, the change towards normal values after maternal oxygen administration supported placental transfer, which could justify continued treatment of these fetuses with maternal oxygen therapy. These findings suggested a potential role of the fetal vascular response to MHO as a test to obtain better insight into the functioning of the feto-placental unit (Table 1).

Additional research from the same Italian group (Rizzo 1990) came 1 year later [3]. In 38 small-for-gestational age (SGA) fetuses before and during MHO, the time to peak velocity was measured at the level of the ascending aorta and pulmonary artery by Doppler echocardiography. The values were compared to a reference range derived from the study of 142 appropriate-for-gestational age (AGA) fetuses. In the SGA fetuses the time to peak velocity at the level of pulmonary artery was significantly lower and at the level of the aorta was significantly higher than in AGA fetuses. During MHO the aortic time to peak velocity decreased towards normal range, but there was no significant change at the level of the pulmonary artery. These results indicated variations of aortic and pulmonary pressures in SGA fetuses that could be partially modified by MHO (Table 1).

Also, in 1990 an Italian group suggested that the MHO test is useful in post-term pregnancies. An increase of at least 20% in the pulsatility index of the internal carotid artery suggested an adverse outcome in post-term fetuses [4].

Another publication on the same subject came from Bilardo et al. in 1991 [5]. They did not find any change in the mean umbilical artery PI during MHO, but they also evaluated aortic blood flow velocity. Cases in which there was no improvement within 72 hours after the start of MHO were associated with poor prognosis, and cases in which there was improvement in aortic flow were associated with a more favourable prognostic. The authors concluded, however, that the value of MHO for treatment of growth retarded fetuses remained to be established (Table 1).

Battaglia in 1992 published research based on 17 pregnancies with intrauterine growth retardation [6]. Fetal blood was sampled by cordocentesis for immediate blood gas analysis at entrance to the study and on the day of delivery were analysed. Significant improvement in Doppler flow patterns in treated patients were found when compared with untreated women. The Doppler variations were associated with complementary modifications in fetal blood gas. These differences resulted in a significant modification in perinatal mortality with an incidence of 29% and 68% ($p < 0.01$) in treated and untreated groups, respectively. Their data suggested a benefit of MHO in the treatment of fetal growth retardation (Table 1).

Soregaroli et al. from Italy studied ductus venosus flow velocity wave forms in heathy fetuses before, during, and after 10 min of MHO [7]. There was a significant increase of both estimated peak velocities during systole, diastole, and atrial contraction. No significant changes were found in fetal heart rate.

In 1998 Caforio et al. evaluated MHO as a test in fetuses with absence or reversal end-diastolic blood flow in the umbilical artery, and they concluded that acute maternal oxygen administration was able to elicit a positive haemodynamic response only in some cases, probably those that are characterized by a 'reservoir' of placental and cardiac function [8]. Nevertheless, because in their absence or reversal end-diastolic blood flow in the umbilical artery population, obstetrical outcome was not significantly related to the fetal responsiveness to the maternal MHO, the clinical significance and prognostic value of such a test in such compromised fetuses seem to be of limited usefulness (Table 1).

In 1999 Brantberg and Sonesson from Sweden suggested that MHO in growth-retarded fetuses caused a redistribution of blood from the brain to the vascular beds, and that the aortic isthmus was the best place to evaluate early signs of blood flow redistribution [9] (Table 1).

In 2002 Broth et at. evaluated fetal lung reactivity before and after MHO in fetal conditions suspected of lung hypoplasia [10]. They published observation based on series of 29 fetuses older than 30 weeks and compared the Doppler blood flow in right pulmonary artery (RPA) and left pulmonary artery (LPA) branches before and after MHO. The study was to determine the prognosis for those likely to survive or not to survive after birth. An increase in the fetal pulmonary blood flow with oxygen (a decrease of ≥ 20% of the pulsatility index) was considered a reactive test. A change of < 20% in the flow pattern during maternal hyper-oxygenation was a nonreactive test and suggested pulmonary hypoplasia. A reactive test predicted 92% of surviving infants; a nonreactive test predicted 79% of fetal deaths from pulmonary hypoplasia.

In 2009 Chanthasenanont from Taiwan published a study of 54 fetuses of preeclamptic pregnant women and suggested that MHO was associated with lower birth weight [11]. They evaluated middle cerebral artery (MCA) PI, umbilical PI, and ductus venosus (DV) PI and stated that MHO was related to a positive test of the MCA, but finally in this group there was lower birth weight. Furthermore, there was a significantly higher rate of SGA neonates and admission to the neonatal intensive care unit (NICU) in cases with positive test of the MCA, meaning reactivity to oxygen.

A study of Deprest's group in 2011 published results on 38 fetuses undergoing a fetal endotracheal oculsion (FETO) procedure due to diaphragmatic hernia. They measured pulmonary vascular reactivity and lung size in relation to oxygen. Despite significant statistical analyses they concluded that MHO testing merited further study in expectantly managed cases (Done et al. 2011) [12]. One year later the same group

published their results regarding MHO text in normal fetuses (DeKoninck et al. 2012) [13]. They found that vascular reactivity in the pulmonary circulation increases in the first branch of the pulmonary artery, but large individual variability limited its use as a management tool.

In 2018 Khatib et al. from Israel published their experience in 12 fetuses with IUGR and 12 control and maternal MHOs [14]. The pulsatility index in the middle cerebral artery increased significantly from 1.5 ±0.27 to 1.88 ±0.48 ($p = 0.006$) in the high-risk group. However, it did not change significantly in the low-risk group. MHO caused a significant decrease in pulsatility indices in the pulmonary arteries for both groups. They concluded that MHO interrupted the relative brain-sparing effect in the intrauterine growth retardation group, but it did not significantly change the PI of the MCA in fetuses with adequate weight. The PI in the pulmonary arteries decreased significantly following hyperoxygenation.

Despite the fact that MHO has been used by obstetricians for over 25 years mainly for risk stratification of multiple disease processes, the overall evidence for its use in these conditions is weak and it is not widely accepted in general practice. Out of 13 selected publications (Table 1), 7 reported positive effects of MHO as a test, 1 had negative conclusion, and in 3 reports the conclusions were limited, with further investigation needed.

MHO as diagnostic test performed by cardiologists

The second pathway of the research on MHO as a diagnostic test came from a fetal cardiologists' group with an initial investigation in 1998 [15] (Table 2). Rasanen et al. published their observational study based on MHO in 40 fetuses: 20 mid gestation (20-26 weeks) and 20 late gestation (31-36 weeks) and came to the conclusion that MHO did not change any of the fetal echocardiographic parameters in mid-gestation fetuses, whereas between 31 and 36 weeks, the PI values of RPA, LPA decreased ($p < 0.0001$) and the PI of DA increased ($p < 0.0001$). In addition, the foramen ovale volume blood flow ($p < 0.03$) decreased. Left and right ventricular cardiac outputs were unchanged. All changes returned to baseline when MHO was discontinued.

In 2010 the fetal cardiologists Szwast et al. published research regarding MHO in fetuses with HLHS as a prediction of pulmonary vascularity response to predict perinatal survival and the need for emergency postnatal care [16]. Doppler echocardiography was performed in 27 normal and 43 HLHS fetuses. In HLHS, sampling was repeated after 10 minutes of MH with 60% FiO(2) and after 5 minutes of recovery. Sampling was performed in the proximal, midportion, and distal branch PA. Pulsatility index was used as a measure of vascular impedance. Of the HLHS fetuses, 34 had an open interatrial septum and 9 had a restrictive/intact atrial septum. At birth, 5 fetuses underwent immediate intervention on the interatrial septum. Middle cerebral artery PI was lower in HLHS versus normal fetuses ($p < 0.001$). There was no difference in UA, DA, or branch PA PI between normal fetuses and those with HLHS. MHO led to a significant decrease in PI at each of the PA sites sampled in fetuses with an open atrial septum ($p < 0.001$); however, there was no significant change in the PI in fetuses that required immediate intervention on the atrial septum at birth. Using a cut-off value of < 10% vasoreactivity, the sensitivity of MHO testing for determining the need for immediate intervention at birth was 100% (0.46-1.0), specificity was 94% (0.78-0.99), positive predictive value was 71% (0.30-0.95), and negative predictive value was 100% (0.86-1.0). No untoward effects were seen with MHO. They concluded that pulmonary vasoreactivity to MHO occurs in the fetus with HLHS. MHO testing accurately identified fetuses requiring urgent postnatal intervention at birth and may be used to select candidates for fetal atrial septoplasty.

Research from the Polish prenatal cardiology centre from 2011 [17] included 40 fetuses with cardiomegaly and lung hypoplasia: 11 cases with negative hyperoxygenation test died, and 17/24 with positive test survived. The probability of survival for fetuses with a positive test was significantly higher than for fetuses with a negative test ($p = 0.016$, Fischer's exact test).

In 2015, the group from CHOP [18] published their experience in 12 fetuses with atrial septal aneurysm creating functional anomalies such as LV hypoplasia with retrograde aortic flow. MHO did alter the atrial septal position, improved LV filling, and normalized aortic flow by increasing fetal pulmonary venous return.

Further research using MHO as a diagnostic test was performed in fetuses with HLHS in 2016 by Enzensberger [19] and again in 2018 by Szwast [20]. According to the Enzensberger study, the response of fetal lung vasculature to MHO in 22 fetuses with HLHS was evaluated, with special attention paid to differentiating between newborns who did not require immediate atrial septostomy and newborns who underwent immediate atrial septoplasty after birth. Lung perfusion was qualitatively assessed by using the PI for veins. Measurements were performed both with the mother breathing room air and after receiving 100% oxygen for 10 minutes. The test was defined as positive if the MHO led to an increase in lung perfusion and as negative if the MHO did not lead to an increase. They concluded that MHO might be a useful adjunct in the assessment of pulmonary vasculopathy in fetuses with HLHS.

In a study by Szwast et al. [20] in fetuses with HLHS, MCA PI was evaluated in fetuses > 28 weeks. The authors concluded that the results may have implications for clinical trials utilizing MHO as a neuroprotective agent (Table 2).

The same year, Schidlow and Donofrio [21] published their experience in MHO testing in 12 fetuses with different cardiac defects: 2 with Ebstein anomaly, 2 with total anomalous pulmonary venous connection (TAPVC), 4 with hypoplastic left heart syndrome (HLHS) with (a) restrictive atrial septum (RAS) or (b) intact atrial septum (IAS) with decompressing vertical vein (VV), and 4 with D-loop transposition of the great arteries (TGA). Pulmonary vascular reactivity and physiological and anatomical changes with MHO and outcomes were recorded. They concluded that MHO was useful to identify fetuses with

CHD at risk for perinatal compromise. Additional studies may yield insights into fetal pulmonary vascular reactivity and elucidate predictors of perinatal outcomes.

MHO as a therapy

The idea that there is a possibility through MHO of enhancing venous return to the left ventricle and aorta of the fetus, and that it could improve development of the left heart when MHO is used for longer time, was proposed for the first time by Kohl in 2010 [22] (Table 3). He suggested that increasing the oxygen concentration in gas inspired by the mother would improve oxygenation of blood in the fetus, induce pulmonary vasodilatation, and thus increase pulmonary venous return and enhance left ventricular output. This analysis found that chronic intermittent MHO administered in late gestation may be associated with improvements of hypoplastic cardiovascular dimensions in fetuses with a variety of left sided cardiac malformations. This finding suggested benefit for postnatal treatment options and prognosis in suitable cases.

Kohl did not find any adverse maternal, fetal, or neonatal events during and after chronic MHO. More specifically, neither detrimental changes to uterine and feto-placental blood flows, fetal cardiac failure, nor preterm constriction of the ductus arteriosus or postnatal pulmonary hypertensive events occurred in any of the fetuses. After MHO, the mothers exhibited normal chest X-rays and normal pulmonary function.

In 2011 Kohl published a case report about fetus with suspected coarctation [23] with a narrow aortic isthmus and reversal of flow in the aortic arch. During MHO over 14 days, 45% of oxygen was administered to the mother via a face mask in 3 daily sessions of 3 to 4 hours' duration. After MHO there was normal blood flow in the aortic arch. The newborn was born at term and did not required any procedure.

In China Zeng [24] studied fetuses with suspected fetal coarctation. Sustained maternal oxygen therapy improved left cardiac dimensions, especially the isthmus dimension. During maternal hyperoxygenation treatment, the Z-scores of the left cardiovascular structures – namely, the mitral valve (MV), aortic valve (AoV), aorta ascendens (AAo), and isthmus – increased significantly, and in the control group with air, the left heart dimension remained unchanged. Of note is that there were more babies with bicuspid aortic valve and aortic valve stenosis in the inefficacy group. They suggested that starting O_2 at 32 weeks is early enough to see changes. The left heart dimension Z-scores increased gradually during MHO therapy periods, especially after 4 weeks of oxygen therapy. There were no complications, including development of retinopathy of prematurity. These findings provide useful information for the development of novel treatment strategies and promote intrauterine therapy in fetuses with coarctation.

Lara in their study they found that chronic MHO is feasible [25]. No mother enrolled in the intervention group discontinued participation in the study, and all underwent chronic MHO therapy until delivery. However, some mothers did find wearing the non-rebreather mask for many hours each day challenging, and this resulted in 2 mothers having mean daily hours on oxygen lower than the goal (8 h) of the study. Their study provided information for future investigations of chronic MHO as a therapy for left heart growth or as therapy for brain immaturity seen in congenital heart disease. They were able to demonstrate that fetuses with left heart hypoplasia undergoing chronic MHO had significantly increased aortic flow and no significant evident maternal or fetal complications. Effect estimates of aortic and mitral annular growth in fetuses undergoing chronic MHO compared with controls were positive, although no differences were statistically significant. Furthermore, fetuses on chronic MHO for more hours per day had greater aortic annular growth. Based on findings, chronic MHO therapy deserves further investigation as a low-risk intervention for fetal left heart hypoplasia.

A note of caution, however: although MHO has been recommended to increase left ventricular size and to limit cerebral damage, there are potential complications. Edwards et al. reported diminished biparietal fetal head dimensions both in fetuses and during postnatal life [26].

The current medical literature on MHO for testing or therapy mostly relies on cases reports and is considered of lower value comparing with big datasets; however, in some instances they present educational values and may provide crucial observations. In 2014 Ishii from Osaka published a case report about diaphragmatic hernia complicated by fetal congestive heart failure, and MHO was administered at the 35th week for 2 weeks: 3 hours 4 times per day [27]. Maternal hyperoxygenation therapy was initiated to increase pulmonary blood flow and promote venous return to the left ventricle. Fetal echocardiography demonstrated improved cardiac performance. A female infant was born at 37 weeks of gestation and underwent diaphragmatic repair shortly after birth. She survived surgery and was discharged at 4 months of age.

Another case is the literature reports using MHO in a fetus with Ebstein anomaly at risk for fetal demise [28]. MHO therapy was proposed to constrict the ductus arteriosus to reduce the aortic-to-pulmonary shunt and augment pulmonary blood flow by decreasing pulmonary vascular resistance. MHO was performed for 2 weeks (Table 3), and at 36 weeks there was emergency CS. At 2 weeks of age, the infant underwent primary repair of the tricuspid valve and reduction annuloplasty, with right atrial reduction. The infant was discharged home at 2 months of age after an uneventful cardiac postoperative course.

In 2020 Rydzewska et al. [29] and our group published a series of 45 fetuses with Ebstein disease. In 3 cases MHO in addition to steroids and digoxin transplacental treatment was used, and all 3 survived.

The cases presented above [27-29] and MHO suggest that stimulating prenatal closure of the ductus arteriosus in late gestation may have a beneficial role in the management of severe fetal Ebstein's anomaly and congestive heart failure. MHO may reduce pulmonary vascular resistance and promote antegrade pulmonary blood flow changing the circulation to support improved cardiac output. So, MHO may be helpful in selected congenital heart defects to better predict perinatal management [30].

Despite this positive information there is, however, a single publication with negative assessment of MHO. Rudolph [31], considering the fact that a beneficial effect of chronic MHO on left ventricular development is questionable and that it possibly interferes with cerebral development, proposed that studies of the use of MHO administered repeatedly for several hours a day be curtailed (Table 4).

Taking into account the data from the literature as well as our own experience from fetal cardiac centres, at the current stage of our knowledge, we would recommend MHO as a test to understand fetal hemodynamics and predict the transitional circulation in high risk fetal cardiovascular, lung, or placental disease.

The gestation age of the fetus for MHO should be at least 32 weeks.

The MHO test can be safely performed on an out-patient basis, the suggested time is 15 minutes with 6-8 l with breathing 100% oxygen. The test should be preceded by a complete echo exam, and after 15 minutes some elements (Table 5) should be repeated for off line analysis.

Based on the current literature, for safety reasons, and to collect more data, MHO as a therapy should be considered mainly on in-hospital basis in fetal cardiology centres, in case the team of experienced fetal cardiologists would approve the plan for further investigation. Ethical committee approval is necessary, as well as maternal consent. A fetal heart examination should be performed at least once a week. The optimal time for MHO as a therapy is at least 2 weeks, 3 times daily for 3-4 hours. It is highly recommended a multicentre study be performed. It is beyond the scope of this review to evaluate MHO by fetal MRI because this modality is currently not widely used.

Conclusions

Based on the current literature, it can be concluded that MHO has no harmful effect on pregnant woman and no harmful effect on the fetus or neonate when used in the short term for testing. More data and longer paediatric and neurological follow-up are needed to determine the safety when used chronically as a fetal therapy. Institutional Review Board approval is recommended as well as the mother's informed consent.

Maternal hyperoxygenation as a test might be a useful tool for testing the fetal circulation, and it gives us insight into the fetal cardiovascular physiology in utero and during transition and might be helpful for the better stratification for perinatal care in fetuses with heart defects, such as HLHS, coarctation, bordelinie left heart, transposition of the great arteries, and Ebstein syndrome.

Assessment of blood flow and cardiovascular status during MHO by fetal echocardiography in the 3rd trimester is challenging and requires a high level of expertise. Optimally it should be performed in fetal cardiac centres.

Conflict of interest

The authors declare no conflict of interest.

Table 4. Maternal hyperoxygenation in experimental examination

Name	Year	No. of lamb fetuses	Conclusions
Rudolph [31]	2020	Review paper	Negative or warning

Table 5. Recommended minimal data from fetal echocardiography before and after maternal hyperoxygenation (MHO) (+BPD measurements during fetal life and later at 3, 6, and 12 months)

Recommended data from fetal echocardiography to evaluate MHO
• Pulmonary venous flow: V max, VTI,
• Pulmonary artery flow: V max
• RPA and LPA: V max
• Ao isthmus in long axis: size (in mm) and V max
• Ductus arteriosus V max and PI
• MCA V max and PI

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Division of work:
Maria Respondek-Liberska (ORCID: 0000-0003-0238-2172): collection and assembly of data, writing the article, final approval of article.
Mary Donofrio (ORCID: 0000-0002-0942-5481): data analysis and interpretation, critical revision of the article, final approval of article.