Title:	Transposition of the Great Arteries: Prenatal Anatomical and Hemodynamic Findings associated with Perinatal Outcomes
Short Title	Fetal TGA
Sponsor	Dr. Edgar Jaeggi/The Hospital for Sick Children
Protocol Date:	20 November 2018

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ABBREVIATIONS AND DEFINITIONS OF TERMS; ALPHABETICAL ORDER

AAo	Ascending aorta
ASO	Arterial switch operation
BAS	Balloon atrial septostomy
CO	Cardiac output
DA	Ductus arteriosus
DAo	Descending aorta
FO	Foramen ovale
IAS	Intact atrial septum
IVC	Inferior vena cava
LA	Left atrium
LV	Left ventricle
MCA	Middle cerebral artery
MH	Maternal hyperoxygenation
PA	Pulmonary artery
PGE	Prostaglandin
PI	Pulsatility index (peak systolic velocity – end-diastolic velocity / mean velocity)
PPHN	Persistent pulmonary hypertension of the newborn
PV	Pulmonary vein
RAS	Restrictive atrial septum
RV	Right ventricle
SVC	Superior vena cava
TGA/IVS	Transposition of the great arteries with intact ventricular septum
UV	Umbilical vein/venous
VSD	Ventricular septal defect
VTI	Velocity time integral

PROTOCOL SUMMARY

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Short Title	Fetal TGA
Sponsor	Dr. Edgar Jaeggi/The Hospital for Sick Children
Principal Investigator	Edgar Jaeggi
Primary Objective	Determine the association between response to MH and neonatal outcome
Secondary Objectives	Determine the change of cerebral perfusion for acute MH
Study Population	Pregnant women with a fetal diagnosis of TGA
Study Design	Prospective pilot study
Sample Size	N = 50
End points	Fetal demise or neonatal death or neonatal discharge
Study Drug/ Intervention Description	Transient maternal oxygen administration during echocardiographic and MRI imaging

1. INTRODUCTION

In transposition of the great arteries (TGA), a condition that affects ~3/10,000 live-births, the aorta arises from the morphological right ventricle (RV) and the pulmonary artery from the left ventricle (LV) while the atrio-ventricular connections are concordant. The inverted great arterial arrangement can be anatomically corrected by an arterial switch operation (ASO) in early infancy with low perioperative mortality and excellent long-term results. In the prenatal circulation with the placenta as the sole source of fetal oxygenation, TGA is usually well tolerated. With the transition to the postnatal circulation at birth, the lesion may become immediately life-threatening as the RV pumps desaturated systemic venous blood back into the aorta while oxygenated blood from the lungs is forwarded by the left heart back into the pulmonary artery. The neonate with TGA will become profoundly hypoxemic and acidotic shortly after birth unless there sufficient shunting of oxygenated pulmonary venous blood into the right heart and aorta. TGA is now predominantly detected before birth but reliable prenatal prediction of the neonatal hemodynamics and risks by conventional fetal echocardiography has remained very challenging. On the other hand, maternal hyper-oxygenation (MH) to increase the fetal O_2 saturation may be used to mimic the drastic events that occur during the normal transition from fetal circulation to the postnatal physiology that includes dilation of the

pulmonary vasculature, increase in pulmonary arterial blood flow and left atrial pre-load, potentially affecting shunting of blood across the atrial septum. In this prospective pilot study we will determine whether MH is a useful diagnostic test to separate fetuses with insufficient intracardiac shunting from those with adequate shunting early after delivery.

2. BACKGROUND & STUDY RATIONALE

2.1 Clinical relevance of TGA

TGA is the predominant cardiac cause of neonatal cyanosis and affects 5-7% of newborns with congenital heart disease (1). The condition is usually repairable with a neonatal ASO, which carries a low surgical mortality risk of 2-5% (2, 3). Indeed, morbidity and mortality is nowadays greater in the preoperative period. Many preoperative problems are secondary to a restrictive or intact atrial septal (RAS) communication, and/or ductal constriction, resulting in inadequate shunting of oxygenated blood to the right heart, systemic hypoxemia and rapid progression to acidosis, neurological injury and shock (4-7, 9). Yet even with an in-utero patent atrial septum, a newborn may become critically ill shortly after birth once the FO closes. Immediate neonatal balloon atrial septostomy (BAS) becomes a life-saving procedure in this situation. Of neonatal survivors, persistent pulmonary hypertension of newborn (PPHN) is another possible association with a poor postnatal outcome, affecting ~1-3% of children with TGA (6, 8).

2.2 Prenatal Cardiac Imaging

Most cases of TGA in Ontario are nowadays detected before birth and referred to the Fetal Cardiac Program at the Hospital for Sick Children. All patients undergo repeated assessment before birth including a final fetal echocardiogram and a fetal MRI before delivery for prediction of the neonatal risk of severe cyanosis. This is standard care and not research-related.

Better prediction of the neonatal hemodynamics before birth would dramatically facilitate the perinatal care of babies with TGA but is not reliably obtained by conventional imaging.

The prenatal risk assessment of TGA is currently based on the two-dimensional and Doppler echocardiographic evaluation of the heart and in particular of possible shunts across the atrial septum, the ventricular septum, and the arterial duct. In the fetal circulation, the foramen ovale (FO) is an important provider of oxygenated umbilical blood from the placenta to the left heart. The crescent shaped FO, located in the central portion of the secundum atrial septum, progressively increases in width up to 6 mm at term. The thin, mobile septum primum is positioned on the left side of the atrial septum and functions as a flap valve of the FO. During most of the cardiac cycle, it is pushed into the left atrium (LA) by the steady stream of blood that enters the FO. The fetal echocardiographic evaluation of the atrial septum mainly relies on the size of the FO, the position, mobility and shape of the FO flap and the documentation of right-left shunting across the foramen ovale. The prenatal evaluation of the arterial duct includes the echocardiographic assessment of its diameter and documentation of ductal patency and flow direction by color and pulse wave Doppler imaging.

Fetal MRI offers a versatile set of additional tools to assess the fetal physiology and is routinely offered to parents at SickKids to examine the hemodynamic alterations of cardiac lesions and the

impact on the perfusion of organs such as the brain (6–8). Our center has significant experience with the clinical-research applications of MRI in the human fetus (9). This includes the application of fetal MRI in combination with MH (REB No 1000048468).

Importantly, MRI and echocardiographic imaging pose no known risks to the fetus and the mother.

2.3 Maternal Hyperoxygenation

This study will examine whether MH is useful as a diagnostic test to more accurately detect TGA patients with poor vs. good neonatal intra-cardiac mixing of blood, based on the in-utero response to oxygen exposure. Acute maternal oxygen administration will transiently increase the fetal oxygen levels to those reached at birth with spontaneous breathing, thus simulating conditions that will naturally occur at the time of birth. Echocardiogram and MRI will be used to examine the effects on the fetal circulation. This is the research-component of this study.

It has been discovered 80 years ago that maternal inhalation of oxygen during labour increases the oxygen content in the umbilical cord. In the sheep model, e.g., maternal administration of 100% oxygen increases the fetal arterial pO_2 from 20-25 mmHg to ~30-35 mmHg and the arterial O_2 saturation from 65% to 80%. Similarly, MH increased the UV O_2 saturation from 75% to 95% and UV pO_2 from 32-35 mmHg to 40-50 mmHg (10).

The effects of MH were also studied in the human fetus. Brief maternal administration of 65-70% O_2 via a face mask during the last trimester, *which is what will be used in our study*, led to a significant increase in UV O_2 saturation in the normal fetus followed by pulmonary vasodilatation. If maternal O_2 was administered over a prolonged period in late gestation, the effect on the pulmonary vasculature disappeared within a few hours.

Limited information is available about the most appropriate amount of O_2 to be used for MH. Experimental data from animal and human subjects showed that increasing FiO_2 from room air to 40% resulted in the greatest increase in fetal PaO_2, and maximal effects on the fetal circulation. Furthermore, inhaled O_2 up to 15L/min is well tolerated via a simple face mask, which results in a FiO_2 of ~40 to 50%. While no adverse effects of chronic MH were reported when used to treat fetal growth restriction (14-16), a Cochrane review (11) of experimental animal data raised the possibility that chronic maternal hyperoxygenation could reduce uterine arterial blood flow, and thus recommended further investigations if chronic maternal O_2 was to be used for this indication. *This is not expected with acute hyperoxygenation. Effects on the arterial duct are also unlikely to occur due to the short duration of O_2 supplementation: it usually takes at least 1-2 days for spontaneous ductal closure at birth. Ductal constriction was not observed in any of the previous studies using MH* (12).

In this study, we will examine the added diagnostic value of acute MH in predicting neonatal maladaptation due to poor intracardiac mixing of oxygenated blood. MH (70% of O_2 by face mask) will be administered in late gestation at two separate occasions, during echocardiography and MRI. The rate and duration of MH (10 to 15L/min by mask for up to 30-45 minutes/test) is considered to be safe to the mother and her fetus. We know that if acute MH is used in the normal 3rd trimester fetus with a patent FO, this leads to pulmonary vasodilation, a 30-50% increase in pulmonary blood flow and in left atrial load, as well as a reduction in DA flow by

fetal MRI (13). Data on the acute effects of MH on fetal TGA are limited and no specific studies have been performed to study the response of the pulmonary vasculature to supplementary O_2. MRI data obtained without the use of MH in 4 fetuses with TGA/IVS and suspected RAS at SickKids (14) demonstrated significantly reduced flow across the FO, increased combined cardiac output, and increased flow in the ascending (AAo) and descending (DAo) aorta, UV, and aorto-pulmonary collaterals when compared with normal fetuses. The fetus with the lowest FO shunting and highest aorto-pulmonary collateral flow died from PPHN after birth.

2.4 Study Rationale

To examine the baseline fetal hemodynamics as well as the response to acute MH as an added diagnostic test, we will combine various fetal echocardiographic and MR imaging tools. The prenatal findings will then be compared to the neonatal presentation.

We postulate that conditions that predispose newborns to acute neonatal compromise will be detectable and distinguishable prior to birth by echocardiography, MRI, or by combining the findings of both exams. We expect to encounter the following 4 clinical scenarios:

1) *TGA/IVS with unrestricted atrial shunting before and after birth*: we expect fetal baseline differences in LV/RV O_2 content and DAo/AAo O_2 content related to unrestricted right-left atrial shunting. MH is expected to further increase the differences in LV/RV O_2 content and DAo/AAo O_2 content, which leads to an increase pulmonary blood flow, LV preload and LV stroke volume due to O_2-mediated vasodilation of the pulmonary vasculature. As a confirmation of pulmonary vaso-reactivity to O_2, the branch PA pulsatility index will decrease by ≥10% and this will coincide with lower peak systolic flow and reversal of end-diastolic flow across the DA.
2) *TGA/IVS with in-utero RAS:* In the absence of intracardiac shunting, RV/LV and DAo/AAo O_2 content will be equal at baseline and with MH and no significant effect on pulmonary flow will be observed.
3) *TGA/IVS with postnatal RAS:* RV/LV and DAo/AAo O_2 content will differ at baseline when the FO is still patent. With MH-induced functional closure of the FO by the septal flap, the RV load and AAo O_2 content will preferentially increase to reach an equal or higher oxygen content and saturation when compared with the LV, MPA, DA and DAo.
4) *TGA with PPHN:* supplementary maternal O_2 will not affect fetal pulmonary blood flow and PA pulsatility.

2.5 Potential Benefits and Risks of Study Participation

The potential implications of this study are clinically important. Not only would it help with the parental counselling and facilitate the perinatal care of future fetuses with TGA but for TGA/IVS with severe RAS it may also offer the possibility of a pre-delivery BAS or a planned delivery with ECMO stand-by to prevent hypoxemic organ damage (18).

The risk to the mother will be the potential of some discomfort related to the oxygen administration and the added time of the exams. We may also detect findings that have not been detected previously by echocardiography, which will then have to be disclosed to the family and may cause additional parental concerns.

3. COMPLIANCE STATEMENT

This study will be conducted in full accordance with all applicable Hospital for Sick Children research policies and procedures, International Conference on Harmonisation Good Clinical Practice (ICH GCP) and all applicable regulations and the PHIPA Privacy Rule. Any episode of noncompliance will be documented.

The investigators will perform the study in accordance with this protocol, will obtain consent, and will report unanticipated problems in accordance with Hospital for Sick Children REB policies and procedures and applicable regulatory requirements. Collection, recording, and reporting of data will be accurate and will ensure the privacy, health, and welfare of research subjects during and after the study. The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the Research Ethics Board (REB) for review and approval.

4. STUDY OBJECTIVES

The purpose of the study is to detect prenatal findings that are associated with early postnatal morbidity and mortality.

4.1 Primary Objective

The primary objective is to examine and characterize the response, or lack thereof, to acute MH as a diagnostic test on intracardiac/ductal shunting and pulmonary blood flow among fetuses with TGA, and to clarify its associations with measures of neonatal outcomes.

4.2. Secondary Objectives

A secondary objective will focus on the acute effects of MH on the cerebral perfusion.

4.3 Study Endpoints

Study endpoints are any of the following outcomes: survival to discharge from Hospital as a primary outcome. A secondary outcome will be any evidence of perinatal compromise as defined in the protocol. This will be associated with the fetal response to oxygen. For cases with PPHT with RV pressure >50% of the systemic pressure at the time of discharge, the outcome to 1 year of life will be ascertained.

5. INVESTIGATIONAL PLAN

5.1 Study Design

This is a prospective single centre study on the association between prenatal cardiovascular findings, the fetal response to MH and neonatal morbidity and mortality.

5.2 Patient Numbers and Study Duration

Recruitment will be from the time of REB approval of this study to the time 50 patients have successfully completed the study. We follow approximately 30 women per year with a fetal

diagnosis of simple TGA, defined as TGA either with an intact ventricular septum or with ventricular septal defect(s) (VSD). The rate of pregnancy termination is low (<5%) as most affected babies do not carry a risk of significant non-cardiac disorders. Parents of a child with congenital heart disease are also highly motivated in participating in research that might help their or other children with the same condition and we anticipate that at least 80% of eligible women will be willing to participate in this research. Based on these assumptions, we anticipate being able to successfully recruit 50 participants within ≤ 2.5 years.

5.3 Eligibility Criteria

Inclusion Criteria:

1) Pregnant mothers ≥18 years of age
2) Fetal diagnosis of simple TGA and intention of active treatment after birth
3) Written maternal informed consent

Exclusion criteria:

1) Termination of pregnancy
2) Complex TGA (e.g. Taussig-Bing anomaly or moderate-severe outflow tract obstruction, fetal arrhythmia such as frequent premature atrial beats, abnormal baseline heart rate (<110 bpm; > 160 bpm) in the third trimester)
3) Major non-cardiac lesions
4) Significant maternal co-morbidities that precludes a fetal MRI (e.g. significant obesity, claustrophobia)

6. STUDY PROCEDURES

6.1 Study Procedures

Antenatal diagnosis of TGA followed by a referral to the Fetal Cardiac Program at SickKids is typically made during mid-gestation. Fetal echocardiography including a late-gestational MRI is routinely used in the assessment of all prenatally diagnosed TGA.

The initial echocardiogram allows differentiating between simple vs complex form of TGA and determining whether or not a patient fulfills eligibility criteria to potentially participate in the study. The physician will explain the possibility of MH in the last trimester that as a diagnostic test may help with the management of future patients with the same condition. If the patient is interested in hearing more details about MH, more information will be provided to help families decide whether they would like to participate in the study. This will allow coordination of echocardiograms and MRI studies on the same day, whenever possible.

Mothers with fetal TGA are routinely seen at SickKids for a final fetal echocardiogram in late gestation (≥34 gestational weeks). The final exam includes detailed re-evaluation of all cardiac structures including blood flows across the atrial septum, AV and semilunar valves, arterial duct, pulmonary and cerebral blood flows, among other. Following the exam, perinatal management recommendations are made and discussed with the family. This typically includes the

recommendation of 1) delivery at Mount Sinai Hospital, 2) initiation of IV prostaglandin at birth, and 3) referral to SickKids critical cardiac care unit for early neonatal care that may include preoperative BAS. Whether a mother elects to participate or not in this study, the baseline echocardiogram and perinatal management will not be affected by the maternal decision.

The following are study-related additional procedures, if a mother who fulfils all inclusion and none of the exclusion criteria consents in writing to participate in this study:

1) A fetal echocardiogram during acute MH
2) A fetal MRI during acute MH

6.1.1 Consent Process

The study may be explained by the fetal cardiology team prior to the last prenatal encounter. Maternal consent will be obtained by a person (research coordinator or another physician) who has no direct involvement in the care of this patient at the second last (generally 28-30 weeks) visit or at the time of the last fetal exam (≥34 weeks). Moreover, it will be explained that she can drop out of the study at any time. Once enrolled, participants (mother and child) will be assigned individual study numbers to allow de-identified data entry in a password protected Excel database that will be securely stored on the SickKids server and be accessible to the research team only.

6.1.2 Fetal Echocardiography

All fetal echocardiograms will be performed with standard GE Voluson E-10 or Philips IU 22 ultrasound systems within the Echo Lab facility or the Cardiac Diagnostics & Interventions Unit (CDIU) at SickKids. Fetal echocardiography poses no known risks to the mother and her fetus.

At the final visit, the mother will initially undergo a baseline fetal echocardiogram that will include the assessment of left and right ventricular outflow tract (peak flow, velocity time integral (VTI), heart rate, aortic and pulmonary valve diameters), the arterial duct (systolic and end-diastolic flow, forward/reverse flow ratio, VTI, diameter), branch pulmonary artery (peak flow, pulsatility index calculated as peak systolic velocity – end-diastolic velocity/mean velocity), pulmonary veins (VTI), atrial septum (FO diameter, atrial shunt direction and velocities, atrial septal excursion), mid cerebral artery (peak, VTI), as well as ventricular dimensions (diameter in 4CV; volumes by 3/4D). These findings will be digitally recorded and all measurements will be made offline by the responsible cardiologist to abbreviate the duration of the exam. The percent changes in flow VTIs, percent changes in flow PIs and DA forward/reverse flow ratios will be calculated using the echocardiography data.

Immediately following the baseline echocardiogram, maternal oxygen will be administered in the same room via a sterile face mask to reach about 65-70% of oxygen and delivered at a rate of 10 to 15L/minute. After a 5 minute-period to allow fetal steady-state oxygenation, the same echocardiographic variables as above will be recorded during continuous maternal O_2 supplementation, which is expected to take maximally 30 minutes or less. During the exam, the fetal wellbeing will be continuously monitored by fetal echocardiography, which allows us to continuously see the baby's movements and heart function. Oxygen supplementation will be

stopped once the above imaging variables have been obtained or after a maximum of 30 minutes (5 minutes initiation + 25 minutes echocardiogram) if the test cannot be completed within this time frame. No further research related measurements will be obtained once the MH has terminated.

6.1.3 Fetal MRI

We routinely perform late-gestational MRI for fetal TGA before birth to examine fetal hemodynamics and the brain. Fetal MRI poses no known risks to the mother and her fetus. Baseline and MH MRI will be performed as usual with a clinical 1.5T MR system in the CDIU. No sedation or invasive techniques will be required to perform MRIs on pregnant women. The MRI study will take a maximum of 90 minutes including MH study, which is expected to take maximally 45 minutes. The subjects will be fitted with their usual supply of oxygen via a face mask during MRI. The same amount of O_2 at the same flow rate will be administered as described above.

As with all our fetal MRI studies, a standard multichannel body surface coil will be placed over the maternal abdomen and imaging performed for a maximum of one hour. MR flow assessments will be acquired according to our previously published technique to examine the distribution of blood flow across the fetal circulation (15). The PC MR acquisitions will be analyzed using a commercial software (Q-flow, Medis) and the oximetry measurements will be analyzed using a region of interest placed over the central 50% of the vessel diameter on the T2 map, according to our previously published techniques (15,16). The imaging protocol has been detailed in previous publications and includes T1 and T2 weighted imaging, diffusion tensor imaging, MR spectroscopy and brain volumetry (15,17). MR oximetry will be recorded in the ascending aorta (AAo), superior vena cava (SVC), descending thoracic aorta (DAo), umbilical vein (UV) and main pulmonary artery (PA). Oxygen content at baseline and during MH will be measured offline at the level of the LV/MPA, RV/AAo and DAo. Blood flow quantifications (baseline and MH; cine-phase contrast) will be made in the AAo, DAo, main and branch PAs, SVC, IVC, UV and DA. Other variables will include estimated hematocrit (HCT), fluximetry, brain volumetry (baseline; 3D steady state), cDO_2 and cVO_2 (baseline and MH; T2 mapping) to measure oxygen consumption. Oxygen supplementation will be stopped once the above imaging variables have been obtained or after a maximum of 45 minutes (5 minutes initiation + 40 minutes MRI) if the test cannot be completed within this time frame. No further research related measurements will be obtained once the MH has terminated.

The MRI data will be used to calculate right ventricle cardiac output, left ventricle cardiac output, combined ventricle output, pulmonary artery flow, aorta-pulmonary collateral flow, foramen ovale flow and aortic isthmic flow.

6.1.4 Neonatal Data

Newborns with antenatally diagnosed TGA are routinely transferred to the Critical Care Unit immediately after their delivery for the preoperative management. Unless a VSD is large enough to allow discharge home with adequate oxygen saturations and to delay surgery to later in infancy, a neonatal ASO is the treatment of choice and mainly completed during the first week of life. Early neonatal preoperative procedures may include BAS and/or the use of IV prostaglandin to improve the oxygen saturation. Less commonly, intubation, ventilation or even ECMO may also be required prior to the surgical intervention. As measure of patient morbidity, a composite

score of 10 variables will be used, assigning a value of 1 for each event that occurred between birth to hospital discharge or in-hospital death respectively: 1) respiratory distress syndrome requiring surfactant; 2) cardiopulmonary resuscitation requiring chest compressions; 3) cerebral vascular injury (intra-ventricular or -parenchymal hemorrhage, ischemic stroke); 4) necrotizing enterocolitis; 5) need of ECMO; 6) infections associated with health care (bloodstream, surgical site, and urinary tract infection); 7) unplanned re-intubation; 8) re-operation for residual cardiac lesions; 9) interventional catheterization for residual cardiac lesions; and 10) unplanned intensive care readmission.

6.2 Data Sources

Potential study subjects that will be identified in the Fetal Cardiac Clinic at the Hospital for Sick Children (see above). Data will be collected from the patient's health chart, echocardiography images and MRI images.

6.3 Collected Patient Data

A) Prenatal Echocardiography

- Date of exam (dd/mmm/yyyy)
- Gestational age at exam (weeks/days)
- Estimated fetal weight (g)
- MPA valve diameter
- Aortic valve diameter

Imaging variables at baseline and with MH:

Atrial septal morphology (2D; 4D) and foramen flow (color; 4D flow)

- FO diameter
- Septal excursion
- Shunt description

Branch PA flow (mid-portion)

- peak flow
- VTI
- PI (peak systolic velocity – end-diastolic velocity/mean velocity)

PV Doppler flow:

- VTI

MPA:

- VTI
- Heart rate
- LCO

AAo:

- VTI
- Heart rate
- RCO

DA flow (color and Doppler):

- minimal diameter
- reversed end-diastolic flow: yes – no
- systolic peak flow
- forward-reverse flow ratio

flow restriction: yes - no

MCA Doppler flow

peak flow

VTI

PI

UA Doppler flow

Peak flow

VTI

PI

RV and LV (4D): volumes

B) Fetal MRI

- Date of exam
- Gestational age at exam (weeks+days)
- Fetal weight estimation (g)
- Fetal weight Z-score
- Fetal weight percentile
- Brain volumetry (mL) (baseline; 3D steady state)
- Placenta volumetry (mL)
- Estimated HCT
- UV
- DAo
- Ventricle (specify R or L)
- Imaging variables at baseline and with MH

Cardiovascular oximetry ($SatO_2$):

LV

MPA

RV

AAo

DAo

UV

SVC

Fluximetry ($ml/min/m^2$):

AAo

DA

Main PA

RPA

LPA

SVC

IVC

UV

DA

Brain ($ml/min/m^2$):

cDO_2
cVO_2
Fetus (ml/min/m^2)
DO_2
VO_2
Placenta Volumetry
T2 star

Patient Safety during MH

- Adverse events

C) Postnatal Outcomes

- Date of birth (dd/mmm/yyyy)
- Delivery place
- Gestational age at birth
- Weight at birth
- Placental weight at birth
- APGAR score (1 and 5 minutes)
- PaO_2 and SpO_2
- Age at CCU admission
- Neonatal interventions: stat BAS, oxygen, intubation/ventilation, ECMO, other
- Neonatal PGE: yes – no; time of start
- Neonatal BAS: yes – no; age at procedure
- Pre-op/pre-BAS: hemoglobin; minimal pH; minimal preductal PaO_2; peak lactate
- Pre-BAS compromise (defined as minimal pre-BAS pH ≤7.1, SaO_2 ≤40%, PaO_2 ≤25 mmHg, maximal serum lactate ≥10 mmol): yes - no
- Pre-BAS echo: ASD and VSD size, shunting, and gradients
  Persistent pulmonary arterial hypertension (defined as combined pre-operative reverse differential cyanosis ≥ 30% and/or postoperative RVp ≥ 75% systemic ≥48h post-surgery and/or ≥50% at postoperative discharge): yes – no
- Pre-op complications: organ failure; NEC, cerebro-vascular injury; death
  - Date of event
  - Age at event
- Date of surgery
- Age at surgery
- Type of surgical repair: ASO; VSD closure, other
- Outcome to discharge or to 1 year if PPHT
- Morbidity score:
  - RDS requiring surfactant
  - CPR requiring chest compressions
  - Cerebral vascular injury (intra-ventricular or –paranchymal hemorrhage, ischemic stroke)
  - NEC
  - ECMO
  - Hospital associated infections
  - Unplanned re-intubation

    - Re-operation for residual cardiac lesions
    - Interventional catheterization for residual lesions
    - Unplanned CCU readmission
- Date of discharge
- Age at discharge

7. ASSESSMENT OF ADVERSE EVENTS

While no adverse events or serious adverse events (AEs or SAEs) have ever been reported in the literature and in our own experience (12) with the transient and sustained use of the study drug (MH), patient safety is an important aspect of any research study. Acute MH will be considered safe if the administration of oxygen is a) well-tolerated by the mother and fetus and b) oxygen delivery is maintained or improved during MH. This is particularly important as MH is considered a potential long-term prenatal treatment option to improve oxygen delivery to the brain.

Although an AE/SAE related to the fetus is unlikely to occur as a result of research participation, if an AE/SAE occurs, the primary physician will be responsible to identify, and to classify the seriousness, severity, causality and expectedness as follows:

a) Assessment if event qualifies as serious:

Serious Adverse Event (SAE): A SAE is any untoward medical occurrence that at any dose:

- Results in death,
- Is life-threatening,
- Requires inpatient hospitalization or prolongation of existing hospitalization,
- Results in persistent or significant disability/incapacity
- Results in congenital abnormalities or birth defect

Other events may be treated as SAEs if the physician considers it to be an important medical event that may jeopardize the participant or require intervention to prevent one of the other outcomes listed above.

b) Severity assessment:

Mild	Events are considered MILD if signs/symptoms are mild, clinical relevance is marginal, laboratory findings are asymptomatic and no specific medical intervention is required.
Moderate	Events are considered MODERATE if they require minimal, local, or non-invasive intervention only.
Severe	Events are considered SEVERE if they interrupt the participant's normal daily activities and generally require systemic drug therapy or other treatment; they are usually incapacitating.

c) Causality assessment:

Definitely related	There is a certainty that the event is related to the study drug(s).
Probably related	There is high likelihood that the event is related to the study drug(s).
Possibly related	There is a likelihood that the study drug(s) is the cause of the event, but other causes cannot be ruled out.
Unlikely related	It is not likely that the event is related to the study drug(s), and other more likely causes are present.
Unrelated	Evidence exists that the event is related to something other than a study drug.

In the event of an AE, we will use a variety of sources of information to identify possible side effects of the MH including direct observations, imaging data, participant reports, laboratory reports and other medical reports. The PI and study team will evaluate the circumstances and clinical correlation of the events. If a serious and unexpected AE occurs that is deemed to be possibly related to the use of MH (e.g. fetal death within a day of the oxygen administration), we will discontinue the use of supplementary oxygen to that study participant as applicable, immediately place the study on hold indefinitely, and the PI will report the case to the DSMB and Health Canada.

In the case of a moderate AE that is considered possibly related to the intervention (e.g. cardiac dysfunction such as fetal bradycardia of less than 90 beats per minute for more than 1 minute), we will discontinue the administration of oxygen in that study participant and the DSMB will review the event at their next scheduled meeting, and continue to enrol other patients for the study.

If an AE is mild, we will discontinue the oxygen supplementation to that study participant, but continue enrolling other patients for the study. Examples of mild maternal AEs that will result in discontinuation of oxygen administration for a subject will include fatigue, nasal or oral dryness or minor nasal bleeding and skin irritation.

In the event that oxygen supplementation is discontinued as a result of an AE, the study participant will not undergo oxygen supplementation at a later time and will be withdrawn from the study. Any data that is collected up until the point of withdrawal will be kept.

We do not expect ductal occlusion to occur within 45 minutes of fetal exposure to saturations that are lower when compared with a neonate. In the unlikely event ductal constriction occurs, it will be reversible once the MH is discontinued.

d) Expectedness assessment:

Unexpected	If the nature, severity or frequency of an event is not consistent with the risk information listed in the Material Safety Data Sheet

AEs and SAEs related to oxygen administration will be documented by the site investigator. Prior to the start of oxygen administration, a thorough medical history should be obtained to document all preexisting maternal symptoms, complaints and health concerns. As many pregnancy related symptoms are intermittent in nature, a thorough history including variations in severity and frequency should be taken. AEs and SAEs should be reassessed at each participant encounter. If signs or symptoms remain similar to baseline or are less in severity, frequency, or both, they will be considered within the usual range and do not need to be documented as AEs. In contrast, signs and symptoms that are new or, if preexisting, are more frequent/severe, need to be documented, assessed for severity and causality, and followed up until resolution.

In addition, the following table of endpoints will be used for the study:

Unexpected fetal demise	Stop the study; review by DSMB, PI and collaborators
Detection of cardiac dysfunction	Discontinue the exam – observe until resolved Review by PI and collaborators
Fatigue, dry/bloody nose, skin irritation	Review by PI and collaborators

8. STATISTICS

This is an observational cohort study to test whether acute MH is a useful diagnostic test for fetal TGA. This requires confirmation of the study concept that among TGA fetuses there will be specific hemodynamic and structural characteristics and responses that will be associated with neonatal compromise shortly after birth. Neonatal compromise is defined as any of these outcomes: pre-op/BAS mortality; minimal pre-BAS pH ≤7.1, SaO_2 ≤40%, PaO_2 ≤25 mmHg, maximal serum lactate ≥10 mmol; and/or PPHN (combined pre-operative reverse differential cyanosis ≥ 30% and/or postoperative RVp ≥ 75% systemic ≥48h post-surgery or ≥50% at postoperative discharge). Twenty-two (31%) of 70 consecutive newborns born at Mount Sinai Hospital for fetal TGA/IVS fulfilled at least one of the outcomes (Jaeggi E et al. AEPC 2016). PPHT affects 1-3% of children with TGA. Based on these data we would expect about 35 cases without severe neonatal compromise, 15 cases with neonatal compromise and 1 case with PPHT.

Simple descriptive statistics will be adequate for this small feasibility and safety study. Data obtained from this study will further help to describe the possible ranges in hemodynamic findings at baseline and during MH in a larger cohort of TGA patients and in comparison with our previous data. The comparison between pre and post MH variables will be analysed using the Brand Altman's plot. Receiver operating statistics will be used to test the diagnostic value of MH.

9. STUDY ADMINISTRATION

9.1 Data Collection, Management and Confidentiality

Data will be collected by the study investigators using the above described sources and their personal usernames and passwords. Study investigators will be responsible for the data management and the accuracy of the records. Only the study team will have access to the

database. Data will be recorded on a Microsoft Excel spreadsheet and will be maintained in a locked digital file on the hospital's secure server. Data will be backed up on the hospital's secure server. Any research information obtained about the patient in this study will be kept confidential. A patient will not be identified by name, only by unique study ID number. The patient's name or any identifying information will not appear in any reports published as a result of this study. All identifying information will be kept behind 2 security measures or as per equivalent institutional policy, under the supervision of the study Principal Investigator and will not be transferred outside of the hospital. Relevant study records will be archived for 25 years following completion of the study, as per the requirements of Health Canada's Food & Drug Act, Part C Division 5. Once the study is complete and the final report has been published, the records will be retained and destroyed in accordance with The Hospital for Sick Children Record Retention and Destruction policy. All information collected in this study will be kept confidential in accordance with institutional policies on subject privacy and PHIPA. Investigators will not use data for any purpose other than conducting the study.

9.2 Data & Safety Monitoring Board (DSMB)

An independent DSMB of 4 members will monitor the progress of the study and review the safety data. The DSMB will review the result of analyses and other safety data and, if required, will provide recommendations to the study sponsor including to stop the trial if there are safety concerns.

9.3 Regulatory and Ethical Considerations

This study involves an experimental examination for pregnant women and fetuses using supplementary oxygen for a limited period of time. Based on earlier experiences by others and our center that includes the prolonged use of MH as a potential treatment for fetuses with single ventricle physiology, no fetal and maternal AEs occurred. However, data on the use of MH for fetal TGA is scarce and therefore fetal and maternal monitoring during oxygenation warranted. All participants will be made aware of the experimental aspects of this research, and the time of oxygen administration will be kept as short as possible and will be shorter than in previous studies. In the unlikely event of a serous complication attributable to the MH we will discontinue the study.

If any incidental findings occur during the study, the study team will share the atypical findings and provide recommendations with the SickKids physician. Clinical care will be provided as needed.

9.3.1 Informed Consent

The study is explained to the patient in detail, including the alternatives to be followed up without participation. Any study related questions will be answered prior to signing the consent form. The person obtaining consent must co-sign the form with date and time. A copy if the consent for must be given to the patient.

9.3.2 Study Withdrawal

A subject is free to withdraw from participation in the trial at any time, for any reason, specified or unspecified, and without prejudice. If the subject withdraws, data that has already been

collected up to that point in time will be kept (as indicated in the patient informed consent).

9.3.3 Reporting of Adverse Events and Serious Adverse Events

Subjects will be carefully monitored throughout their study participation. They should stop at any time they start to feel uncomfortable; even if they feel as though their ailment is unrelated to study intervention. If any unanticipated problems related to the research involving risks to subjects or others happen during the course of this study these will be reported to the REB in accordance with SickKids Policy. AEs that are not serious but that are notable and could involve risks to subjects will be summarized in narrative or other format and submitted to the REB at the time of continuing review.

All serious, unexpected adverse drug reactions to the study medication will be reported to Health Canada within 15 calendar days or for death or life-threatening events, within 7 calendar days. In the latter case, a follow-up report must be filed within 8 calendar days.

10. PUBLICATION

It is expected that study results will be published in peer reviewed papers. Individual authorship will be based on the investigator's contribution to a study component and journal guidelines of authorship. As per the International Committee of Medical Journal Editors (http://www.icmje.org/recommendations/browse/roles-and-responsibilities/defining-the-role-of-authors-and-contributors.html) authorship will be based on these 4 criteria: a) Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; AND b) Drafting the work or revising it critically for important intellectual content; AND c) Final approval of the version to be published; AND d) Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

11. REFERENCES

1. Digilio, Maria Cristina, Casey, Brett, Toscano, Alessandra, Calabro, Raffaele, Pacileo, Giuseppe, Marasini, Maurizio, Banaudi, Elena, Giannotti, Aldo, Dallapiccola, Bruno, Marino B. Complete Transposition of the Great Arteries Patterns of Congenital Heart Disease in Familial Precurrence. Circulation. 2001;104:2809–14.
2. Kirklin, John W.,Blackstone, Eugene H.,Tchervenkov Christo I., Castaneda, Aldo R. CHSS. Clinical Outcomes After the Arterial Switch Operation for Transposition Patient, Support, Procedural, and Institutional Risk Factors. Circulation. 1992;86:1501–15.
3. Khairy P, Clair M, Fernandes SM, Blume ED, Powell AJ, Newburger JW, et al. Cardiovascular outcomes after the arterial switch operation for D-transposition of the great arteries. Circulation. 2013;127(3):331–9.
4. Luciani, Giovanni Battista, Chang, Anthony C., Starnes VA. Surgical Repair of Transposition of the Great Arteries in Neonates with Persistent Pulmonary Hypertension. Ann Thorac Surg. 1996;61:800–5.
5. Kumar A, Taylor GP, Sandor GGS, Patterson MWH. Pulmonary vascular disease in

neonates with transposition of the great arteries and intact ventricular septum. Br Heart J. 1993;69:442–5.

6. Bulas D, Egloff A. Benefits and risks of MRI in pregnancy. Semin Perinatol. 2013;37(5):301–4.
7. Manganaro L, Bernardo S, Antonelli A, Vinci V, Saldari M, Catalano C. Fetal MRI of the central nervous system: State-of-the-art. Eur J Radiol. 2017;93(May):273–83.
8. Tocchio S, Kline-Fath B, Kanal E, Schmithorst VJ, Panigrahy A. MRI evaluation and safety in the developing brain. Semin Perinatol [Internet]. Elsevier; 2015;39(2):73–104. Available from: http://dx.doi.org/10.1053/j.semperi.2015.01.002
9. Sun L, Macgowan CK, Sled JG, Yoo SJ, Manlhiot C, Porayette P, et al. Reduced fetal cerebral oxygen consumption is associated with smaller brain size in fetuses with congenital heart disease. Circulation. 2015;131(15):1313–23.
10. Battaglia FC, Meschia G, Makowski EL, Bowes W. The effect of maternal oxygen inhalation upon fetal oxygenation. J Clin Invest. 1968;47(3):548–55.
11. Say L, Gülmezoglu AM, Hofmeyr GJ. Maternal oxygen administration for suspected impaired fetal growth. Cochrane Database Syst Rev. 2003;(1):CD000137.
12. Co-Vu J, Lopez-Colon D, Vyas H V., 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(12):1822–33.
13. Porayette P, Madathil S, Sun L, Jaeggi E, Grosse-Wortmann L, Yoo SJ, et al. MRI reveals hemodynamic changes with acute maternal hyperoxygenation in human fetuses with and without congenital heart disease. Prenat Diagn. 2016;36(3):274–81.
14. Porayette P, van Amerom JFP, Yoo S-J, Jaeggi E, Macgowan CK, Seed M. MRI shows limited mixing between systemic and pulmonary circulations in foetal transposition of the great arteries: a potential cause of in utero pulmonary vascular disease. Cardiol Young. 2015;25(4):737–44.
15. Seed M, F P van Amerom J, Yoo S-J, Nafisi B, Grosse-Wortmann L, Jaeggi E, et al. Feasibility of quantification of the distribution of blood flow in the normal human fetal circulation using CMR: a cross-sectional study. J Cardiovasc Magn Reson. 2012;14(1):79.
16. Nield LE, Qi X-LL, Valsangiacomo ER, Macgowan CK, Wright GA, Hornberger LK, et al. In vivo MRI measurement of blood oxygen saturation in children with congenital heart disease. Pediatr Radiol. 2005;35(2):179–85.
17. Dimitropoulos A, McQuillen PS, Sethi V, Moosa A, Chau V, Xu D, et al. Brain injury and development in newborns with critical congenital heart disease. Neurology. 2013;81:241–8.
18. Mawad W, R.Chaturvedi R, Ryan G, Jaeggi E. Percutaneous Fetal Atrial Balloon Septoplasty for Simple Transposition of the Great Arteries With an Intact Atrial Septum. Can J Cardiol. 2018;34(3):342.e9-342.e11.