Thesis Submission for MRes:

Short Title: The NEST Study

Study Title: Nicom vs Echo in the Screening of Transient Hypertrophic Obstructive Cardiomyopathy (HOCUM)

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Declaration:

"This is to certify that the work I am submitting is my own and has not been submitted for another degree, either at University College Cork or elsewhere. All external references and sources are clearly acknowledged and identified within the contents. I have read and understood the regulations of University College Cork concerning plagiarism and intellectual property."

Dedication:

I dedicate this work to those wonderful souls who helped my recovery to the point I could write once more- my parents Martina and Pat who have been my mast and rudder in the storms of life,

my healers- T.L, S.R, E O'S & TR and finally to Prof Gene Dempsey and Dr Colm O'Tuathaigh for getting me this far.

1 Figures and Tables List:

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2 Abbreviations:

NICOM: Non-invasive cardiac output monitoring- a broad term used to describe various measurements of non-invasive cardiac output measurements.

NICOM^{TM}: The original trademarked name of the bioreactance device we used for out study. Of note, this trademark has now been cancelled on the trademark register. To prevent confusion, NICOM^{TM} will only be used as the name of the device.

ECHO: Echocardiogram

LVO: Left ventricular output

GDM: Gestational diabetes mellitus

VSD: Ventricular septal defect

ASD: Atrial septal defect

PDA: Patent ductus arteriosus

PFO: Patent foramen ovale

HOCUM: Hypertrophic obstructive cardiomyopathy

LVPWd: Left ventricular posterior wall in diastole

LVPWs: Left ventricular posterior wall in systole

LVIDd: Left ventricular internal diameter in diastole

LVIDs: Left ventricular internal diameter in systole

IVSd: Interventricular septum in diastole

IVSs: Interventricular septum in systole

LVH: Left ventricular hypertrophy

RVH: Right ventricular hypertrophy

3 Abstract:

Background:

Gestational diabetes mellitus (GDM) is the most common metabolic disorder of pregnancy. An increasing number of infants are exposed to hyperglycaemia antenatally with the national prevalence estimated at 10.1-12.4%. Transient HOCUM (Hypertrophic Obstructive Cardiomyopathy) as well as interatrial/interventricular communications remain the most common cardiac sequelae for such infants. In particular, transient HOCUM has a broad estimated international incidence of 13-44%.

The current standard of care for infants born to mothers with GDM (Gestational Diabetes Mellitus) is unchanged from routine care, consisting of a bedside newborn examination. A further echocardiogram is subsequently performed if clinically indicated as a key investigation for the detection of congenital heart disease. There has been a rising interest in NICOM (Non-invasive Cardiac Output Monitoring), a range of novel non-invasive measurements of cardiac output and left ventricular outflow using an array of techniques from electrical bioimpedance to transthoracic bioreactance. The appeal is that these investigations can be carried out at the patient's bedside without a trained ECHO (Echocardiogram) technician.

Aim:

Our primary aim was to assess the ability of transthoracic bioreactance (a novel method of cardiac output measurement) in detecting left ventricular outflow tract obstruction in a high-risk group. Echocardiography at present is the most commonly used tool in the detection of such cases, whereby left ventricular outflow tract obstruction is secondary to transient hypertrophic obstructive cardiomyopathy (HOCUM) for infants born to mothers with GDM. We hoped to determine if bioreactance (a NICOM branch technology) could be used as a screening tool when compared with the best available standard of echocardiography.

Methods:

A single centre prospective observational cohort study was conducted.

Our primary objective was to compare bioreactance using the NICOM ^{TM} device against the most commonly used method of obtaining LVO measurements: echocardiography in infants born to mothers with GDM. Our goal was to ascertain if NICOM could be used as a screening tool to detect those infants at risk of symptomatic transient HOCUM with LVOTO (left ventricular outflow tract obstruction). For the purposes of secondary objectives, maternal demographic characteristics including BMI (Body Mass Index), maternal age, maternal HbA1C (glycosylated haemoglobin) and method of diabetes control were collected from the electronic healthcare record. Infant demographic and clinical variables collected included infant gestation, anthropomorphic measurements, newborn clinical examination findings and if the infant was admitted to the neonatal unit (indication and treatment received).

The data analysis strategy employed was primarily using Pearson's correlation co-efficient to determine if bioreactance had comparable efficacy to echocardiography in the detection of reduced left ventricular outflow as expected in clinically significant transient HOCUM. Preliminary statistics revealed for Pearson's correlation- a sample size of 29 patients was required to detect a large correlation (Cohen's r = 0.5)). This was further assessed using a Bland Altman plot. Otherwise, univariate analysis of the transient HOCUM cohort was carried out using Chi Square tests for categorical variables and independent T-tests for continuous variables.

Results:

Fifty infants underwent echocardiography while 28/50 of these infants were paired with a NICOM assessment (four echocardiogram data sets lost due to HSE cyberattack). 4/46 patients (8.7%) were noted to have a z-score of >2 for both the interventricular septal wall thickness and left posterior ventricular wall in diastole (LVPWd) consistent with a diagnosis of transient HOCUM with LVOTO. 26 out of 46 infants born to mothers with diabetes had significant thickening (Z-score >2) of either the interventricular septum or the left posterior ventricular wall. Regarding congenital heart defects, VSDs (ventricular septal defects) were found in 8.7% (4/46) of the study population with one patient found to have a >3mm ASD secundum. The incidence of transient

HOCUM was not associated with the degree of maternal glycaemic control, maternal BMI or the method of diabetes control (all $P > 0.05$). Bioreactance LVO measurements poorly correlated with ECHO LVO values ($r(25)= 0.2$, $p=- 0.31$) with an ambiguous agreement on Bland Altman analysis.

Conclusion:

The incidence of transient HOCUM in our cohort (8.7%) was lower than previous studies -13-44%. Transthoracic bioreactance does not appear to be an effective screening tool for transient HOCUM with LVOTO in this high-risk cohort of patients. This is on the basis of a poor Pearson correlation with ECHO derived LVO values and the wide limits of agreement found with the Bland Altman plot. Infants born to mothers with GDM would not benefit from routine echocardiography screening beyond the current standard of care. This is owing to our findings that all cases of clinically relevant congenital heart disease in our cohort would have been detected with the current standard of care- a newborn bedside examination followed by a targeted ECHO as clinically indicated.

4 Introduction:

The goal of any study is to determine if we can make a change to improve the care we deliver to our patients. Despite ever evolving technologies, often the paediatric and neonatal community find themselves on the outskirts as our patient cohorts are not immediately amiable to partaking in study trials of new inventions. Indeed, this can be a huge rate limiting step to pushing the boundaries of care for our most vulnerable patients. With the evolution in non-invasive cardiac output monitoring devices in the last two decades, our patient cohort has only been the recipient of opportunistic observational studies to determine the utility of each new adapted technology. The ultimate goal of this thesis when it was initially conceived was to test a new type of non-invasive cardiac output monitoring device and determine if it could improve the care we provide to our patients in the neonatal community.

The initial cohort we settled on was a cohort of patients which are ever increasing in number in the last two decades- infants born to mothers with gestational diabetes mellitus. The number of infants born to mothers with diabetes is increasing every year with an estimated 10-12% of mothers having a diagnosis of gestational diabetes in Ireland(1-3). There is a growing recognition that not only does this pose risks for mothers but also carries an increased risk of short- and long-term consequences for their infants. The risks can range from birth defects affecting the brain and the heart in the early stages of pregnancy to infants who have difficulties maintaining their blood sugars when they are born(4-6). As a result, this group of infants tend to be at higher risk of significant cardiovascular and neurological sequelae in the perinatal period.

The broader aim of this thesis was to determine if a relatively new form of NICOM technology called bioreactance could be used to identify patients at risk of a particular cardiac sequelae – transient hypertrophic obstructive cardiomyopathy (HOCUM) in this cohort. Transient HOCUM refers to a condition whereby infants born to mothers with diabetes have thickened heart walls(7). A few medical studies have estimated anywhere between 13-44% of infants born to mothers with diabetes possess thickened heart walls(8-12). Thankfully, most of these infants experience no complications and this abnormal thickening usually resolves spontaneously by six months of age. However, a small number of infants require intravenous fluids, respiratory support and medications to improve the heart's ability to pump blood(13-15) (Table 1). The reason for this is that the heart wall is so thick, it narrows the openings that allow blood to leave the heart causing a partial obstruction- more commonly known as Left Ventricular Outflow Tract Obstruction (LVOTO). A challenge with previous studies is the lack of a denominator exploring the proportion of children within the transient HOCUM population who require these additional medical supports. Most studies reporting interventions as described below are predominantly older case series (Table 1).

In the past, the infant would become unwell with breathing and feeding difficulties and would be transferred to the NICU for support. Only then would they receive cardiovascular investigations e.g., echocardiography (ECHO)- an ultrasound scan of the heart. Echocardiography invariably comes with its own challenges. Firstly, there is a paucity of trained technicians capable of performing neonatal echocardiography. Indeed, whilst some neonatologists are trained in

functional echocardiography delineation of anatomical abnormalities tends to be left to a paediatric cardiologist(16-19). Nevertheless, a neonatologist may be the first to perform an ECHO on an infant and equally, will often be the first to detect congenital heart disease(20). There are also the challenges of discomfort, of keeping a newborn warm and relatively still to facilitate effective imaging. Most Irish centres would rely upon a consultant neonatologist or cardiologist to perform neonatal echocardiography. There are simply insufficient resources to perform a bedside ECHO on every infant born to a mother with gestational diabetes in Ireland at this time. Indeed, most tertiary level sites can perform a couple of hundred echocardiograms at most for infants on the postnatal wards a year(21). Our own centre provides an example of the logistical challenges of bedside ECHO for every patient. Cork University Maternity Hospital (CUMH) cares for 7,500 newborns every year with a single paediatric cardiologist available for one session a week. Bioreactance – a branch of NICOM (non-invasive cardiac output monitoring technology, is a recent technology in the last decade whereby placing four electrodes on the infant's chest akin to an ecg, cardiac output data can be obtained(22, 23). This method does not require an expert with experience in echocardiography and can be performed without any invasive needles or discomfort for the child. The technology is called NICOM- Non-Invasive Cardiac Output Monitoring

Ultimately, we aimed to assess if introducing bioreactance assessments on the postnatal wards would help us identify infants with potential cardiac complications in this high-risk group. On this basis, we wished to compare bioreactance against the current key diagnostic test in our toolbox in assessing the infant heart- the echocardiogram. Echocardiography remains the mainstay diagnostic tool for structural congenital heart defects in our neonatal patients. Furthermore, we wished to determine if bioreactance could be used as a potential screening tool for these infants to help determine who may need an echocardiogram beyond our current standard of a newborn physical examination as well as pre and post ductal oxygen saturations. Secondly, we aimed to quantify the incidence of transient HOCUM in this cohort as other studies have reported it as high as 44% which does not fit with what we witness subjectively on the ground as clinicians here in our institution. Finally, we hoped to carry out secondary analyses to ascertain the relationship

between antenatal care and glycaemic control with the incidence and severity of transient HOCUM- a phenomenon which arises in response to the presence of increased antenatal glucose exposure. During the study we aimed to opportunistically asses the frequency of other congenital heart defects in this cohort to ascertain if we needed to introduce further cardiac assessments beyond NICOM on the postnatal wards.

If bioreactance was found to be as effective as an echocardiogram for determining cardiac output and left ventricular outflow in this population, it would provide an alternative non-invasive way to assess a baby's heart for evidence of this temporary thickening of the heart walls. No data to date has been collected using NICOM for infants of mothers with diabetes.

5 Background: Literature Review:

5.1 Gestational Diabetes:

Gestational Diabetes Mellitus (GDM) is the most common metabolic disorder of pregnancy(24). It is defined as any degree of glucose intolerance with the first onset or recognition occurring during pregnancy to help differentiate this metabolic state from other pre-existing forms of diabetes mellitus(25). An increasing number of infants are exposed to hyperglycaemia antenatally (approximately 16% worldwide in 2019) with the national prevalence of gestational diabetes mellitus in Ireland estimated at 10.1-12.4%(1-3). Gestational diabetes remains under-recognised(26). The challenge is that diagnostic criteria vary globally between different consensus best practice statements(27). This is in response to an insufficient evidence base to guide us on the definitive glycaemic level to determine an increased risk to a mother and their infant(27). Ireland experienced a five-fold rise in GDM diagnoses following adoption of new IADPSG (International Association of the Diabetes and Pregnancy Study Group) diagnostic criteria over a ten year period (3.1% in 2008 to 14.8% in 2017) on the basis of a retrospective review. (28). Indeed, Ireland adopted these new guidelines in 2010 in response to the findings of the HAPO (Hyperglycemia and Adverse Pregnancy Outcomes) trial and subsequent

endorsement by the International Association of the Diabetes and Pregnancy Study Group for more frequent screening of GDM (29, 30). This study group recommended adopting more sensitive GDM diagnostic criteria based on well-established risk factor groups (maternal and fetal risk factors associated with increased glycaemic levels). This was in recognition of the HAPO trial's outcomes demonstrating a consistent relationship between increasing maternal glycaemic values and adverse perinatal outcomes. The IADPSG study group's risk factors were subsequently adopted by the World Health Organization in 2013(31). NICE diagnostic criteria at present follows similar risk factor groups- last updated 2020(32). Ireland adopted this GDM screening criteria back in 2010 and continues to use this screening criteria in the present day(33). A further step which may result in a higher prevalence again would be the introduction of universal screening which is not in effect at this time, albeit our colleagues in the US have been looking at the introduction of same(34). Indeed, the introduction of universal screening at 24-28 weeks gestation would like see a further rise in GDM diagnoses beyond our current 10-12% to 15-20% which has been considered and trialled in about one third of European institutions(35, 36). Remaining dilemmas worldwide is whether we should be using a one-step Oral Glucose Tolerance Test (OGTT) at 24-28 weeks or a two-step approach with an initial glycaemic 50g assessment before a formal OGTT(37). The very method of determining if a mother has GDM is still under review worldwide with ongoing randomized controlled trials weighing up improved outcomes against the increased psychosocial burden on the expectant mother.

In CUMH, we have on average 500 infants a year born to mothers with GDM. Diabetes in pregnancy can cause short- to long-term complications for the infant. These include macrosomia, an increased risk of perinatal morbidity, major congenital anomalies as well as the sequelae of hyperinsulinism in latter trimesters- a vast proportion of which involve the cardiovascular system (8.5 in 100 live births approximately)(4-6, 38) Poor antenatal maternal metabolic and glycaemic control can fuel ''diabetic'' embryopathy and subsequent organ teratogenesis(39). The issue remains however, that despite our knowledge of the multiple sequelae of infants born to mothers with GDM, our management of these infants has not changed much in the past fifty years(40). Instead, the majority of advances have been placed on

optimising the mother's antenatal glycaemic state with a timely diagnosis and strict glycaemic control(41).

5.2 Cardiac sequelae of maternal diabetes:

Albeit pre-existing diabetes mellitus disease states had been well recognised for thousands of years (Egyptian Ebers Papyrus 1500 BC), the phenomenon of gestational diabetes mellitus was a much later discovery with initial case reports in the first half of the 18th century(42, 43). Prior to the discovery of insulin in 1922, most women who suffered from diabetes mellitus often had great difficulties conceiving and suffered from the sequelae of infertility(44). Following the discovery of insulin, obstetricians and midwives began caring for groups of women previously thought to have high risks of infertility, taking their first steps into the antenatal journey(45). It was only in the 1950s when clinicians began to differentiate care between mothers with pre-existing diabetes mellitus and mothers suffering from a separate recognisable clinical entity- gestational diabetes mellitus(46-49).

Despite the existence of separate clinical entities- T1DM, T2DM, Gestational Diabetes Mellitus as well as rarer subtypes again (e.g. Maturity Onset Diabetes of the young), the mechanisms in which a persistently elevated blood glucose affects the developing fetus remains the same(50). Nevertheless, there is a recognition, that the type of diabetes mellitus has a direct impact on embryopathy due to earlier glycaemic exposure and higher HbA1C values with T1DM resulting in worse outcomes for infants(50, 51). Due to the later recognition of GDM as a separate clinical entity, the initial recognition of the infant heart as one of the key end organ targets to suffer complications of maternal diabetes came from studies on mothers with pre-existing diabetes

(T1DM &T2DM). Indeed, it has been over 50 years since the Pederson Hypothesis was first coined exploring the relationship between maternal glycaemic control and the foetal heart(52). The infant heart is susceptible to poor maternal glycaemic control, with such infants experiencing three times the rate of congenital heart defects and cardiac hypertrophy(53, 54). Jergen Pederson found during his work with mothers with type 1 diabetes mellitus, that foetal overgrowth was likely related to increased transplacental transfer of glucose, stimulating the release of insulin by the foetal pancreatic beta cells(52). This foetal hyperinsulinemia is associated with increased metabolic demands and an increased risk of hypoxaemia(55). The first reported cases of cardiomegaly and abnormal cardiac function in response to these biochemical pressures arose in the mid-1940s(56). Mehta et al had one of the first prospective studies demonstrating the impact of gestational diabetes mellitus in isolation on the developing heart with impaired right ventricular function. These altered diastolic filling patterns were likely secondary to reduced ventricular relaxation during diastole(57). This impaired diastolic function was suspected to place these infants at higher risk of morbidity if an intercurrent illness e.g., bacterial sepsis occurred. Gandhi et al subsequently demonstrated impaired systolic function due to outflow obstruction along the left outflow tract irrespective of the type of diabetes mellitus(58). As a result, Pederson strived to optimise maternal glycaemic control to improve perinatal morbidity and mortality(52).

Benchmarking is key in this situation- identifying which mothers with diabetes are at higher risk for diabetic embryopathy. There is a recognition that infants born to mothers with T1DM bear the highest risk, albeit make up a much smaller percentage (0.2-0.5%) of mothers with diabetes in pregnancy in the US (national prevalence of diabetes antenatally 10%)(59). As time has moved on, we are witnessing an increasing BMI for many expectant mothers and an increasing prevalence of GDM and T2DM(1, 60, 61). We can appreciate from retrospective analysis that the mothers we care for tend to be older, possess a higher BMI and although they may have good glycaemic control and a ‘’normal HbA1C’’ i.e., their HbA1C value still tends to be much higher than their non-diabetic counterparts(62). Antenatal imaging has demonstrated foetal myocardial dysfunction even in well controlled gestational diabetes. D’Ambrosi et al demonstrated that a diagnosis of maternal gestational diabetes adversely affected right

ventricular filling timing and atrial systole relative to controls on the bases of antenatal ultrasounds carried out at 34-37 weeks gestation(55). Infants born to mothers with GDM had to alter their very cardiac cycle with a statistically shorter time spent in right atrial diastole and systole compared to infants born to mothers without GDM. Mean left ventricular filling time was also shorter in this study albeit the difference was not statistically significant.(55).

Hypertrophic cardiomyopathy is generally rare in children (4.7 per million) and is associated with adverse outcomes(7). However, transient hypertrophic cardiomyopathy is a frequent finding in infants of mothers with diabetes, with hyperinsulinemia stimulating fat and glycogen deposition in the myocardium. Fortunately, infants born to mothers with diabetes tend to have better outcomes if they go on to develop transient HOCUM when compared with other infants who develop foetal cardiomyopathies(63). It has also been reported in congenital hyperinsulinism and insulin resistance syndromes(64). The glucose rich intrauterine milieu primarily drives this ventricular hypertrophy during the second and third trimesters, with fetopathy remains primarily a feature of the first trimester(65, 66). Antenatal echocardiography has even demonstrated visible ventricular hypertrophy as early as the second trimester in infants of mothers with diabetes(67-69).

Table 1: Documented Case Reports and Case Series of some of the earliest Transient HOCUM cases on record:

Demographics	Clinical Features	ECHO findings	Management	Outcome
Case 1(13): 40 wks. gestation	Signs of cardiac failure	DOL 6: hypokinetic enlarged left ventricle, normal wall thickness	Digoxin 15micrograms/kg/da	Survival at 2 yrs. follow up with no cardiac or

female infant 4.45kg BW	appeared on DOL 4- tachypnoea, hepatomegaly	DOL 7: Improved left ventricle dimensions and shortening fraction but thickening of interventricular septum was first noted DOL 8: Severe overall myocardial hypertrophy Ventricular wall thickness decreased from DOL 16 and normalised by DOL 31.	y and furosemide (1mg/kg/day) Subsequently intubated and ventilated- received inotrope support- dopamine and dobutamine Rapid clinical improvement post intubation and inotrope support. Due to ECHO findings of left ventricular outflow obstruction, calcium channel blockers- verapamil were commenced.	neurological sequelae
Case 2(13): Male infant 40 wks. gestation 2.7kg	Acute foetal distress led to emergency c-section Apgar's 4,5 & 7 at 1,5,10 minutes. Meconium-stained amniotic fluid. Grey, tachypnoeic 100bpm, systolic mitral murmur	ECHO demonstrated two enlarged ventricles with normal muscle thickness and good LV systolic function. ECHO DOL 5 revealed evolving hypertrophic cardiomyopathy without obstruction	Intubated Furosemide 1mg/kg/day Fluid restriction 50mls/kg/day Co-existent staphylococcus aureus septicaemia noted DOL 4 treated with vancomycin and septicaemia Verapamil commenced DOL 10 4mg/kg/day due to evolving hypertrophic cardiomyopathy	Survival at two years follow up with no cardiac or neurological sequelae
Case 3(13): Male infant 39 weeks 2.87kg	Mild cyanosis: O2 sats 90% without O2 dependence	ECHO enlarged hypokinetic left ventricle with right to left auricular and arterial bidirectional shunts HOCUM appeared on ECHO on DOL 2 affecting the interventricular septum and right posterior free wall	Isoproterenol 0.01 micrograms/kg/day (x 3/7)	Survival at 2 years with no cardiac sequelae. However, due to bilateral intraventricular haemorrhages with ventricular dilatation- advanced encephalopathy with psychomotor retardation

Case 5:(14) 11 infants born to mothers with GDM	All eleven infants presented with cardiorespiratory distress	All eleven infants had disproportionate septal hypertrophic cardiomyopathy. 4/11 cases underwent cardiac catheterisation- 3/4 had significant subaortic stenosis	One infant received propranolol with clinical improvement in cardiorespiratory distress. Two infants who received digoxin deteriorated clinically.	All 11 cases had a natural resolution of symptoms within two to four weeks and a resolution of septal hypertrophy within two to 12 months irrespective of therapy.
Case 6 (15) Of note- - all 12 mothers had poor glycaemic control. 5/12 mothers had ketoacidosis secondary to infection, 5/12 mothers were hypertensive and 6/12 mothers had polyhydramnios. 9 of the 12 infants studied were on or above the 95th centile of weight- mean gestational age 37 wks.	12 infants from two sites (San Francisco and Belfast) in last 1970s- transferred from peripheral sites within hours of birth to central sites. Group 1: >90th centile for wt. (10 infants) Group 2: <90th centile for wt. (2 infants) 8/10 infants in group 1 presented with resp distress shortly after birth- respiratory distress syndrome.	Group 1: All 10 infants had cardiomegaly on CXR (mean cardiothoracic ratio 0 72). Nine infants had abnormal ECGs (electrocardiograms) with either flat T-waves in the anterior chest leads (4 babies), right ventricular hypertrophy of moderate degree (6 babies), or ventricular ectopic beats (1 baby) Each infant in group 1 had ECHO evidence of thickening of interventricular septum and left posterior ventricular wall. Group 2: The two smaller infants had cardiomegaly secondary to ventricular dilatation rather than septal thickening.		2/12 infants passed away within 48 hours of birth- both children were large for dates (>90 th centile). Both children had hyaline membrane disease on autopsy with no structural evidence of subaortic stenosis (this does not out rule a functional obstruction). In group 1: All 10 cases had normalised cardiac function within 4-7 days on the basis of fractional shortening and resolution of the hypertrophic cardiomyopathy by two weeks of age. Both smaller infants in group 2 had normalisation of cardiac contractility following treatment of hypoglycaemia and acidosis with subsequent survival and normal cardiac function on follow up.

Note: The above table is a collection of case reports from the 1980s demonstrating the first reported cases of transient HOCUM for infants born to mothers with GDM from Pubmed's database.

5.3 The relationship between glycemic control and congenital heart disease:

The relationship between glycaemic control and congenital heart disease (e.g., transient hypertrophic cardiomyopathy) is not fully clear. It might be assumed that improved glycaemic control would reduce cardiac sequelae postnatally. However, the data does not fully support this assumption(70-74). Initially, this is easy to accept at face value on the basis of antenatal modified myocardial performance index assessments using serial echocardiograms on maternal GDM cases with poor glycaemic control (HbA1C >64mmol/mol-8%). Such imaging demonstrated significantly impaired myocardial function when compared with controls in the form of healthy normal pregnancies(70). However, despite the presence of adverse outcomes including 9% of infants requiring neonatal resuscitation, it becomes more tenuous in the absence of neonatal deaths or stillbirths(70). Likewise, the requirement for CPR was not greater when compared with controls.

The choice of controls is important. Serial echocardiograms throughout the third trimester in a similar study demonstrated that the presence of gestational diabetes mellitus was strongly associated with the expected cardiac changes, however improved glycaemic control did not necessarily alter the severity of these changes(71). Infants born to mothers with poorly controlled GDM possessed thicker ventricular walls than normal pregnancy controls as in the previous study. However, the authors also compared those mothers with good glycaemic control against those with poor glycaemic control. Of note, the only difference was that poor glycaemic control increases the degree of posterior left ventricular wall thickening when compared to mothers with good glycaemic control. Additionally, the left posterior ventricular wall is one of the criteria typically used for diagnoses of HOCUM which would go against the authors initial conclusions of there being absolutely no difference between cohorts with different levels of control. Both poorly controlled and well controlled glycaemic control groups had similar levels of impaired right ventricular diastolic function when compared with controls. In a different study, where authors performed echos on 61 infants born to mothers with GDM with an incidence of cardiac hypertrophy of 31%, they found that maternal HbA1C levels were

higher in the third trimester for affected infants(72). The evidence suggests that the presence of GDM alone can precipitate transient HOCUM changes, however optimal glycaemic control is not necessarily preventative. This would be akin to coronary artery disease in our adult cohorts- a healthy lifestyle reduces your risk but if you have a familial hypercholesterolaemia, there is still a significantly elevated risk.

However, some authors have suggested screening all infants born to mothers with a HbA1C above 6.1%(73) while other authors have not demonstrated a relationship between HbA1C and ventricular wall thickening(74). While a high maternal HbA1C can help predict which mother will unfortunately suffer a spontaneous miscarriage or infants with a major congenital anomaly, the relationship with transient HOCUM is unclear. If it is difficult to detect the infant who will have transient hypertrophic cardiomyopathy from the mother's antenatal care, then there is a benefit in predicting who will have transient HOCUM from a potential screening tool in early postnatal life before symptoms manifest. Subsequent asymmetrical septal hypertrophy with impaired left ventricular outflow is often self-limiting but may result in a need for beta-blockers, intravenous fluids, and possibly mechanical ventilation(4, 58, 75). This asymmetrical thickening of the intraventricular septum and ventricular free walls has been seen to occur in infants irrespective of the degree of glycaemic control during antenatal care(58, 65, 67, 76). Rather than the glycaemic basal state of the mother, it has been suggested that fluctuating glucose levels triggers an accelerated growth phase during the second trimester onwards which persists until delivery, and which likely contributes to development of transient hypertrophic cardiomyopathy(53). Nevertheless, careful glycaemic control can significantly reduce the chance that these infants subsequently develop congestive heart failure in the postnatal period secondary to transient hypertrophic cardiomyopathy and avoid potentially fatal outcomes(77, 78).

5.4 Transient hypertrophic cardiomyopathy:

Transient hypertrophic cardiomyopathy secondary to maternal GDM finally became a clinical entity in its own right following a small collection of case series and observational studies in the 1980s- three decades after the first case reports of this mysterious cardiomegaly(8, 9) (See

Table 1 above). Case reports frequently report this phenomenon up to the present day with associations with macrosomia and other congenital heart defects e.g., transposition of the great arteries, although this is not a common occurrence(79-81). Way et al provide one of the earliest prospective studies, following up 11 infants born to mothers with diabetes for at least 30 months(14). The symptomatology of cardiorespiratory distress led to echocardiography demonstrating asymmetric septal hypertrophy. Cardiac catheterization in a small number of these infants revealed a muscular subaortic stenosis. This hypertrophy resolved within 2-12 months irrespective of treatment, with the beta-adrenoceptor blocker propranolol found to be effective at addressing symptoms. Further studies estimated its incidence at 13-44% including non-clinical cases detected on echocardiography(9-11, 82). One group of authors reported an incidence of 30% in their own regional centre, advocating routine echocardiograms for infants of diabetic mothers(12). Others have raised concerns that we should be monitoring for foetal cardiac diastolic dysfunction as transient HOCUM with LVOTO can result in cardiac insufficiency(26). Tan et al reported an incidence for transient HOCUM of12% from a cohort of fifty mothers with varying clinical diagnoses of diabetes mellitus ranging from GDM to T1DM in the course of their investigation into umbilical artery resistance indices which were not found to be related to maternal diabetes(83). A large issue with this area is that the majority of these studies are small sample size studies which provide incidence rates which are not statistically significant. For instance, one paper quoted an incidence of 9'% for hypertrophic cardiomyopathy, but on reviewing their results, the absolute number was 9 patients out of a cohort of 35 patients providing an incidence of 25.7%(84). Further limitations to the evidence base are the fact that many of these infants are asymptomatic which may result in underrepresentation of the incidence figures quoted. Equally, previous studies fail to give details regarding the mother's diagnosis of diabetes- whether pre-existing type 1 or type 2 diabetes, the mother's glycaemic control and the method of referral for echocardiography(82, 83). There is no subset analysis of small for gestational age infants and infants born to mothers with documented poor glycaemic control. The need for a reliable original incidence or prevalence of a condition is a cornerstone of any screening tool, which transient HOCUM sorely lacks.

5.5 Non-invasive cardiac assessments:

For infants born to mothers with diabetes irrespective of cause, the current cardiac assessment in our institution consists of a newborn baby check within the first 48 hours of life and a pre and post ductal oxygen saturations measurement pre discharge. Routine bedside measures previously we would rely upon in our cardiac assessment toolbox e.g. blood pressure and three-lead cardiac monitoring offers little diagnostic utility in cases of transient HOCUM. Indeed, our current standard of care does not take into account the higher incidence of congenital heart disease (cyanotic and acyanotic) in this group of patients.

An ECG (electrocardiogram) is one of the most readily available non-invasive assays of cardiac structure and function. For example, in a case of HOCUM for instance, one would expect high voltages in precordial leads and a potentially shortened PR interval(85). The challenge with an ECG is that it often points a clinician towards a likely pathology, yet often requires an ECHO to provide a final diagnosis. The ideal situation would be a method of investigation which provides a clear diagnosis in isolation e.g the suggestion of universal neonatal screening with an ECG on DOL 3 for long QT syndrome(86). Other challenges with an ECG are the dependence on a suitably trained workgroup who can interpret ECGs and likewise manage the additional information an ECG provides beyond transient HOCUM in isolation. One study of 100 infants born to mothers with diabetes mellitus (83 GDM, 17 pre-gestational), found that 8% had an abnormal ECG. Of note 28 infants in this study had congenital heart disease- 5% cyanotic and 23% acyanotic. A limitation of the study is that there were seven cases of asymmetric septal hypertrophy, yet we are not informed what percentage of abnormal ECGs made up this cohort. Indeed, multiple studies have recognised that a bedside ECG can detect univentricular and biventricular hypertrophy in this cohort of patients(50, 87, 88). The challenge as discussed by Bacharova, is that albeit an ECG can detect a left axis deviation, the prevalence of infants meeting the ECG criteria for left ventricular hypertrophy is lower than expected. The question remains is an ECG in isolation enough of an adjunct for the cardiac assessment and evaluation of an infant born to a mother with GDM. One could certainly argue we should consider adding an ECG into our repertoire of cardiac assessments on the postnatal wards. Due to the poor pick up

rate for other forms of congenital heart disease, it has not been embraced at this time as part of screening.

An echocardiogram is the current best standard at present in confirming a diagnosis of suspected transient hypertrophic cardiomyopathy. Functional point of care bedside echocardiography has become a key non-invasive investigation in recent decades in neonatology(89). Indeed, during our study, most parents were incredibly comfortable with an ECHO for their infant from their own antenatal experiences of ultrasound. The challenge is having a trained ECHO technician available to screen every infant born to a mother with diabetes which is beyond the resources of most countries. Cardiac troponin I values on the second day of life have also been suggested as they demonstrate a significantly strong positive correlation with intraventricular septal wall and posterior wall thickness in these infants although phlebotomy is an invasive investigation. Likewise, troponin values are non-specific, remaining dependent on an echocardiogram for the final diagnosis(90).

Other surrogate markers of cardiac function and output in infants have always been challenging to interpret irrespective of cause (91). Even a simple blood pressure measurement at the bedside gives very little useful information as a screening tool despite being a composite variable of cardiac output and systemic vascular resistance(91). The challenge with blood pressure measurements as surrogate markers of cardiac output, is that we are unsure of what a 'normal' blood pressure value is for an infant- indeed, if we obtain a blood pressure measurement on every infant born to a mother with gestational diabetes, it is unlikely that we will be able to determine which infant may have underlying congenital heart disease by interpreting these values in isolation. Multiple attempts have been made to determine a 'normal' blood pressure value(92-95). Challenges include discrepancies between non-invasive blood pressure cuffs against invasive assessments using umbilical arterial catheters(96). Often, we only begin to assess the infant's perfusion status with a blood pressure reading once the child becomes symptomatic as a surrogate marker of end organ perfusion(22). By this time point, the detection of transient HOCUM or other forms of critical congenital heart disease may be too late. Although on paper we can appreciate that severe HOCUM with LVOTO can impair cardiac output, the differential for a 'low' BP measurement is broad. A more accurate

assessment would record cardiac output and systemic vascular resistance separately. Likewise a tool which can provide a continuous assessment of a patient's cardiac status would be invaluable for many neonatal conditions provided they are not invasive e.g. umbilical arterial/pulmonary arterial catheters or an intra-oesophageal doppler(97). Indeed, such a tool could be applied in advance and offer a timely assessment.

5.6 Non-invasive Cardiac Output Monitoring (NICOM):

A growing field of research relates to the use of non-invasive cardiac output monitoring in the neonatal intensive care unit(22). The ideal cardiac investigation for an infant would be as minimally (or non-) invasive as possible, sensitive, timely, cost effective, and operator independent to remove biases. Up until the last decade, ECHO was the only way to non-invasively assess cardiac structure and function directly which is completely operator dependent.

The subsequent issue with ECHO is that this is an opportunistic assessment at a single time point. An alternative, non-invasive assay which can be performed at the bedside at any time and run continuously to provide data at multiple time points would be a helpful triage process. This would allow patients to be screened and help determine who would ultimately require an ECHO. Likewise, an advantage over ECG is that it removes any subjectivity of interpretation and does not require an experienced individual in its interpretation.

NICOM - historically called impedance cardiography -potentially fits the above criteria. To date, there are two main branches of NICOM technology- - electrical velocimetry (an improvement on the original bioimpedance technology) which is the most widely researched to date(98-101) and Transthoracic Bioreactance which the device in our study- the NICOM Cheetah - is based upon (102, 103). Cardiac output measurements have become a key benchmark of both perfusion assessments as well as ascertaining the validity of non-invasive cardiac assessments in the academic world. The choice of cardiac output as a frequently used marker of an assay's ability is that it provides a marker of systemic perfusion and global oxygen delivery which is essential in

the critically unwell patient as well as a useful aid in the practices of cardiology, anaesthesiology and emergency care which neonatology encompasses at its most basic level(102, 104).

The issue with an assay as broad as cardiac output is that it can only broadly inform a healthcare provider that there may be a cardiac issue. It does not point a clinician towards an issue with preload, afterload or myocardial contractility. The advantage of the device in our study is in its ability to deliver heart rate, stroke volume and cardiac output as separate values.

In 1966, electrical bioimpedance was first discovered as a way to assess cardiac output in astronauts but only adapted to non-invasive cardiac output assessments for adults in the clinical medicine setting later in 1980 (23, 99, 100, 105). Electrical bioimpedance works upon the principle of a high frequency electrical current of known amplitude being transmitted across the thorax with the subsequent measurement of voltage(101)(Image 1). By comparing the voltage measured by the detector in comparison to the initial amplitude, a measure of transthoracic direct current resistance is formed- known more simply as impedance.

Figure 1: Schematic of Electrical Bioimpedance - the basis of NICOM technology (Image designed on https://biorender.com/)

As the amount of blood within the chest cavity varies, so does impedance and an estimation of blood flow through the aorta and subsequent measures of stroke volume and cardiac output can be made. Osthaus et al recognised the benefits of non-invasively assessing cardiac function during cardiothoracic procedures for children and found a significant correlation between measures of cardiac output between the new electrical bioimpedance model against the invasive transpulmonary thermodilution approach in piglet models- the previous academic gold standard(106). Transpulmonary thermodilution is the ultimate cardiac assessment but is not a safe procedure to be performed routinely on infants. Similarly, Norozi et al found an excellent correlation (r=0.97) between electrical impedance (bias 10ml/min, precision 230ml/min) and direct Fick oxygenation measurements in 32 children ranging between 11 days and 17.8 years during right and left heart catheterization procedures(107).

Noori et al subsequently found electrical velocimetry, a further improvement on bioimpedance technology by altering the algorithm, to be a useful alternative for collecting data on left

ventricular outflow (precision 234ml/min) when compared with echocardiograms(23). Their study provided baseline cardiac output and stroke volume values for a previously unexplored patient population of term infants on the postnatal wards utilising the 'Aesculon' device- a cardiac velocimetry device capable of measuring bioimpedance. Issues highlighted include the fact that the original cardiac output calculations in the Aesculon device were based on adult cardiac models with the machine adapted by the manufacturer at the author's request. Nevertheless, the final precision of the Aesculon device at determining at patient's left ventricular outflow was at a similar level to an ECHO's estimated precision, both of which are sufficient for use in clinical practice(108, 109). Indeed, this study spurred on the authors to investigate its use in critically unwell infants albeit we await this later data. Similarly, Song et al found electrical velocimetry recordings for cardiac output, left ventricular outflow and right ventricular outflow to correlate strongly with echo but not for superior vena cava (SVC) flow (110).

Finally, the NICOM CHEETAH device employed in the current study is based upon transthoracic bioreactance. Bioreactance was developed to combat some of the challenges bioimpedance technologies were facing which potentially makes it a more suitable technology for the newborn infant. Bioimpedance has been found to be less reliable in ICU settings where there is significant electrical noise and motion(111, 112). Bioreactance was designed to allow just four leads to be placed on the body with some variation allowed in their position. As a result, transthoracic bioreactance technology could take into account changes in the return signal during changes in intrathoracic pressure. The original bioimpedance signal was unable to consider a change in the patient's clinical condition between the release of the original signal and its subsequent detection at the receiving end. Pulsatile aortic blood flow, time delays, and phase shifts can all have an impact on the measured stroke volume and needs to be taken into account. Bioreactance delivers an oscillating current while measuring these gentle phase shifts which occur during movement artefacts and respiration unlike the bioimpedance branch of NICOM technology, which measures a single change in signal amplitude.

The NICOM^{TM} (NICOM; NICOM TM, Cheetah Medical, Portland, Oregon, USA) Cheetah and Starling devices are designed to have four points of contact- two stickers applied to the left side

of the body and two applied on the right. Each sticker possesses two electrodes. The initial upper electrode releases a high frequency signal which the other electrode receives. The stickers are paired so the sticker on the left releases a signal which the corresponding sticker on the right receives and vice versa. The average of these two values are used to generate the final cardiac output value. (Figure 1:(113))

Figure 2: Image of CHEETAH NICOM non-invasive cardiac output monitoring device and sensor placement (113)

NICOM determines left ventricular stroke volume (SV) as: $SV = C \times VET \times d\Phi/dt\ max$, where C is a constant of proportionality, VET is the ventricular ejection time and $d\Phi/dt\ max$ is the peak rate of change of the phase shift of the NICOM electrical current induced by the blood ejected from the left ventricle(101, 114). The original pilot study of the technology in 27 adult patients post-coronary artery bypass grafting or valve replacement surgery found no side effects of the assessment. NICOM technology is able to provide measurements of heart rate, stroke volume, cardiac output and total peripheral resistances as well as indexes of same based on the patient's body surface area. An issue with adapting this technology for infants is that the constant of proportionality is based on adult data with a presumption that an infant is 'just a small adult' and fails to take into account profound differences in physiology. The first successful studies with this technology were in post-operative cardiac patients and the critically unwell adult in the ICU (115, 116).

Table 2: NICOM studies to date for neonatal cohorts:

Reference	Study Population	Study Type (Level of Evidence)	Method:	Key Result
Weisz et al(97)	10 infants (all >30 weeks gest-median gest age 37 wks (range 31-41 wks), >1500 grams-median birth	Prospective observational study	2-4 hour study duration: 5-10 paired NICOM and ECHO measurements	Normative NICOM and ECHO stroke volumes Normative NICOM and ECHO left ventricular outflow Nicom consistently underread LVO measurement by 31+/-8%

	weight 2.72 kg (range 1.44–4.00))			Median NICOM-derived SV and LVO readings were lower than ECHO
McCarthy et al(113)	49 infants (median gestational age 39 wks (IQR 39-40 wks), median birth weight 3.5kg (IQR: 3.14–3.91kg)	Prospective Observational Study	Heart rate and cardiac output measurements obtained via the NICOM device at two timepoints: 10 minutes post-delivery and 10 minutes again at two hours of life	The mean cardiac output was 101 (24) mL/kg/min in the delivery room and 89 (22) mL/kg/min at 2 hours of life. There was a statistically significant decrease in cardiac output and heart rate from birth to 2 hours of life.
Weisz et al(114)	25 extremely preterm infants (24.5-25.9 wks. gestational age) who underwent a PDA ligation.	Prospective Observational Study	Left ventricular stroke volume, left ventricular cardiac output and heart rate measurements were obtained continuously over an 18-hour period. After PDA ligation, infants underwent echocardiography assessments of Left ventricular output at (hr, 6-8 hrs and 16-18hrs post ligation.	‘’The mean (SD) LVO based on ECHO during T1, T2, and T3 was 212 (68), 217 (65) and 252 (73) ml/kg/min, respectively, while the mean (SD) LVO NICOM was 134 (45), 130 (54), and 139 (40) ml/kg/min across the same time points.’’
Miletin et al (117)	39 preterm infants born with a birth	Prospective Observational Study	NICOM™ monitor (Cheetah NICOM™, Cheetah Medical, USA)	Cardiac output values measured via transthoracic bioreactance in this preterm cohort were significantly

	weight of <1250 grams (mean gestational age 27.5 weeks)		applied pre 6 hours of life. Full bioreactance monitoring from 6 to 48 hours of life.	lower in infants who went on to develop a peri/intraventricular haemorrhage (PIVH) or NEC (necrotizing enterocolitis) in the first 24 hours of life. Higher cardiac output values were also noted from 24-48 hours of life in the subset of patients with NEC/PIVH suggesting an ischaemic insult followed by reperfusion. Normative data on Cardiac output and LVO in a subset of extremely preterm infants without NEC or PIVH.
Forman et al (118)	27 infants >35 weeks gestation who underwent therapeutic hypothermia in response to neonatal encephalopathy	Prospective Observational Study	NICOM system (Cheetah Medical Inc, MA) applied to obtain cardiac output values during therapeutic hypothermia and rewarming process.	Illustrated that NICOM cardiac output monitoring values reflect the expected cardiac physiology during therapeutic hypothermia and the subsequent rewarming process. NICOM underreports cardiac output when compared to ECHO cardiac output values by 27% approximately as experienced by Weisz et al's original papers above – this is suspected to be a complication of using adult aortic diameters in the underlying algorithm(101).
Mullaly et al (119)	10 infants (term and preterm included) undergoing elective extubation from conventional	Prospective Observational Study	NICOM™ (Cheetah Medical, Inc., Portland, Oregon., USA) monitor measuring transthoracic bioreactance was used	Statistically significant decrease in cardiac output secondary to a decrease in stroke volume post extubation was noted. The exception to this finding was in those infants with a haemodynamically significant PDA or PDA with

	ventilatory support. (median (range) corrected gestational age of 29 + 5 (25 + 2 to 41 + 2) and weight 1150 g (500 g to 3900 g)		to measure Cardiac output and LVO values for 120 minutes prior to and post extubation.	bidirectional flow across their PDA with a rise in cardiac output post extubation. Ultimately demonstrated the feasibility of NICOM monitoring of cardiac output as part of the extubation monitoring process in potentially unstable infants e.g. patients with haemodynamically significant PDAs.

Weisz et al wrote the seminal article on the use of transthoracic bioreactance for neonates, demonstrating its feasibility with a small sample of ten patients. Here 97 paired NICOM and ECHO measurements were carried out providing normative data yet recommended further validation studies before its routine clinical use(97)(Table 2). Nevertheless, this was the first published study assessing the feasibility of a bioreactance device in use in the neonatal population. McCarthy et al subsequently demonstrated the feasibility of carrying out transthoracic bioreactance measurements for infants in the delivery room as a readily available tool for the acutely decompensated term neonate as well as providing some raw data values for the term clinically well infant(113). McCarthy et al also highlighted some challenges with the NICOM^{TM} cheetah device which is most frequently used for transthoracic bioreactance measurements in most studies to date (Table 2) : the sensors are not newborn specific and take up a larger volume of the chest and abdominal wall's than anticipated, several patients did not provide measurable data due to movement artefact from active infants as well as poor sensor adhesion secondary to vernix and liquor in the delivery suite. No adverse events were noted from the NICOM device or it's sensors. Weisz et al demonstrated the efficacy of transthoracic bioreactance in extremely preterm infants following PDA ligation(114). They highlighted that the technology consistently underestimated cardiac output values in this cohort of 25 patients (Median gestation age of 25 weeks (24.5–25.9) and median weight of 700 g (615–775)), a similar

finding to McCarthy et al's findings(113, 114). This was the first study demonstrating this subset of NICOM technology's utility for the extremely preterm infant, albeit a cohort of infants without congenital heart disease as congenital heart disease was an exclusion criterion. Weisz et al also demonstrated that bioreactance was able to qualitatively match with infants in high outflow states and those in low outflow states who required inotrope support in the form of milrinone(114). The authors suggest that transthoracic bioreactance in isolation should be treated with caution but is a useful complement to ECHO analysis. There has been concerns raised regarding the validity of bioreactance in critically unwell patients. In 48 critically unwell adult patients, there was a percentage error rate of 82% for the NICOM device against the more invasive but more reliable transpulmonary thermodilution although the study in question has been refuted due to the original author's not using the device as per the instructions(120, 121). Nevertheless, specific uses of transthoracic bioreactance monitoring have been demonstrated in the care of both term and preterm infants at the time of extubation as well as the monitoring of infants during therapeutic hypothermia and subsequent rewarming(118, 119). Indeed, the addition of transthoracic bioreactance can help predict when an extremely vulnerable preterm infant may deteriorate from NEC or an intraventricular haemorrhage which is an incredibly useful adjunct in a physician's toolbox(117). These studies show the potential of NICOM using bioreactance as a method for assessing infants in a wide variety of clinical situations. From routine monitoring in the delivery suite to acting as a useful clinical adjunct in higher risk scenarios for the critically unwell neonate.

In our study, we planned to carry out a prospective observational study assessing the utility and feasibility of the relatively novel NICOM system in identifying term infants with transient HOCUM born to mothers with GDM when compared with standard echocardiography data. This study is novel in that it is the first to collect NICOM data in this subset of patients. Equally we will be carrying out secondary analysis to determine the true incidence of transient HOCUM in infants born to mothers with gestational diabetes mellitus as previous studies have often combined data on pre-existing diabetes mellitus and GDM (82, 83). Likewise, we hope to identify current risk factors for the incidence of septal hypertrophy in this cohort e.g poor

glycaemic control & mode of GDM management as well as providing normative data on this previously unassessed high risk patient cohort.

The ultimate question prior to commencement of the project is to identify a uniform definition for transient hypertrophic cardiomyopathy.

5.7 Definition of Transient Hypertrophic Cardiomyopathy:

The definition of transient HOCUM is unfortunately variable between clinical studies describing this clinical phenomenon. HOCUM is defined as ''myocardial hypertrophy that occurs in the absence of other disease capable of producing the magnitude of wall thickening that is evident(122).'' This definition excludes hypertrophy secondary to other forms of congenital heart disease as a form of compensation e.g., RVH in response to Tetralogy of Fallot. It generally reflects changes at the level of the sarcomere with myocyte disarray and fibrosis in the general population(123, 124). The secondary HOCUM which occurs in transient HOCUM secondary to maternal GDM is presumed to affect the infant at the level of the sarcomere, however the autopsy results available from previous case reports (please see table 1) does not report findings at a microscopy level.

The challenge for our study was to use a definition which encompassed previous case definitions to allow comparisons between our findings and the pre-existing literature while being robust enough to ensure we did not overcall cases of transient HOCUM. The classical key measurements outlined in table 3 demonstrates the three constant findings in most definitions in the larger studies and textbooks. These criteria are on the basis of some variability in the pattern and degree of left ventricular hypertrophy in HOCUM. HOCUM typically involves hypertrophy of the basal and mid-interventricular septum. This hypertrophy tends to be asymmetrical with a ratio of >1.3 when comparing the septal wall thickness to the left ventricular wall thickness in >60% of cases in children(122, 125-128). Indeed, this ratio of the ventricular septal thickness to the left ventricular posterior wall thickness during diastole exceeding 1.3 appears to be a key marker and diagnostic for asymmetric septal hypertrophy (9,

57, 100). Concentric LVH has been noted in as many as 50% of infants but once again the challenge with these measurements and descriptors is that they may not be fully relatable to the transient HOCUM phenomenon in this patient cohort(7, 129).

The clinical significance for this patient cohort is the description of a dynamic pressure gradient across the left ventricular outflow tract which may results in symptoms if there was more significant outflow obstruction(130, 131). Our hope with transthoracic bioreactance is the ability to detect cases who are likely to develop symptoms secondary to left ventricular outflow tract obstruction. Previous studies of left ventricular outflow in cases of hyperinsulinism albeit with different aetiologies have witnessed impaired left ventricular stroke volumes which we hope transthoracic bioreactance may be able to detect(81, 132, 133).

A challenge is clinical uncertainty regarding the incidence of left ventricular outflow tract obstruction among cases of transient HOCUM. Adult studies of HOCUM have reported an incidence of 66-75%, with one third of cases demonstrating LVOTO at rest(134, 135). Unfortunately, there is no reported incidence of LVOTO among such cases of transient HOCUM bar an acknowledgement in case reports and observational studies of a more severe presentation(13-15).

HOCUM may appear in various cardiac locations resulting in various descriptions including asymmetric septal, concentric, posterior LV, mid ventricular and apical with many of these liable to impair left ventricular outflow(122). An international consensus is the preference for Z-scores for all measurements of wall thickness and the diagnosis of transient HOCUM should be based primarily on measurements obtained at the end of diastole(136). The use of z-scores also allows us to accommodate for the increased incidence of large for gestational age and small for gestational age infants in this cohort. One study defined transient HOCUM exclusively as the presence of ventricular and/or interventricular wall thickness z-score>2 (or >2 SD above weight adjusted values) with or without ventricular dysfunction(10).A final approach adopted was to compare ventricular wall thickness to the infant's weight as a ratio(11, 74). Of note, LVOTO is not part of the diagnostic criteria for transient HOCUM as transient HOCUM can affect any part of the ventricular wall. Unlike adult patients whereby there is time for mitral valve elongation,

the mechanism for LVOTO secondary to transient HOCUM is more likely to be exclusively secondary to septal hypertrophy. There is no standard case definition of transient HOCUM with LVOTO on the basis of LVO values in isolation. Instead, we hope to identify all cases of transient HOCUM with echocardiography, and subsequently identify the percentage of LVOTO cases which were successfully identified by transthoracic bioreactance.

Table 3 demonstrates the classical key measurements which we would be using for the purposes of our study which combines the previous key definitions for transient HOCUM to create a strict, robust definition. Table 4 is a collection of the measurements obtained in previous studies assessing transient HOCUM in infants born to mothers with GDM. Of note, most textbooks report that the muscular midportion of the septum is the most affected area in HOCUM and recommend a combination of parasternal long axis, short axis, apical 4- and 2-chamber views(122, 137). Three other key hallmarks noted with a high specificity for HOCUM include: 1. Asymmetric septal hypertrophy (90% specificity), 2. septal disorganization (93% specificity), 3. Systolic anterior motion of the anterior mitral leaflet (97% specificity)(137). Both the presence of asymmetry and systolic anterior motion of the anterior mitral leaflet are not pathognomonic for transient HOCUM (can be seen in other conditions) but are highly specific for HOCUM in general(122, 137).

Table 3: The key classical measurements for transient HOCUM:

Classical Key Measurements	Criteria
Diastolic septal wall thickness	>4mm
Diastolic left ventricular wall thickness	>3.7mm
Ratio of ventricular septal thickness to left ventricular wall thickness	>1.3

For HOCUM- require a Z-score of >+2.0 SD for above measurements

.

Table 4: Previous measurements obtained to determine the presence of transient HOCUM in reported studies:

Measurements taken in previous studies	Criteria (mm)	Reference No
Interventricular septal end diastolic thickness	>4	(137)
Interventricular septal end systolic thickness	>6	(9)
Left ventricular posterior wall thickness (systole)	>5	(9)
Left ventricular posterior wall thickness (diastole)	>3.7	(138, 139)
Left ventricular end diastolic dimension	>23.3/<12	(138, 139)
Left ventricular end systolic dimension[a]	>18.6/<8	(138, 139)
Right ventricular anterior wall thickness	>5	(9)
Aortic valve diameter/ presence of regurgitation	present-supports Diagnosis	(79)
Fractional Shortening	Normal/supranormal	(137)

Notes: [a:] Expect to be decreased in HOCUM

6 Aim of the study

The primary goal of our study was to assess the feasibility and utility of transthoracic bioreactance- a NICOM subbranch as an alternative screening tool to echocardiography in the assessment of infants born to mothers with diabetes mellitus for cardiac sequelae- in particular transient HOCUM with LVOTO.

6.1 Potential Implications- what will this study add?

The primary goal of the goal of the study is to determine if transthoracic bioreactance could be used as a screening tool for infants born to mothers with gestational diabetes. At present, there is a broad suggested incidence of anywhere between 13-44% of infants born to mothers with gestational diabetes mellitus possessing the cardiac features of transient HOCUM. There is great uncertainty as to how many of these infants truly have transient HOCUM and furthermore, how many of these children become symptomatic from same. The greatest question is to determine if there would be benefit in pre-emptively screening these infants born to mothers with GDM from a transient HOCUM viewpoint or perhaps from a congenital heart disease viewpoint beyond the current standard of care. If transthoracic bioreactance was found to be as effective as echocardiography in identifying transient HOCUM with LVOTO, then it could be used to identify those infants who should be referred on for a formal echocardiogram with a cardiologist/neonatologist. The evidence base to date suggests that many infants born to mothers with gestational diabetes, have abnormal cardiac morphology and structure. Due to

the lack of resources, NICOM could become part of the current bedside routine screening assessments performed on infants on the postnatal wards which could be performed by midwives/non-consultant hospital doctors (NCHDs). Albeit an ECG is a further bedside assessment available to the clinician in transient HOCUM screening, it requires a degree of expertise not routinely taught to midwifery colleagues.

Secondary outcomes we hope to measure would be the true incidence of transient HOCUM in infants born to mothers with GDM in the current era where greater emphasis is placed on glycaemic control than when compared to older studies. This study would also provide baseline data on 'normal' transthoracic bioreactance results for a baby born to a mother with GDM when compared to an infant with a 'true' diagnosis of transient HOCUM with LVOTO. This specific group of patients have not been previously assessed by bioreactance despite a strong evidence base pointing towards a higher risk of altered cardiac morphology and function.

7 Study Objectives

7.1 Aim:

To assess the utility of transthoracic bioreactance as a potential screening tool to detect the presence of transient hypertrophic cardiomyopathy with LVOTO in a previously unassessed study population- infants born to mothers with diabetes, when compared with the current standard of care.

7.2 Hypothesis:

Our hypothesis is that for infants born with transient hypertrophic cardiomyopathy with LVOTO secondary to maternal diabetes, transthoracic bioreactance will be able to demonstrate reduced left ventricular outflow stroke volumes when compared to normal infants, ultimately

demonstrating its effectiveness as a screening tool when compared with the most commonly used method of diagnosing transient HOCUM with LVOTO-echocardiography.

7.3 Primary objective:

To compare transthoracic bioreactance LVO values with the current best standard of non-invasively assessing left ventricular outflow tract obstruction-echocardiography in the ability to detect the presence of transient hypertrophic cardiomyopathy with LVOTO.

7.4 Secondary objectives:

5. To identify key risk factors for the development and severity of transitional hypertrophic cardiomyopathy including maternal mode of diabetes control and degree of maternal glycaemic control.
6. To assess the utility and feasibility of transthoracic bioreactance in the assessment of a previously unstudied patient population with a high risk for cardiac sequelae in comparison to the general population- infants born to mothers with gestational diabetes mellitus as well as pre-gestational diabetes.
7. To calculate the incidence of transient hypertrophic cardiomyopathy in infants born to mothers with diabetes locally at CUMH which could be extrapolated to the Irish population.
8. To calculate the incidence of congenital heart disease (both acyanotic and cyanotic) in this group of patients.

8 Methods:

8.1 Study Design:

This was a prospective observational cohort study carried out at CUMH, Cork, Ireland following ethical approval being granted by both the hospital ethics committee and University College Cork ethics board review (Cork Research Ethics Committee Study Reference Number: 2105, ECM 4 (s) 10/11/2020

& ECM 3 (y) 09/02/2021). The Clinical Research Ethics committee for our study covers the wider Cork and Kerry area and oversees all clinical studies at all hospital sites (public and private) in their catchment area. The University College Cork ethics board also reviews all studies carried out as part of a degree programme in UCC. Dual ethics committee approval was granted for our study. As there was no retrospective data available in our hospital on cases of transient HOCUM bar

some selective recall of individual cases within the department, a prospective study was the preferred choice. Likewise, the prospective observational format allowed us to compare NICOM and ECHO data in a cohort of patients recruited over the same time period. As NICOM has not previously been assessed in this patient cohort, and we were uncertain regarding its clinical utility prior to study commencement, a prospective observational study format was selected rather than a pilot RCT/ screening trial. A prospective observational study format was also preferred on discussion with the local university ethics committee as there was not enough evidence to suggest our study would be viable as an initial pilot for a screening tool. Informed consent was obtained from all parents prior to inclusion in the study. All parents were approached following the birth of their children. The reason for this was so as to ensure that no mother who wishes to be part of the study was excluded. Infants born to mothers with diabetes enrolled in the study underwent a paired NICOM assessment and echocardiogram over a five-month period at CUMH from February to June 2021.

CUMH is a model four tertiary referral centre and University teaching hospital for the local Cork County area as well as acting as a referral site from secondary obstetric sites in the wider Munster region (South Tipperary General Hospital, University Hospital Kerry and University Hospital Waterford.) Typically more than 7000 infants are born in CUMH per year (There were 7577 births in CUMH in 2018 according to a HIQA report and 7040 infants as per a CUMH annual statement(140, 141)).On discussion with our obstetric colleagues, approximately 500 mothers with diabetes are cared for under CUMH in a year. CUMH was chosen above alternative sites due to access to such a large cohort of mothers with GDM as well as access to a pre-existing research centre- the INFANT centre (The Irish Centre for Maternal and Child Health Research located at CUMH). Likewise, CUMH has access to the expertise of a paediatric cardiologist who attends the unit weekly while many other Irish centres lack similar access.

8.2 Data Collection:

Maternal demographic data collected from the electronic healthcare records via the CERNER system in place at CUMH (and some paper charts during the HSE cyber-attack) included infant's gestational age in weeks, their birth weight in kg, their gender and their method of delivery. Maternal demographic data collected included the maternal age in year, their BMI expressed in Kg/m^2, their maternal HbA1C expressed in mmol/mol and the method of glycaemic control chosen by their care provider (Please see Table 5 for a more comprehensive breakdown). Of note, on the 14th May 2021 there was a HSE wide cyberattack which halted the study for a period and resulted in us returning to obtaining data from paper charts for ten cases. The exact same data was obtained irrespective of usage of the electronic CERNER system or a paper chart.

Table 5: Infant Demographic Data Recorded

Infant Clinical Data	Units	Additional Notes
Gestational age	Weeks	Gestational age describes how far along the pregnancy was at the time of delivery and is measured in weeks, from the first day of the woman's last menstrual cycle to the current date.
Birth weight	Kg- up to two decimal places	Birth weight as documented at time of delivery- this weight was used for all Z-score calculations as well.

Gender	Binary- Male/Female	There were no disorders of sexual differentiation, ambiguous genitalia or alternate parental gender preferences during the study so male and female were as previously described in general population terms.
Mode of Delivery	Spontaneous vaginal delivery (SVD) (including instrumental births) or caesarean section	Most mothers with GDM are induced at 37 weeks unless there is a parental preference as part of standard practice at CUMH
Infants age at time of ECHO	Hours of life since birth	This was done to ensure all infants received an ECHO & NICOM within the first 48 hours of life- the criteria for the study.
Admission to neonatal unit	Binary-yes/no	The indication for admission was also documented in a separate column
Need for respiratory support	Binary-yes/no	Need for supplemental oxygen and other respiratory aides including high flow, non-invasive ventilation, and invasive ventilation – this data was input into a second column beside the binary entry
Need for cardiac support	Binary-yes/no	Need for cardiac medications/inotropic agents/cardiac intervention

Table 6: Maternal Demographic Data Recorded

Maternal Clinical Data	**Units**	**Additional Notes**
Maternal Age	Years	Age at birth of child

Maternal Diagnosis	Gestational Diabetes Mellitus or Type 1 diabetes mellitus or type 2 diabetes mellitus	If there was a pre-existing Type 1 / 2 diabetes mellitus diagnosis, this was documented
Maternal BMI	Weight and height measurements were obtained from the clinical record and the BMI was calculated using the formula kg/m^2	As height measurements were often taken in outpatient clinics at the earlier stages of the pregnancy, the latest possible paired height and weight measurement was chosen for the purposes of BMI calculations
Maternal HbA1C	Mmol/mol	The most recent HbA1C prior to delivery was chosen
Maternal mode of diabetes control	One of three options: diet controlled or metformin usage or insulin controlled	Some mothers would have initially been commenced on a diet-controlled regimen but subsequently switched to metformin or insulin prior to delivery. On this basis, the method of glycaemic control pre-delivery was documented.

8.3 Cardiac Examination:

Every infant born at CUMH undergoes a routine 'baby check.' This is a national screening process where every infant born within a maternity hospital has a complete physical examination from head to toe in an endeavour to detect congenital defects or potential medical issues as soon as possible. This examination typically occurs within the first 48 hours of life and includes a full cardiac examination. This includes palpation of the brachial and femoral pulses, palpation of the precordium for heaves and thrills as well as auscultation for a murmur. These are recorded within

the electronic Cerner system as part of an automated yes/no binary template to indicate normality. If an abnormality is detected, the junior doctor or consultant escalates as appropriate and a description of the abnormality as well as the action taken is recorded. During the HSE cyber-attack, a paper template similar to the electronic healthcare record was used to document the newborn examination findings(142). The findings of the newborn examination were recorded as part of the study.

8.4 NICOM assessment:

Transthoracic bioreactance data was collected using a NICOM^{TM} Cheetah device (manufacturer: Baxter International Inc. One Baxter Parkway / Deerfield, Illinois 60015 in conjunction Cheetah Medical INC- Cheetah Medical INC is a subsidiary of Baxter, software version V1); the haemodynamic parameters of stroke volume, heart rate and cardiac output measurements were obtained continuously over a one-hour period within the first 12-48 hours of life. All transthoracic bioreactance assessments were obtained within one hour of the ECHO assessment. We collected values every four seconds which could then be used to generate subsequent one minute average values.

Four dual electrode sensors were placed on the infant's chest wall akin to ECG electrodes from which transthoracic bioreactance measurements were obtained. The electrodes are placed in a box like distribution surrounding the heart as previously described(113).

The Cheetah device reports based on the electrocardiogram tracing if a good signal is being generated. The use of four seconds values initially allows us to determine if the 1-minute average values calculated will be reliable. The Cheetah device can be set up to produce cardiac output and stroke volume results at regular time intervals which not only appear on the screen but are also recorded on a downloadable excel file. The question we had was whether the Cheetah transthoracic bioreactance device's one minute average results would be reliable if there was a poor connection e.g., a vigorous infant and the one-minute average values were extrapolated from intermittently high and low 4 second values due to an intermittently poor connection.

Following completion of the study, complete assessments including all data points for heart rate, stroke volume and cardiac output were downloaded from the cheetah device as excel files.

8.5 Echocardiography Data:

An echocardiograph was performed at approximately 12-48 hours of life for all infants recruited into the study. A GE vivid E95 ECHO machine (Manufactured by GE Healthcare, Chicago Ill, USA) was used for 48 of the ECHOs performed. Two ECHOs were performed using an older model- the GE vivid-I during the HSE cyber-attack due to limited space on the memory of the current working model. However, due to the poorer quality imaging obtained from same, these ECHOs were subsequently excluded from the study. A full segmental sequential ECHO was performed including subcostal, long axis, short axis, 4 chamber and suprasternal views. The ECHOs were performed by two trained physicians in echocardiography.

8.5.1 Key measurements obtained:

- The presence of an interatrial or interventricular communication- Atrial septal defect/ventricular septal defect/Patent foramen ovale or a patent ductus arteriosus
- The presence of pulmonary hypertension (determined by a measurement of the tricuspid valve regurgitation peak velocity to estimate the systolic pulmonary artery pressure(143).)
- The maximal tricuspid regurgitation
- The aortic diameter (AoD), aortic annular cross-sectional area (AoCSA) and the Aortic Velocity/time Integral (AoVTI) as well as the presence of aortic regurgitation
- The interventricular septal diameter in systole (IVSs) and diastole (IVSs)
- The left ventricular posterior wall thickness in systole (LVPWs) and diastole (LVPWd)
- The Left Ventricular Internal Dimension in Systole (LVIDs) and diastole (LVIDd)

- Fractional shortening- expect to be normal or supranormal- if < 36% is considered abnormal filling
- Z scores were calculated from the interventricular septal wall thickness during diastole using estimated body surface area. The Cardio Z application was used which used reference data from MD Pettersen et al's Detroit dataset(144).

The ECHO images were subsequently reviewed by a paediatric cardiologist to ensure no congenital heart disease was missed from a safety viewpoint.

The ECHO images were stored on the electronic hard drive for the hospital via the Intellispace Cardiovascular (Koninklijke Philips N.V, US).

8.5.2 Transient HOCUM Case Definition:

Transient hypertrophic cardiomyopathy was defined based on these classical key measurements:

- Diastolic septal wall thickness >4mm
- Diastolic left ventricular wall thickness >3.7mm
- Ratio of ventricular septal thickness to left ventricular wall thickness >1.3

The standard diagnosis of HOCUM is one of these measurements being > 2 standard deviations or Z score > +2.0 for the above measurements. The use of standard deviations and z-scores allows us to accommodate for any potential overestimation of the large for gestational age or small for gestational age infants in this cohort.

In essence, we are defining transient HOCUM as ventricular and/or interventricular wall thickness z-score>2 (or >2 SD above weight adjusted values) with or without ventricular dysfunction.

Z-scores were calculated using the Cardio-Z mobile application (version 1, developed by Evelina Children's Hospital, London, UK in collaboration with UBQO).

Z-scores were determined using the Detroit reference range data set from Petersen et al's baseline cohort(144). This study provides two-dimensional and M-mode echocardiography baseline data from 782 patients ranging in age from 1 day to 18 years. This provides normative reference data against which our cohort could be compared. The calculation of body surface area was based on the infant's birth weight and length using the Dubois body surface area formula(145). To ensure accuracy, repeat Z-score calculations were carried out for the interventricular septal diameter using the Boston Children's Hospital Z-score calculator (BCH Z-Score Calculator - Home (chboston.org)). The Boston Children's Hospital z-score system is based on data gathered over the last 12 years on normal children, using methods described by Sluysman et al and Colan et al(146, 147).

8.6 Patient Recruitment Process:

This was a single centre prospective observational cohort study.

8.6.1 Participants:

50 patients were recruited into the study between February and June 2021. For Pearson's correlation co-efficient to be calculated to compare NICOM and ECHO LVO values, a sample size of 29 patients is required to detect a large correlation (Cohen's r = 0.5) between both variables, with a power of 80%, a level of significance of 0.05 and a 2-tailed test. The sample size calculation was performed using the G-Power 3.1 program(148, 149). All infants of mothers with diabetes irrespective of whether pre-gestational or gestational diabetes mellitus were approached for the study irrespective of underlying diagnosis and mode of delivery. The reason for this is that if we acquired a large enough sample size, we hoped to assess infants born to mothers with pre-gestational diabetes mellitus as well as a separate subset. However, this was not possible due to the low frequency of such presentations (typically 0.2-0.5% for T1DM)(59). All mothers were initially invited to participate via a face-to-face meeting where the author approached the mother +/- birthing partner, described the study and left a patient information

leaflet. The author subsequently gave the parent(s) time to think and review the literature always prior to obtaining written consent. Both a prepared parent information leaflet and consent form were given to the parent(s) prior to returning to obtain signed consent irrespective of the parent(s)' enthusiasm for the study (please see appendices 1 & 2 for copies of the parent information leaflet and consent form for detailed information over what was described to parents.) No patients were born during the study time period who met the exclusion criteria. Infants were recruited both from the postnatal wards as well as from admissions to the neonatal unit.

8.6.2 Inclusion criteria for participant selection were:

- Infant of a mother with diabetes (formal diagnosis of gestational diabetes, or diagnosis of T1DM, T2DM, MODY or another diabetes subtype resulting in chronic maternal hyperglycaemia antenatally).
- As a cohort of children will have congenital heart defects detected antenatally they will still be included in the study irrespective of detection of an anomaly on antenatal scans.

8.6.3 Exclusion criteria for participant selection are:

- Infants requiring therapeutic hypothermia,
- Infants requiring palliative end of life care following delivery.

8.7 Statistical Analysis:

Simple descriptive statistics were first undertaken within Microsoft Excel to characterise baseline patient demographics. This included ascertaining the mean and standard deviation for continuous variables – the infant's birth weight, infant's gestational age at birth, maternal age, maternal BMI and maternal HbA1C. Frequency and percentages were calculated for infant gender, mode of delivery and method of maternal diabetes control.

Further analysis was carried out using SPSS (IBM SPSS Statistics v.28.0, Chicago Ill, USA,). To ascertain the correlation between NICOM and ECHO LVO values, a Pearson Correlation Coefficient was carried out as well as a Bland Altman Plot. A Pearson correlation coefficient was settled on following proving normally distributed data despite two outliers. We decided to use both Pearson and spearman correlations initially to fully ensure the assumptions of Pearson's correlation co-efficient would be reached if both produced similar results. Spearman's correlation coefficient is based off of ranking data which could be applied to our data set and would determine if there was a monotonic relationship. The challenge with our data set is that our data points were very accurate and a linear relationship could also be determined. As both correlations could be justified, the decision was made to utilise both initially and if the assumptions for Pearsons were met with similar results for both Pearsons and Spearmans correlations, we would finalise a report with Pearsons alone. In most practical cases, they will both give similar measures of association while any results which would produce a significant difference in association between the two warrants further exploration to determine why a relationship would be exclusively monotonic or linear. The decision to perform a spearman correlation coefficient alongside the Pearson correlation coefficient was also to take into account two outliers as the data was not normally distributed as a result of these two outliers. Ultimately, as will be demonstrated in the results below, the data remained normally distributed despite two outliers and met the Parametric assumptions for Pearsons's correlation co-efficient. Ultimately, only the Pearsons correlation co-efficient is reported.

A Bland-Altman plot was chosen as we are trying to determine if NICOM LVO values have a close agreement with ECHO values. Use of correlation alone can be misleading in clinical measurement, when determining if one new measurement technique could be used to replace an older established measurement technique. Although NICOM would be used to determine who requires the gold standard assessment of echocardiography, the use of a Bland Altman plot is appropriate. We are trying to assess how much NICOM LVO values will differ from the established gold standard of ECHO values as an indirect measurement of LVO. The Bland Altman Plot was initially calculated using MedCalc Software as this application is not currently available on SPSS- MedCalc® Statistical Software version 20.110 (MedCalc Software Ltd, Ostend, Belgium;

https://www.medcalc.org; 2022). To confirm our Bland Altman plot was correct as well as to provide a better graphical representation, GraphPad Prism (statistical software version 9.4.1, GraphPad Software, 2365 Northside Dr., Suite 560, San Diego, CA 92108) was used. If both sets of LVO data were shown to have a close correlation, this would help to determine if reduced LVO values as expected in the case of a transient HOCUM patient would be reflected in a NICOM assessment of the same patient. This would help answer our primary objective as to determining if NICOM could detect a statistically significant drop in LVO which would correlate with the detection of transient HOCUM on echocardiography. As we are assessing the same clinical variable with two different methods of measurement, a Bland-Altman plot is ideal (109, 150).

Regarding our hypothesis, that NICOM would be able to separate transient HOCUM cases from the non-HOCUM group, a Kruskal-Wallis test was chosen (a non-parametric equivalent of the one-way ANOVA- analysis of variance test).

Further sub analysis was carried out to determine the impact of categorical and continuous variables upon our deep end variables allowing us to target our specific secondary objectives. This would allow us to assess our secondary objectives as to the impact of maternal glycaemic control and type of diabetes on the incidence of transient HOCUM. Chi Square tests were carried out to determine the impact of maternal categorical demographic characteristics on the occurrence of interventricular septal wall thickening to a Z-score of >2. For continuous maternal variables e.g., maternal BMI, maternal age, maternal HbA1C values, independent T-tests were carried out. We also carried out statistical analysis to determine if there was an association between the infant's weight and the incidence of transient HOCUM to determine if an infant meets the criteria for small for gestational age, would they have a higher incidence of transient HOCUM.

9 Results:

9.1 Infant Demographics

50 patients (20 males, 30 females) were recruited into the study. The median gestational age of the cohort was 38wks and 2 days gestation (interquartile range 38-39 wks.). The median birth weight of the cohort was 3.465kg (interquartile range 3.23-3.83kg). Regarding the mode of delivery, 27 infants underwent a c-section, 23 underwent a vaginal delivery with three of these requiring instrumental assistance.

Table 7 Baseline Demographic Clinical Characteristics for Infant and Maternal Study Sample:

Infant Clinical Data	**N = 50**	**N=27 (ECHO and NICOM)**
Gestational age (weeks)	38.3 (38-39)	38.3 (38-39)
Birth weight (kg)	3.47 (3.23-3.83)	3.48 (3.02-4.16)
Gender (Females)	30/50	19/27
Mode of Delivery (c-section absolute no.)	27/50	15/27
Maternal Clinical Data		
Maternal Age (years)	35 (31-37)	33 (28.5-37.5)
Maternal BMI (kg/m^2)	31.57 (26.4-39.6).	35 (24.442.4)
Maternal HbA1C (mmol/mol)	35 (32-37)	32.37 (28-45)
Maternal mode of diabetes control (GDM N=49), one pt. T1DM	Diet 33/49 Metformin 8/49 Insulin 8/49 One Pt T1DM (N=1)	Diet 23/26 Metformin 1/26 Insulin 2/26 One Pt T1DM (N=1)

Note: Results presented as the median (interquartile range) unless otherwise stated

Legend:

N= Number of Patients

ECHO= Echocardiogram

NICOM= Non-Invasive Cardiac Output Monitoring

BMI= Body Mass Index

HbA1C= Glycosylated Haemoglobin

GDM= Gestational Diabetes Mellitus

T1DM= Type 1 Diabetes Mellitus

Pt= Patient

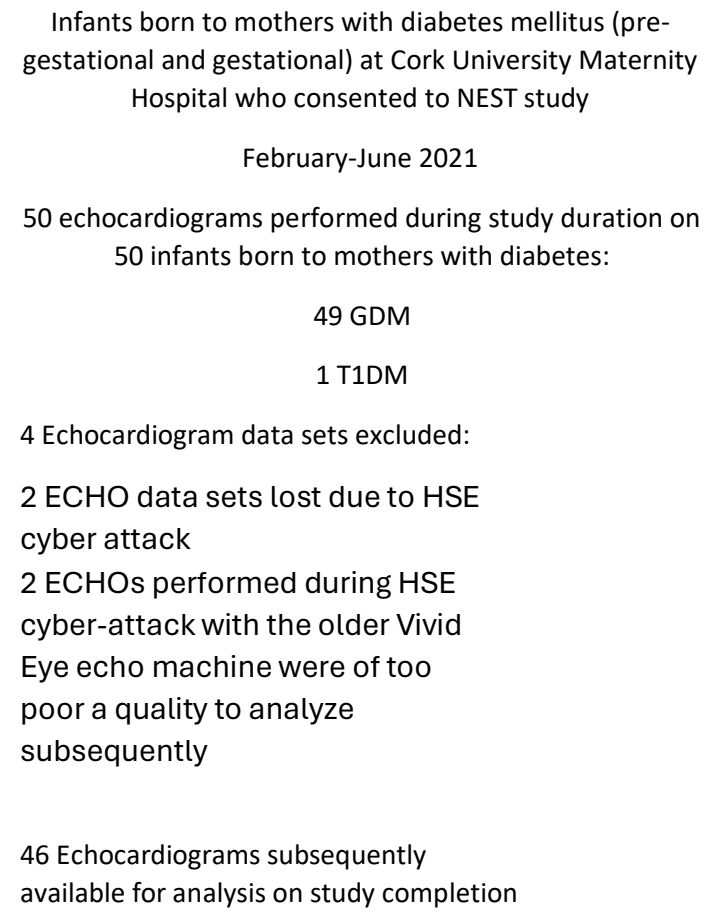
Of these patients, all 50 patients underwent an Echocardiogram, however only 28 patients underwent a bioreactance assessment. The mean time of life for the ECHO was 36 hrs (IQR 29.5-46hrs of life). All 28 bioreactance assessments using the NICOM^{TM} Cheetah were completed within one hour of the ECHO assessment. The reason for the incomplete NICOM data set was due to delays in acquiring further NICOM^{TM} Cheetah leads during the study duration so only the first 28 patients underwent a paired NICOM and ECHO assessment.

Only one family declined the bioreactance portion of the study as the mother in question had a history of contact dermatitis to plasters and had concerns that the electrodes would cause a contact dermatitis for her child.

Of the 50 Echocardiograms performed, 46 sets of images were subsequently available for analysis at the data analysis section of the study (see Figure 3: Flowchart below). The reason for this was due to a HSE cyber-attack during the spring of 2021 which impaired file transfer and storage. Two sets of ECHO images obtained on an older machine were not suitable for reanalysis and all ECHO data sets used in this study were based on the newer model Vivid Eye ECHO machine. The final data set of complete NICOM^{TM} Cheetah and ECHO data was a cohort of 27 patients.

Sixteen patients from the cohort were admitted to the neonatal unit during the study duration. Of note, two infants were admitted to the neonatal unit due to ECHO findings of significant pulmonary hypertension. The first case was due to suprasystemic pulmonary hypertension noted on ECHO with intermittent desaturations to the high 80s on assessment during the ECHO. The infant in question underwent a partial septic work up which was negative, was re-echoed by our paediatric cardiologist with subsequent resolution of pulmonary pressures within the subsequent 48 hours of life.

Figure 3: Flowchart of patient recruitment and Echocardiograms available for analysis



The second case was similar in evidence of pulmonary hypertension resulting in bidirectional interatrial flow. The infant was subsequently re-echoed by both the research team and admitted to the neonatal unit due to persistent pulmonary hypertension. She underwent a partial septic work up which was negative. There was no supplemental oxygen requirement and has a normal Echocardiogram performed by the paediatric cardiologist with subsequent discharge 48 hours later.

Other reasons for admission to the neonatal unit include: five (5) cases of hypoglycaemia detected on the postnatal wards or delivery suite, four cases of tachypnoea noted on the postnatal wards- three of whom were determined to be cases of transient tachypnoea of the newborn and one cases of congenital pneumonia who received five days of intravenous antibiotics (benzylpenicillin and gentamicin.) One case of an empiric partial septic work up due to multiple septic risk factors (maternal Group B Strep and prolonged rupture of membranes) which was negative.

One infant is of particular note: our 49th patient was an infant (39 wks., 4.05kg) admitted from the delivery suite at 35 minutes of life due to a significantly increased work of breathing with bedside echo demonstrating significant pulmonary hypertension. He subsequently required intubation, ventilation and inhaled nitrous oxide. He had a subsequent ECHO repeated which was used to complete the measurements as required for the study within 48 hours of life. He had no sequelae, his pulmonary pressures settled within a week and he was subsequently discharged from the neonatal unit on DOL 9.

The remaining cases admitted include suboptimal feeding on the postnatal wards and one case of a large meconium plug post the study with serial PFAs demonstrating normalisation of the bowel gas pattern.

Of note, no cases required propranolol or other inotrope support or cardiac medications during the study. The indications for supplemental oxygen were predominantly for transient tachypnoea of the newborn presentations bar two cases of pulmonary hypertension with subsequent resolution of same. Likewise, the indications for intravenous fluids were for hypoglycaemia and respiratory distress.

There were no specific treatments required for transient HOCUM during the study duration.

9.2 Maternal Demographics:

The median age of mothers who participated in the study was 35 years of age (IQR 31-37 yrs.) (Table 7).

Of this cohort, there were 49 cases of gestational diabetes and one case of pre-existing type 1 diabetes mellitus (with only case of pre-existing diabetes, this is insufficient for any analysis on pre-existing diabetes). Of the gestational diabetes cohort, 33 cases were diet controlled. 8 mothers required metformin and 8 mothers required insulin. The patient with type 1 diabetes mellitus required significant dosages of insulin: Levemir (insulin detemir) 113 units a day towards the end of the pregnancy, typically Levemir (insulin detemir) 50 units bd and Humalog (insulin lispro) 15-17units TDS.

The median maternal HbA1C was 35mmol/mol (IQR 32-37mmol/mol) (Table 7). Of note, there were only two patients of the GDM cohort with a HbA1C above 42- both patients were 43mmol/mol with our patient with type 1 diabetes mellitus possessing a HbA1c of 76mmol/mol.

The median maternal BMI was 31.57kg/m^2 (IQR 26.4-39.6 kg/m^2) (Table 7).

9.3 ECHO findings:

Of the 46 ECHOs fully analysed, from a congenital heart disease viewpoint, 4 VSDs and 11 possible ASDs were noted on ECHO. Of these 11 possible ASDs, only 1 was a confirmed ASD secundum with left to right flow. The remaining 10 possible ASDs (> 3mm interatrial communications) were subsequently re-reviewed and determined to be overstretched PFOs on review or repeat imaging. 78% (36/46 infants) had a PFO visible at the time of initial Echocardiography.

From the viewpoint of other incidental defects, 15 patent ducts (33%) were visualized, 3 cases of pulmonary hypertension were noted as described above and there was one case of an incidental finding of a mitral valve cleft.

From review of the cardiac examination findings, only five of the original fifty infants recruited for the study had an audible cardiac murmur on examination during the routine newborn infant examination. Of these five infants, only one infant had a small 2-3mm muscular VSD who was offered neonatal follow up. One infant with a grade 3/6 ejection systolic murmur loudest at the left lower sternal edge was noted to have an ASD secundum with left to right flow. Of the remaining three infants, two had a small PFO and a small restrictive PDA while the final infant had a normal echocardiography study. Otherwise, all infants recruited into the study had a normal routine bedside newborn examination.

Table 8: ECHO results:

	Full patient cohort (N=46)	Incidence (%, N=46)
VSD	4/46	8.7
ASD Secundum	1/46	2
Possible ASDs requiring follow up (>3 mm diameter)	10/46- subsequently confirmed overstretched PFOs - added to PFO section below	22
PFO	36/46	78
PDA	15/46	33
Pulmonary Hypertension	3/46	6.5

Legend:

VSD= Ventricular Septal Defect

ASD= Atrial Septal Defect

PFO= Patent Foramen Ovale

PDA= Patent Ductus Arteriosus

9.4 Transthoracic Bioreactance findings:

A comparison between left ventricular outflow (LVO) values between transthoracic bioreactance and ECHO was undertaken. 28 patients underwent a transthoracic bioreactance assessment- of whom, one was subsequently excluded from further analysis as we were unable to extract the ECHO data from the machine for further analysis. The LVO echocardiogram measurements in mls/kg/min were compared with bioreactance LVO measurements. Initially, the cardiac output from the NICOM^{TM} Cheetah device is provided in litres/min. To convert the data to mls/kg/min, we divided the numeric values by 1000, and then divided by the patient's weight.

The median cardiac output from ECHO data was 148.98mls/kg/min (Interquartile range 66.07-251.65 mls/kg/min). (N=27, Please see appendix 3 for the raw cardiac output values).

The median cardiac output from bioreactance data was 133.54 mls/kg/min (Interquartile range 104.21 -191.31mls/kg/min).

For the transient HOCUM cohort (N=4), there were only two bioreactance values obtained- 155mls/kg/min and 122mls/kg/min.

For the cohort with significant intraventricular septal wall thickening (Z-score >2 on two separate calculations, N=18), there were 10 bioreactance measurements available to assess. The median values of these 10 bioreactance measurements was 123.38mls/kg/min (Interquartile range 117.52-147.75 mls/kg/min). The median value of the seventeen remaining bioreactance measurements which did not fit the Z-score criteria for hypertrophy was 139.24 (Interquartile range 118.53-163.58 mls/kg/min.)

9.4.1 Pearson Correlation:

A Pearson correlation co-efficient calculation was calculated to evaluate the relationship between transthoracic bioreactance LVO and ECHO LVO values using SPSS. The results indicate that there was a poor non-statistically significant correlation between LVO values from transthoracic bioreactance when compared with ECHO as the p value was >0.05. ($r(25)= 0.2$, $p=0.31$).

Two outliers had been noted on the preliminary scatterplot with profoundly elevated left ventricular output values when compared with the other values obtained- one datapoint from both the ECHO and NICOM data sets. The outlier from the NICOM data set was a cardiac output value of 280mls/kg/min from a NICOM measurement of 1L/min which did not fit with any of the other data points. The original NICOM entry data appeared correct on review, yet this was a well infant who was noted to be tachypnoeic during the ECHO. An ASD secundum with left to right flow was detected on echocardiography, yet the infant was subsequently admitted to the neonatal unit for a partial septic work up. The infant in question received five days of benzylpenicillin and gentamicin as the initial CRP was 33 suggestive of early onset culture negative neonatal sepsis. The elevated transthoracic bioreactance value was likely in response to cardiac compensation for a likely evolving infectious picture. The second outlier was a cardiac output value obtained from echocardiography of 576mls/kg/min. This was an accurate ECHO with no data entry issues, reconfirmed on the ECHO machine. As a result, this outlier was included in the analysis.

Figure 4: Scatterplot demonstrating relationship between NICOM and ECHO LVO values:

9.4.2 Bland-Altman plot

A Bland-Altman plot was also performed comparing LVO measurements in mls/kg/min between ECHO and NICOM data sets (N=27). Figure 4 demonstrates this comparison of LVO values between the standard ECHO assessment with the newer NICOM assessment. A bias of 11.1 was calculated both on 'GraphPad Prism' as well as 'Medcalc' with a standard deviation of 94.15. There was a poor agreement between LVO measurements obtained via bioreactance and ECHO as evidenced by the limits of agreement (calculated as -173.4 to 195.6.)

9.5 Transient HOCUM incidence

Four out of 46 patients (8.7%) were noted to have a z-score of >2 for both the interventricular septal wall thickness and the left posterior ventricular wall in diastole. Z-scores were obtained from two different software for the purposes of the IVSd to ensure accuracy. Both Z-scores had to be >2 for to be included. Equally, these same four patients had a ratio of >1.3 in comparing the interventricular septum to the left ventricular posterior wall in diastole. As a result, these four patients met our strict criteria for a true diagnosis of transient HOCUM, suggesting an incidence of 8.7% for our study population. Furthermore, none of the four patients demonstrated symptoms nor evidence on echocardiography of left ventricular outflow tract obstruction. Of note, 18 out of 46 patients (39%) were noted to have an IVSd z-score of >2 for both the Cardio Z and Boston Children's Hospital software which was suggestive of significant thickening of the interventricular septal wall. 11 out of 46 patients were noted to have significant thickening of the left ventricular posterior wall with a z-score of 2 as well. Once again, neither of this groups of patients with more isolated thickening demonstrated LVOTO. Unfortunately, the Boston Children's Hospital software does not allow us to calculate Z-scores for the left ventricular posterior wall. Therefore, 26 out of 46 infants born to mothers with diabetes had significant thickening (Z-score >2) of either the interventricular septum or the left ventricular posterior wall. This cohort had similar demographic data to the main patient cohort (table 7).

Table 9: Demographic Data Subset for infants with transient HOCUM and IVSd Z-score >2:

Infant Clinical Data	**Transient HOCUM (n=4)**	**IVSd Z-score >2 (n=18)**
Gestational age (weeks)	39	38
Birth weight (kg)	3.58	3.71
Gender (Females)	2/4	11/18
Mode of Delivery (c-section absolute no.)	2/4	9/18
Maternal Clinical Data		

Maternal Age (years)	35	35
Maternal BMI (kg/m^2)	27.9	27.8
Maternal HbA1C (mmol/mol)	31.5	36
Maternal mode of diabetes control	Diet 4/4 No cases born to mothers using metformin or insulin	Diet 13/18 Metformin 2/18 Insulin 3/18

Note: Median values obtained for above criteria unless otherwise stated

The population of four true cases of transient HOCUM was too small to run further analysis on to assess the impact of categorical variables on the incidence of transient HOCUM in our study population using Chi Square or Fisher Exact tests. Instead, using the population of 18/46 patients with significant interventricular septal wall thickening as per two Z-scores of >2, we performed sub analysis to determine the impact of infant and maternal demographic characteristics on our outcomes of abnormal heart muscle thickening.

9.5.1 NICOM LVO values comparison:

The null hypothesis for the overall study is that there would be no difference in LVO cardiac output values obtained with transthoracic bioreactance for infants with transient HOCUM with LVOTO against those infants without transient HOCUM. Initially we hoped to perform a one-way ANOVA (Analysis of Variance) test, however the sample sizes for both cohorts were too small. We were unable to carry out statistical analysis on the cohort of true transient HOCUM cases with a sample size of four patients- two of whom did not have NICOM^{TM} Cheetah data available. Instead to determine if our null hypothesis was false, we used the cohort of 18 cases with significantly increased heart muscle thickness as demonstrated on two z-score measurements of the IVSd as demonstrated above. This left us with ten cases of significant heart muscle

thickening with available bioreactance data to be compared against 17 cases without significant heart muscle thickening with available bioreactance data.

However, despite the standard deviations demonstrating equality of variance (neither standard deviation exceeded twice the absolute value of the other group's), the histograms produced for each sample did not demonstrate normal distribution for the thickened IVSd cohort. This likely reflects the smaller sample size.

Figure 6: Simple Histogram demonstrating distribution of LVO for IVSd Z-score >2 cohort:

Figure 6: Simple histogram demonstrating LVO distribution and frequency in normal IVSd control group:

Due to the histogram findings, despite the absence of outliers, the non-parametric equivalent of the one-way ANOVA test, the Kruskal-Wallis test was chosen. There was not a statistically significant relationship between LVO values obtained with NICOM and the incidence of transient HOCUM irrespective of clinical evidence of LVOTO ($H(2) = 1.05$, $p = 0.591$ from the Kruskal-Wallis test.

9.5.2 Univariate analysis of transient HOCUM cohort

Initially Chi Square tests for independence were performed for the following infant characteristics (categorical variables): infant gender, infant mode of delivery. This is to determine if there is an association between infant gender and incidence of transient HOCUM and again for mode of delivery. The percentage of females with transient HOCUM was slightly higher than males (61%) but this result was not statistically significant (p= 0.968) as expected. Likewise, there was no statistically significant difference between mode of delivery- caesarean section (50%) vs Vaginal delivery (50%) (p= 0.864).

For the analysis of continuous variables: Maternal age, Maternal BMI and Maternal HbA1C which do not fit neatly into subcategories, an independent T-test was performed. From a maternal age viewpoint, there was a minimal difference in the mean maternal age between our cohort with significant thickening of the heart muscle (mean 34.6, SD+/-2.89) against normal heart muscle thickness (mean 33.5 SD +/- 4.89) which was not statistically significant (t (44) =0.913, p=0.366). For maternal BMI, once again there was a minimal difference between our cohort with significant thickening of the heart muscle (mean 31.14, SD +/-6.59) against normal heart muscle thickness (mean 32.88, SD +/- 8.45) which was not statistically significant (t (42) =-0.710, p=0.482). (Of note- N=16 for the Z score >2 heart muscle thickened group as two mothers did not have heights documented in the maternal clinical notes so we were unable to calculate the BMI for two cases- as a result, they were excluded from the analysis.) Finally, from a maternal HbA1C viewpoint, the mean HbA1C for our significantly thickened heart muscle group (Mean 36.55mmol/mol, SD +/- 4.7) was very similar to the normal heart muscle group (Mean 35.6mmol/mol, SD +/- 8.5). Once again this was not statistically significant (t (44) =0.43, p=0.669.)

One final key secondary characteristic was regarding the potential relationship between small for gestational age infants and the incidence of transient HOCUM. Unfortunately, our sample size was always going to be too small to assess such a relationship- in a cohort of 50 infants, one would expect around 4-5 infants to meet the criteria for small for gestational age. There were three infants in our study who met the criteria for small for gestational age as defined as a birth

weight less than the 10th centile for gestational age(151). Of these three infants, none of the three met the case criteria for transient HOCUM set out in our study with only one of the three infants possessing a Z-score >2 S.D. on two separate scoring systems for interventricular septal hypertrophy in isolation.

10 Discussion:

10.1 Hypothesis:

The overarching question we hoped to answer with this study was to determine whether there would be a benefit for our patients by screening infants born to mothers with gestational diabetes for cardiac sequelae. In particular, our original hypothesis that transthoracic bioreactance could be an effective and feasible screening tool on the postnatal wards to detect cases of transient HOCUM with LVOTO. Our hope was that we could identify those infants who would require a further ECHO study and medical intervention (those 5-10% of infants who go on

to develop impaired cardiac output secondary to reduced left ventricular outflow in the transient HOCUM cohort(40)). Albeit an observational study like this cannot answer this question definitively, it does provide some important information.

Our key primary objective was to determine if transthoracic bioreactance could be an effective screening tool in detecting cases of likely transient HOCUM with LVOTO on the basis of reduced left ventricular outflow values when compared to normative control data from previous studies e.g. McCarthy et al(113). This would then identify those infants who would require a subsequent ECHO and potential medical intervention. Our initial analysis was aimed at determining if transthoracic bioreactance and ECHO LVO values would correlate. The reality was that our Pearson correlation coefficient reported a very poor correlation which was not statistically significant due to our sample size. Likewise, the Bland Altman plot demonstrated a poor agreement (ambiguous at best), reducing the ability to use bioreactance in this clinical setting. Effectively, bioreactance was unable to closely correlate with ECHO data and therefore, was nowhere near as effective as the most commonly used assay of non-invasively measuring LVO-echocardiography.

The next greater question was as to whether transthoracic bioreactance could detect those infants who would have transient HOCUM with LVOTO on the basis of reduced LVO values albeit acknowledging it was not as effective as an echocardiogram. Unfortunately, the limits of this study take on a greater role here due to the small sample size. Our incidence of true transient HOCUM was defined by Z-scores >2 for the interventricular septal wall diameter and left ventricular posterior wall as well as the necessary ratio of >1.3. On applying this more robust criterion prior to study recruitment, we found an unexpectedly low incidence of 8.7% for our cohort, which did not fit with previous reported incidence rates (13-44%). However, 41% of our cohort had a Z-score of >2 for the interventricular septal wall thickness, which may explain why some previous studies reported an incidence of transient HOCUM as high as 44%. It is imperative that a strong definition is applied as to overcall such diagnoses could place an unnecessary burden on families which may be unnecessary. Furthermore such unnecessary medical interventions may cast further doubt on screening assessments already in the eye of the public(152). We acknowledge that the definition of HOCUM does not intrinsically include

LVOTO, as this abnormal thickening can occur at any point on the ventricular wall. Nevertheless, as with any condition, we are more interested in identifying patients at risk of developing complications from an illness considering transient HOCUM's relatively benign natural history demonstrating spontaneous resolution.

Coming back to our primary objective, with such a small population of four cases of true transient HOCUM, we only have two bioreactance data sets from this small group. Both patients provided absolute values of 155mls/kg/min and 122mls/kg/min which was within the interquartile range for those patients without significant myocardial thickening. These infants did not have clinical symptoms or signs of LVOTO. As a result, we cannot determine if a patient may have transient HOCUM from an assessment using transthoracic bioreactance. Our original hypothesis was to determine if transthoracic bioreactance could be an effective and feasible screening tool to detect transient HOCUM with LVOTO. This is highly unlikely at present on the basis of the data we have in this study unless it was a severe case with symptoms and signs of impending heart failure.

10.2 Secondary Study Objectives:

Below we will discuss in more detail each of the secondary study objectives, but in summary:

9. To assess the utility and feasibility of transthoracic bioreactance in a previously unstudied high-risk patient population – ultimately providing bioreactance data on this previously unassessed patient cohort: We have acquired 28 NICOM data sets for this patient cohort with a median cardiac output value of 133.54 mls/kg/min (Interquartile range 104.21 -191.31mls/kg/min). Data for both infants with normal and hypertrophied myocardium was collected. Albeit LVO values demonstrated poor correlation with Echocardiography, we have still obtained values in this patient cohort.
10. To determine if maternal glycaemic control can have an impact on the degree of transitional hypertrophic cardiomyopathy: Our study was unable to demonstrate an association between maternal glycaemic control and the incidence of either transient

HOCUM or abnormal isolated ventricular wall thickening which was statistically significant p=0.669. The sample size was too small for univariate analysis of the four true transient HOCUM cases.

Likewise, we could not demonstrate a statistically significant relationship between maternal age or BMI with the incidence of transient HOCUM or abnormal myocardial thickening.

11. To calculate the incidence of transient hypertrophic cardiomyopathy in infants born to mothers with diabetes locally at CUMH which could be extrapolated to the Irish population: We have reported an incidence of 8.7% for transient HOCUM as per our case definition. 18/46 infants (39%) were noted to have a Z-score >2 for the interventricular septal wall in diastole (IVSd) while 26/46 (58%) of infants had a z-score of >2 for either the IVSd or Left ventricular posterior wall in diastole.
12. To determine the incidence of congenital heart disease in our study population: 8.7% incidence of VSDs, 2% incidence of ASDs, no other forms of cyanotic heart disease. There was a disproportionately high incidence of pulmonary hypertension likely secondary to imaging these infants too early. There was one incidental finding of a mitral valve cleft which is not associated with GDM. These findings would not provide evidence advocating for echocardiography screening for all infants born to mothers with GDM.

10.3 Incidence of transient HOCUM:

Our incidence of transient HOCUM at 8.7% is far lower than previous studies have reported(9-11, 82). Beyond the strict pre-recruitment criteria we applied, other reasons why our cohort may have such a smaller percentage of transient HOCUM cases include improvements in glycaemic control over the last few decades. These include a move towards oral hypoglycaemics like metformin in this cohort of patients as well as a move towards newer insulin preparations e.g. insulin aspart and lispro as well as newer antenatal screening practices in the last decade(153). A move towards improved diet and exercise during pregnancy has played a significant role as well(33). Four of five studies are from the 1980s and 90s, where glycaemic

control options for expectant mothers were less and multidisciplinary input was very poor(7-11). In our institution, dietetic and diabetes nurse specialist support for expectant mothers is part of routine care. Previous authors have speculated that fluctuations in glycaemic control may have an impact antenatally where our cohort is screened for gestational diabetes mellitus at an early stage in the pregnancy with frequent follow up as well as easy access to both endocrinology and obstetric clinics(53). Frequent diabetes nurse specialist and clinic follow up reduces the risk of fluctuating glycaemic control for mothers(154).

10.4 Transient HOCUM- a clinical entity

The unusual aspect of our study is that none of our cases of transient HOCUM demonstrated symptoms or cardiac sequelae requiring medical intervention as had previously been noted in case reports and case series when this clinical entity was first reported on within the literature(13-15, 78, 155, 156). Of note, none of the patients in our cohort had symptomatology or clinical signs suggestive of transient HOCUM. Indeed, only one of our patients was deemed to have clinical symptoms at birth which warranted an urgent echocardiogram in the first 24 hours of life. This case of pulmonary hypertension and respiratory distress syndrome was an atypical case and we are confident this was not a clinical manifestation of potential LVOTO, as despite a Z-score of >2 for the interventricular septal wall depth, the case did not meet the criteria for transient HOCUM. The LVO values on echocardiography were within normal limits and the case was a suspected infective aetiology. Indeed, there were no cases of cardiac insufficiency suggestive of impaired left ventricular outflow in our cases of transient HOCUM. This is very reassuring. Over the four-month period we recruited patients into our study, we did not identify a case of transient HOCUM requiring medical intervention. Indeed, a potential bias would have been that such a patient would have been far easier to recruit into the study.

The ultimate question of cardiac screening for transient HOCUM in isolation is of questionable clinical utility. There would have been no direct clinical benefit for any of our patients involved in the study from the detection of transient HOCUM alone as none of the four cases of transient HOCUM developed any subsequent medical issues secondary to same. There were no patients who required supplemental oxygen, propranolol, IV fluids or respiratory support. Albeit there is an incidence of 8.7%, there is also an absence of clinical symptoms in our cohort. Transient HOCUM as a clinical entity may not be worth screening for in isolation. Instead, it may be a situation that we act appropriately for an infant with respiratory distress born to a mother with gestational diabetes mellitus with an early echocardiogram rather than commit to performing echocardiograms on this entire population.

10.5 Congenital Heart Disease- a better target

From a congenital heart disease screening viewpoint, our incidence of congenital heart disease may be a better rationale for screening in this cohort. The vast majority of these cases would not have been detected clinically during the routine newborn baby check assessment performed by junior doctors at present (only 10% of our cohort had a murmur which would have led to further assessment and investigations). The question is how many of these congenital heart structural findings are of clinical significance and would have an impact on the infant. Our findings of a PFO in 78% of infants and a persistent ductus arteriosus in 33% of infants is actually not of major clinical significance. A persistent ductus typically gains the title of PDA if it remains open for >72 hours. Likewise, the incidence of PFOs is not unexpected either considered all infants were screened in the first 48 hours of life and were still transitioning from a cardiac physiology viewpoint to extrauterine life.

Our key congenital heart disease findings were a VSD incidence of 8.7%, a true ASD incidence of 2% (albeit interatrial communications > 3mm are followed up as potential ASD secundums in our centre until proven otherwise) and finally, 6.5% of infants were noted to have pulmonary hypertension on imaging. Albeit 11 infants were initially viewed as possible ASD secundums, on re-review and further follow up only one infant had a true ASD secundum. There was one incidental pick up of a mitral valve cleft which can result in progressive cardiac failure. Although

this was a benefit to this individual case as it allows a surgical intervention at a much younger age, if necessary, there is no evidence in the literature which suggests an increased risk of mitral valve clefts associated with gestational diabetes mellitus or antenatal hyperglycaemia exposure(157-159). On this basis, it is far more likely that this was an opportunistic incidental pickup and speaks more for universal congenital heart disease screening for newborn infants rather than this cohort of patients in isolation. The key unexpected question which arose from our study was whether gestational diabetes led to such a significant rise in the incidence of congenital heart disease that screening infants for this purpose alone would be worthwhile.

The incidence of congenital heart disease is variable- Wren et al suggest 0.64% of children are born with congenital heart disease(160) while Lynch et al suggest 0.8% of the Irish population are born with some form of congenital heart disease(161). The prevalence of VSDs and ASDs at birth in the European population are reported at 15.5 cases per 10000 live births for ASDs and 36.6 per 10000 live births for VSDs from 2013-2019. Our figures are higher than this international average as expected. It has previously been reported that congenital heart disease occurs in 8.5 per 100 live births to mothers with diabetes(38). However, these European figures are not based on screening with echocardiography of every infant born to a mother. Instead, these figures are based on diagnoses obtained from initial clinical features leading to a subsequent ECHO.

One of the key findings was the unusually high incidence of possible ASDs initially. In retrospect, the probability is that many of these ASDs are more likely to be PFOs distorted by raised pulmonary pressures in the first few days of life(162). We defined an ASD in our study as either an interatrial communication >3mm in diameter warranting follow up as a potential ASD secundum or an ASD primum based on location. The challenge we faced was that many interatrial communications were likely overstretched PFOs due to a delayed transition in reducing pulmonary pressures in this cohort. This required review with our paediatric cardiologist and often reimaging to confirm same. Many studies have previously reported on the challenges of differentiating between PFOs and ASDs(163-165). This is increasingly challenging when imaging such infants at such an early stage in their transition to extrauterine life. Despite this disproportionately high PFO incidence of 78%, this does not support the

intervention of a screening tool for infants born to mothers with GDM. An international consensus statement released in 2020 from both the American Heart Association and Paediatric echocardiography society has argued that it is not appropriate to screen infants with echocardiograms who are asymptomatic with the goal of detecting a PFO. Likewise, this same consensus statement argues that it is not appropriate to offer follow up to asymptomatic infants who have incidental PFOs detected on neonatal imaging(166). One of the main reasons for this is that PFOs tend to spontaneously close (61-66% of PFOs)(167, 168). Likewise, from an ASDs viewpoint, only one of the 11 suspected ASDs noted was found to be >3mm in size and later confirmed as an ASD secundum. It has been suggested that ASDs <3mm in size do not require neonatal follow up as Radzik et al found that 100% of their cohort had spontaneously closure of such lesions by 18 months of age(163). Indeed, other studies have only reported on small ASDs as being at least 3mm in size(164, 165). Ultimately, the combination of the incidence of ASDs in our study with pre-existing evidence would suggest that screening infants born to mothers with gestational diabetes mellitus for the detection of ASDs would not be beneficial. Our current standard of care with a newborn bedside examination detected the key case of an ASD >3mm in size and this infant would have received an echocardiogram without being part of the study as part of our current protocol. Interatrial communications are common in the newborn period and the risk of cryptogenic infarcts in lesions <3mm has not been demonstrated in the literature to date(169).

The incidence of pulmonary hypertension was disproportionately high in our study population. When the normal cardiopulmonary transition fails to occur, pulmonary hypertension typically ensues(170). This is often due to delayed transition secondary to a constellation of additional confounding factors for infants born to mothers with GDM(171, 172). However, all of our patients with elevated pulmonary pressures demonstrated resolution on follow up imaging during the following few days of life. Albeit there is a well described association between persistent pulmonary hypertension of the newborn and GDM, only one infant required significant support in the form of nitrous oxide as well as ventilatory support. Of note this infant was born at 35 weeks and at higher risk of respiratory distress syndrome. The reality is that this key clinical case of pulmonary hypertension with symptoms of same was detected in the

delivery room on birth. The other two cases were screened while still transitioning and their pulmonary pressures did not require medical intervention. On this basis, the incidence of 6.5% in our small cohort, was in reality secondary to imaging these infants too early.

Regarding the impact of pregestational diabetes mellitus on transient HOCUM and congenital heart disease, we were only able to recruit one such patient into the study- a mother with known poorly controlled T1DM. The subsequent infant had a small PFO and PDA with no indication for further cardiac follow up. Nevertheless, Øyen et al have clearly demonstrated that the presence of pregestational diabetes mellitus significantly increases the incidence of congenital heart disease in a nationwide cohort study (318 per 10 000 live births (n=232) in comparison with a baseline risk of 80 per 10 000)(173).

10.6 Transthoracic bioreactance's clinical utility

Furthermore, we sought to investigate whether transthoracic bioreactance could be used as a potential screening tool long term to determine which infants born to mothers with GDM would benefit from an ECHO to detect transient HOCUM with LVOTO (as well as other forms of congenital heart disease in a broader sense). Indeed, if it had been effective in this high-risk cohort for congenital heart disease, we may have been able to investigate its utility in other high-risk groups.

As we can see from our data, the poor correlation between transthoracic bioreactance and ECHO fits with the findings of Van Wyk et al's systematic review of NICOM technologies overall(174). NICOM technology has struggled to adapt to our neonatal cohort. This technology was originally created with the adult ICU patient in mind and although the technology has been adapted to the neonatal cohort, its adaptation is suboptimal. A further issue noted was the phenomenon of skin irritation from the NICOM™ Cheetah sensor leads. The actual electrodes applied to the skin covered large areas of the infant's trunk. Often there were physical difficulties with applying the electrodes. Likewise, a contact dermatitis type picture was occasionally noted on removal of the NICOM™ Cheetah electrodes. Although these spontaneously resolved over 24 hours typically, their physical appearance was an unexpected

sequela from such leads. Previous studies had reported that there were no adverse events from the NICOM^{TM} Cheetah device(97, 113). This would leave bright red marks on the infant's skin for up to several hours after removal of the electrodes. We would frequently use gentle removal wipes and swabs to slowly remove the electrodes, but irrespective of the gentleness of the removal process, this was an unavoidable side effect. This is a side effect which warrants explanation in advance to parents in the future. No intervention was required in any case and no creams/ointments were required. There was no subsequent scarring and all lesions were resolved within 24 hours approximately.

Harm from screening is often unintended and what is unusual is that this skin reaction was not commented on in previous studies(97, 113, 114). For this author, on subjective discussions with colleagues who has used the electrodes previously on infants, it appears this reaction is known to users. This is one unintended skin reaction which is off putting as a user of the device. Even the usage of Cavilon brand skin protection products were ineffective.

The transthoracic bioreactance assessment itself is a well-tolerated procedure. No parent asked to stop the bioreactance assessment during the study and the bioreactance assessment was better tolerated by infants than the ECHO assessment in this subjective investigator's opinion.

Nevertheless, despite the small number of patients who underwent bioreactance assessment, the time and effort for an individual to carry out such assessments for one hour on each child was significantly more than the time and effort required for a bedside echocardiogram. Challenges included soothing the infant to sleep, the size of the machine at the bedside, the timing around meals and the physical weight of the device. These are further challenges to the device's day to day usage.

To determine if bioreactance technology is as effective as ECHO in detecting reduced LVO, significant statistical analysis was undertaken. Of note, the Pearson correlation coefficient demonstrated a poor correlation between both technologies. As Echocardiography remains the current best non-invasive assay of LVO short of invasive pulmonary thermodilution studies, this leaves transthoracic bioreactance with the burden of proving that is possesses a similar capacity to reliably determine cardiac output and left ventricular flow as ECHO. Cecconi et al have

previously reported on the importance of clear criteria for comparing new technologies to measure cardiac output(109). There is a degree of subjectivity however when interpreting a Bland Altman plot in isolation(150, 175).

10.7 Bioreactance and ECHO – as screening tools

One of the key questions we set out to answer in this study was to ascertain if transthoracic bioreactance could be used in isolation as a screening tool for potentially symptomatic cases of transient HOCUM in this historically high-risk cohort. We had envisioned a process akin to a faecal occult blood test being used to determine who requires a colonoscopy as part of colon cancer screening. Albeit a good screening method does not need to provide a diagnosis at the time point of first patient contact, it needs to be both accurate and precise. Unfortunately, our study demonstrates that the correlation and agreement of LVO measured by echo and bioreactance is poor. This effectively demonstrates that bioreactance does not come close to detecting potential LVOTO when compared with the far more frequently used method of echocardiography.

If we look at the WHO's regional report on screening practices for Europe, even if bioreactance had demonstrated an ability to detect cases of transient HOCUM, it would not have 1. Reduced mortality as no infants in our study died from transient HOCUM, 2. Reduced the incidence of the condition as the prerequisites for this condition occur antenatally, 3. Reduced the severity of the condition as no children were symptomatic and our treatments are supportive- not preventative. Albeit bioreactance as a screening tool does not need to be diagnostic(176), in our study it could not identify those infants who would have needed a subsequent ECHO.

Nevertheless, for a new technology 'to be safely used in the clinical environment for therapeutic decisions, it must be proven to be accurate and precise' (174).' Unfortunately, our small cohort did not demonstrate any remote ability for NICOM to determine impaired LVO in the context of transient HOCUM.

The next question which arises then is whether there is merit in screening infants born to mothers with GDM for congenital heart disease with the more frequently used method of

echocardiography based on our data. The purpose of screening is to identify an unrecognised condition in a healthy population, in essence to identify those with the disease and separate them from those who don't have transient HOCUM in our case. The ultimate hope of any screening intervention is that the earlier identification of such individuals with the disease, will result in better health outcomes for the patient by earlier recognition and medical intervention. The question often asked by the WHO regarding new screening interventions in the European region is whether there is a clearly demonstrated proof of effectiveness(177).

10.8 Risk factors- the impact of a mother's health

Following univariate analysis of our transient HOCUM cohort, the incidence of transient HOCUM was not associated with the degree of maternal glycaemic control, maternal BMI or the method of diabetes control (all $P > 0.05$).

Equally, we were not able to demonstrate a relationship between these three univariate factors and the presence of significant interventricular septal wall thickening. As ascertaining if there was a relationship between maternal glycaemic control via HbA1C and the incidence of transient HOCUM was one of our key secondary objectives, we were unable to demonstrate an association between glycaemic control and abnormal thickening of heart muscle as had previously been demonstrated(70, 72).

Chi square testing did not demonstrate a statistically significant link between gender or mode of delivery with an increased incidence of significant thickening of the interventricular wall as expected.

From a maternal demographics' viewpoint, independent T-tests for maternal age, BMI and HbA1C did not demonstrate a statistically significant relationship between maternal characteristics and an increased incidence of abnormal interventricular wall thickening. Our study was too underpowered to allow us to perform statistical testing to determine if there was an association between these maternal characteristics and the stricter case definition. Nevertheless, one would have expected that the greater a mother's BMI or higher her HbA1C, the greater the thickness of cardiac muscle. The rationale was that a higher HbA1C would be

biochemical evidence of a richer glucose milieu for the purposes of antenatal cardiomyocyte growth. Of note, despite there not being a statistically significant relationship between these maternal factors and abnormal heart wall thickening, the descriptive statistics alone suggests a hint that mothers who deliver infants with such changes tend to have higher BMIs and worse glycaemic control. We suspect that there would be merit for future research in assessing the impact of maternal BMI on infant cardiac outcomes.

On the basis of these findings, we cannot recommend the screening of infants born to mothers above a certain HbA1C threshold as reported by Shields et al(73). However, our data set demonstrates excellent HbA1C values (Median HbA1C 35 mmol/mol (IQR 32-37) for this study population. It may be that our study population is a healthier study population than others.

10.9 Limitations:

There are some limitations to this study: Some data was incomplete- most notably the absence of NICOM data for a large subset of patients. This was a logistics issue as there was a significant delay acquiring further NICOM leads beyond the first delivery. On a practical viewpoint, this is something that would go against the feasibility of routinely using transthoracic bioreactance on the postnatal wards but more forward planning may have overcome this issue. Equally the loss of some data sets secondary to the HSE cyber-attack was frustrating and led to a reduction in our final sample size available for statistical analysis. Furthermore, a delay in recruiting during the HSE cyber-attack had a further impact on our final sample size.

One of the key limitations of this study is the timing of both the echocardiography and transthoracic bioreactance assessments. As we have seen from previous research(114), an ideal comparison in cardiac output measurements between NICOM and ECHO would be for both assessments to be carried out at the same time. Due to the limitations of a small team, we were unable to do this but were able to carry out the NICOM assessment within one hour of the ECHO assessment. One of the challenges was carrying out an ECHO while the NICOM leads were in situ. We found it more practical to apply the NICOM leads once the ECHO assessment was

complete. Equally, we could not provide temporal data over a longer time period to assess for bioreactance's ability to detect trends when compared to echocardiography(178).

One of the more generalized questions we were considering with this study was to assess transthoracic bioreactance as a potential screening tool to help determine those who would need subsequent ECHOs. We had envisioned a potential situation whereby the ECHO assessment would take place potentially a day after the bioreactance assessment. Greater limitations were an inability to determine what constitutes a 'normal' bioreactance result. In reality, we were dependent on echocardiography as although we could recognise a grossly abnormal NICOM LVO or stroke volume result, there is no previous normative data in the literature at 24-48 hours of life. Even now at the end of our study, we would have uncertainty at looking at the Cheetah device and saying with confidence that this was a normal result. In retrospect, we would have obtained further funding to perform NICOM assessments on a cohort of well newborn infants without a maternal history of gestational diabetes mellitus. As a result, we were left using NICOM data from our non-hypertrophied cohort as controls. The expense of the NICOM leads is a great challenge as well- with an approximate cost of €100 per leads set. This would be an extensive cost on any study and require far greater funds for the future to recruit a true control group.

Final limitations to the study ultimately arise from our small sample size. A much larger sample size would have allowed us to ask more specific questions regarding the impact of pre-gestational diabetes and bioreactance's utility in this cohort as well as investigating a cohort of small for gestational age infants with maternal diabetes.

10.10 Future Directions:

Regarding future directions for this research area, one of the key areas that we are still unclear on is whether screening of infants with echocardiography alone would be a worthwhile endeavour in infants born to mothers with gestational diabetes. From our small sample size, the current standard of care consisting of newborn bedside examinations followed by echocardiography as indicated would have detected all cases of relevant (requiring medical intervention/follow up) congenital heart disease in our study. Likewise, only one infant with pulmonary hypertension required NICU care but this child would have received this care without screening as they were clinically unwell from birth. One key flaw of the study is that we assessed infants at a very early point in time- within 48 hours of life. A previous study had suggested that the true features of transient HOCUM continue to develop in the first two weeks of life and our patient cohort may have benefitted from serial echocardiography at two weeks of life(15). Equally, we need to follow up these infants' long term to ensure these were truly all cases of transient HOCUM rather than the autosomal dominant form of congenital HOCUM. None of our four patients with transient HOCUM developed symptomatology or sequelae suggestive of clinical manifestations of LVOTO which warranted medical intervention. On this premise alone, there would be no direct benefit for patients by screening for transient HOCUM alone based on our data. This does contradict previous data from other studies as there have been isolated cases which have been severe and led to neonatal death(78, 155, 156). The question remains as to whether there would be benefit in screening infants of mothers with diabetes with early echocardiograms to detect those infants at risk of severe/life-threatening illness. As always, every researcher desires a larger sample size for their study but for us, we would have liked to assess a large enough sample to detect severe/life threatening cases during the study duration. We have provided standard neonatal and paediatric cardiology follow up for those patients who required follow up as part of standard care, but the greater volume of patients with isolated septal hypertrophy may have benefitted from same albeit unlikely.

This leads us to whether there would be benefit for infants born to mothers with GDM undergoing screening for congenital heart disease alone. The timing of further ECHOs would ideally be performed at serial intervals preferably after 24 hours of life as previous studies

suggest transient pulmonary hypertension in otherwise healthy newborns resolves after 24 hours of life(179-182). This would ideally remove cases of transient appropriate neonatal pulmonary hypertension from being inappropriately detected. Of note, in appendix 1 of our raw data set, only two patients in the cohort were screened in the first 24 hours of life and neither had pulmonary hypertension. From our experience, those cases of pulmonary hypertension detected in our study via screening alone were admitted to the neonatal unit for additional medical investigations and follow up imaging to ensure these elevated pulmonary pressures normalized. This was an additional and potentially unnecessary medical burden on families without a direct benefit for the infant as these infants with pulmonary hypertension detected through screening were asymptomatic.

There is still uncertainty regarding the role of maternal BMI and glycaemic control in outcomes for infants. Our study contradicts previous evidence which found elevated maternal glycosylated haemoglobins were linked with septal hypertrophy(72). Our data does not demonstrate a meaningful link between optimising glycaemic control and reducing the risk of septal hypertrophy. However, our patient cohort had excellent glycaemic control for the most part. The usual regret for a researcher is that we did not recruit enough patients and with enough time in the future and a larger sample size, the data may suggest a different path. Ultimately, based on our data, the next step for such research would not include transthoracic bioreactance as a method of screening in this patient population. Albeit bioreactance may have a use in some cohorts in the neonatal population, as a generic screening tool outside of the NICU, our data does not support its usage on the postnatal wards. On reviewing recent publications in NICOM technology, the evidence promoting its utility is really thin. Albeit the technology can tell you if there is a deterioration in cardiac output in the NICU setting for a potentially unstable infant e.g. those infants with multisystemic organ dysfunction in cases of therapeutic hypothermia, it appears useful only as an adjunct for the same patient with a comparison of cardiac output values over time(183). Likewise, the poor correlation between LVO values in NICOM and ECHO has been replicated in other studies, even with the most vulnerable of NICU patients(174, 184). A future focus would be the addition of an ECG to the

data collection process as there was a high incidence of congenital heart disease in this cohort of patients. Likewise, an ECG may be a far more effective screening tool.

Another future direction of research would be to assess the impact of pre-gestational type 1 or 2 diabetes mellitus on the incidence of transient HOCUM when compared with gestational diabetes mellitus. The expectation was that hyperglycaemia from the moment of conception would result in a greater degree of teratogenesis, especially in the first six weeks of life(50, 65, 185). Unfortunately, we were only able to recruit one mother with poorly controlled pre-existing type 1 diabetes mellitus. A further larger study could look at mothers with pre-existing diabetes mellitus and furthermore, a subset analysis determining the impact of maternal glycaemic control in this cohort. A further key subset analysis would also apply to small for gestational age infants and a further attempt at characterising the incidence of transient HOCUM in this specific cohort as an additional risk factor.

11 Conclusion:

In conclusion, transthoracic bioreactance has a poor correlation and agreement with LVO values obtained via echocardiography. For the purposes of detecting transient HOCUM with LVOTO as a disease entity towards healthcare screening for a potentially high-risk population, we could not recommend transthoracic bioreactance on the basis of our data set.

The incidence of transient HOCUM in our study population at 8.7% from echocardiography data would be a figure which could be extrapolated to the wider Irish population on the basis of similar care for all mothers in the Irish system and similar demographic characteristics. As a clinical entity, transient HOCUM and abnormal heart wall thickening secondary to maternal GDM did not produce clinical symptoms and signs which required medical intervention. On this basis, albeit the phenomenon can be demonstrated on echocardiography, it does not appear to place a medical burden on our patients. As a result, although this clinical entity could be detected via screening with echocardiography in isolation, it would not be a beneficial step for our patients.

From a congenital heart disease viewpoint, albeit we have a higher incidence of congenital heart disease in this cohort of patients, our data would suggest that there would be no additional benefit for patients if universal echocardiography was introduced for infants born to mothers with gestational diabetes mellitus as discussed above. The current standard of care appears to be effective in recognizing congenital heart disease in high-risk groups.

The final question which remains from our research is the role of maternal glycemic control in the incidence of transient HOCUM. Our expectation was that an elevated maternal HbA1C and/or elevated maternal BMI would have been associated with a higher incidence of transient HOCUM. This has not been demonstrated in this study. The basic science would provide a rational supporting this hypothesis and yet, perhaps the standard of care to expectant mothers is at such a level that it is hard to demonstrate such an association without a larger study looking at mothers with very poor glycemic control against mothers with excellent glycemic control.

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