Associations Between Cardiac Manifestations Of Noonan Syndrome And Adverse Pregnancy Outcomes

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Associations Between Cardiac Manifestations of Noonan Syndrome and Adverse Pregnancy Outcomes

A Thesis Submitted to the
Yale University School of Medicine
in Partial Fulfillment of the Requirements for the
Degree of Doctor of Medicine

By
Christopher Alex Chow-Parmer
2021
ASSOCIATIONS BETWEEN CARDIAC MANIFESTATIONS OF NOONAN SYNDROME AND ADVERSE PREGNANCY OUTCOMES

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The goal of this study was to characterize a population of woman with Noonan syndrome who had been pregnant in order to determine the safety and feasibility of pregnancy. We performed a retrospective chart review of patients evaluated at Yale-New Haven Hospital from 2012-2020 with a diagnosis of Noonan syndrome and pregnancy. We identified 5 women with Noonan syndrome who had a total of 10 pregnancies. In terms of maternal cardiac disease, 3/5 patients had mild pulmonary valve stenosis at the time of pregnancy, 2 of which had previously undergone interventional cardiac procedures. Out of 10 pregnancies, 5 (50%) resulted in preterm labor (less than 37 weeks gestation). 80% of all deliveries were converted to Cesarean section after a trial of labor. 1 pregnancy resulted in intra-uterine fetal demise at 36 weeks while 9 pregnancies resulted in the birth of at least 1 live infant, for a total of 10 livebirths (due to 1 set of twins). 6/10 (60%) livebirths required care in the neonatal intensive care unit (NICU). One infant passed away in the NICU at 5 weeks of age prior to discharge. One pregnancy was complicated by post-partum hemorrhage and 1 pregnancy by a bleeding placenta previa. In conclusion, the majority of mothers had pre-existing though mild heart disease. Although many of the pregnancies resulted in living infants, this sample experienced high rates of prematurity, conversion to Cesarean section, and NICU stays for the neonate, as well as one occurrence of intrauterine fetal demise and one infant who died in the NICU. Although some serious maternal complications occurred, none resulted in long-term morbidity.
ACKNOWLEDGEMENTS

I wish to foremost acknowledge the guidance and support of my thesis advisor and research mentor, Dr. Robert Elder, without whom this project would not have been possible.

I would also like to thank Dr. Katherine Campbell for her expertise and contributions.

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Finally, I wish to express my deep appreciation to my family for giving me the opportunity to be where I am today: my parents, Chee and Joan Chow, my sister and brother-in-law, Kimberly and Hugh Sullivan, and my nephew, Martin Sullivan.
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INTRODUCTION

Noonan syndrome is a genetic disorder with a constellation of malformations involving a variety of systems, including distinctive facial features, developmental delay, renal anomalies, lymphatic malformations, and congenital heart disease [1-3]. The syndrome was first described by Jacqueline Noonan, a pediatric cardiologist, in a 1963 paper in which she described nine patients with pulmonary valve stenosis, small stature, hypertelorism, mild intellectual disability, ptosis, undescended testes, and skeletal malformations [4]. In 1968 she published a case series including these nine patients as well as an additional ten patients [5]. Since its initial description, the understanding of Noonan syndrome has expanded greatly to include a broad spectrum of phenotypes, from seemingly asymptomatic carriers to severe disease. Short stature, distinctive facial features, and mild cognitive delay are common manifestations, while more significant morbidity can be caused by coagulation defects, lymphatic malformations, and, most commonly, congenital heart disease, as discussed below. However, many other organ systems have been reported to be affected in some proportion of cases, including the eyes, ears, gastrointestinal system, skeletal system, and genitourinary systems [1]. A 2007 study exploring the long-term natural history of the disease in 112 patients reported a 9% mortality rate during the 13-year study period, with a mean age at death of 23 years and a plurality of deaths attributed to cardiac complications of the disease [6]. Similar large-scale studies are scarce and there is little data available.

Noonan syndrome is relatively common compared to many other genetic syndromes, with an estimated prevalence of 1 in 1,000-2,500 live births [1]. However, the true prevalence is difficult to measure because initiation of a workup for Noonan
syndrome is typically based on the observation of characteristic clinical features, and thus many phenotypically mild cases likely go undiagnosed. The advent and increasing popularity of genetic testing may contribute to more cases being recognized, although those without a clinically significant phenotype are still less likely to undergo this testing due to barriers to affordability. Although mandatory routine newborn screening for genetic conditions in the United States currently identifies many cases of metabolic disorders, immunodeficiencies, and cystic fibrosis, among others, Noonan syndrome is not currently included on these screens [7]. Whole exome sequencing, the non-targeted method that sequences the entire protein-coding portion of the genome, may become a increase diagnoses of Noonan syndrome in the future as technology continues to improve and costs become less prohibitive [8]. Whole exome sequencing may be particularly revealing and cost-effective when utilized prenatally when abnormal fetal ultrasound findings, often present in Noonan syndrome, are detected [9, 10].

Noonan syndrome is either inherited in an autosomal dominant fashion or occurs sporadically due to a de novo mutation caused by a variety of gene mutations affecting the RAS-MAPK pathway [11, 12]. This cellular pathway, studied extensively with regards to its involvement in a variety of oncological processes, is involved in cellular response to growth factors and results in modulation of cell cycle control, differentiation, and cell growth. Involvement of this critical pathway places Noonan syndrome within a larger family of genetic syndromes referred to as “RASopathies,” named for the RAS-MAPK pathway. This group of syndromes includes neurofibromatosis type 1, Costello syndrome, LEOPARD syndrome, and cardio-facio-cutaneous syndrome, all of which have distinctive phenotypes as well as some overlapping features [13]. Advancements in
genetic testing have demonstrated the genetic heterogeneity of Noonan syndrome and provided some understanding for the wide spectrum of phenotypes associated with Noonan syndrome. In 2001, the PTPN11 gene was the first candidate gene to be identified as causing Noonan syndrome, and is now estimated to be the responsible gene in approximately 40% of cases [12]. Subsequently, mutations in the genes SOS1, KRAS, NRAS, RIT1, and RAF1 have been identified as causing large percentages of Noonan syndrome cases, among many others. While all of these genes can cause Noonan syndrome, there are certain phenotypic features that are more heavily associated with specific affected genes. For example, pulmonic stenosis is more often associated with mutations in SOS1 [14].

While Noonan syndrome affects many organ systems, the cardiac anomalies are among its more notable manifestations and cause significant mortality and disability among Noonan patients. Noonan syndrome is the second most common syndromic cause of congenital heart disease after trisomy 21 [3]. The presence of congenital heart disease is one of the major factors that led to the original description of the syndrome [4]. The prevalence of cardiovascular disease among Noonan patients is approximately 80-90% [15]. The cardiac manifestations of Noonan syndrome can put patients at risk for arrhythmia, decreased function, or even sudden death, and thus it is important that they are identified and addressed on an individual basis. Intervention and treatment are tailored to the structural issue. The cardiac phenotypes most commonly seen in patients with Noonan syndrome are pulmonary valve stenosis (60-70%), hypertrophic cardiomyopathy (20-30%), and atrial septal defect (10-30%), with lower prevalence of atrioventricular canal defect, mitral valve anomalies, coarctation of the aorta, tetralogy of
Fallot, ventricular septal defect, and aortic root dilatation [16, 17]. The pulmonary valve stenosis seen in Noonan syndrome is characterized by a dysplastic pulmonary valve with fibrotic thickening of the annulus and the leaflets, as well as fusion of the valvular cusps with the wall of the pulmonary artery [16]. This phenotype can put patients at risk for cardiac remodeling and reduced function, leading eventually to heart failure or arrythmia. While mild pulmonary valve stenosis does not typically progress in Noonan syndrome patients, moderate-to-severe stenosis will usually require therapeutic intervention to prevent progression [18]. Pulmonary valve stenosis is typically treated with balloon valvuloplasty, notoriously ineffective for the dysplastic pulmonary valve commonly encountered in Noonan patients, followed by pulmonary valve surgery in refractory cases [19].

Hypertrophic cardiomyopathy due to Noonan syndrome is often present in early childhood, and the severity of the condition and high mortality often necessitates extensive medical and surgical treatment, including but not limited to beta-blockers, pacemaker placement, and septal myectomy [18]. Cardiac transplantation has been reported in a handful of severe cases as a potential option for pediatric Noonan syndrome patients with hypertrophic cardiomyopathy as well [20]. Improved detection and treatment of congenital heart disease has led to a growing population of adults with congenital heart disease, with or without an association with a genetic syndrome [21].

As discussed above, there are some loose genotype-phenotype associations between the abnormal gene and the likelihood of specific cardiac anomalies. Patients with mutations in the PTPN11 gene are most likely to exhibit pulmonary valve stenosis, while hypertrophic cardiomyopathy is the dominant cardiac phenotype seen among
patients with a mutation in RAF1. Meanwhile, nearly all patients (97%) with a RIT1 mutation express cardiac abnormalities, whereas 79% of patients with a PTPN11 mutation had cardiac manifestations in a 2016 study [22].

Advances in genetic technology and increased survival of Noonan syndrome patients have led to the identification of an increasing population of adults with Noonan syndrome. Given that survival to adulthood with Noonan syndrome is improving, and many of the most common forms of congenital heart problems in this population are manageable in childhood with surgical and transcatheter strategies, women may wish to become pregnant and start families of their own. Because Noonan syndrome affects multiple organ systems, it is reasonable to ask how the condition may affect maternal health, fetal health, and the impact of maternal and fetal Noonan syndrome on the antepartum, intrapartum, and postpartum course. However, there is a dearth of research addressing the likelihood of successful pregnancies despite the known medical complications of the syndrome. Several case studies have collectively described safe outcomes for nine women with Noonan syndrome who have become pregnant [23-30]. Most notably, a case study published in 1999 described 2 women with Noonan syndrome who had successful pregnancies despite significant cardiac abnormalities (pulmonary stenosis and coarctation of the aorta, respectively) [24]. Another study from 2005 describes a single case of a woman with Noonan syndrome who experienced three pregnancies with fetal demise due to fetal hydrops, likely due to fetal Noonan syndrome, who was ultimately able to deliver a healthy infant [27]. Interestingly, the majority of cases published with regards to pregnant Noonan syndrome patients have come from the field of anesthesiology. Because of the multi-organ system effects of Noonan syndrome,
multiple case studies have been published in which anesthesiologists had to navigate challenging pregnancy scenarios including bleeding diathesis, hemodynamic instability, and difficulty accessing the airway [23, 26, 28-30]. However, no larger studies exist that explore or compare pregnant patients with Noonan syndrome. Additionally, most of the existing publications do not take a comprehensive approach to examining both maternal and fetal health outcomes.

One noteworthy reason for studying pregnant patients with Noonan syndrome is because of the complex physiological cardiovascular changes which occur during pregnancy. While systemic vascular resistance decreases throughout pregnancy due to widespread vasodilation and development of the uteroplacental circulation, cardiac output increases by as much as 45% by 24 weeks of gestation [31]. Average heart rate also increases 20-25% by the third trimester, while plasma volume and red blood cell mass also undergo major increases (30-50% and 50-60%, respectively). Labor itself is associated with the greatest increase in cardiac output during pregnancy, with increases of 60-80% compared to levels before onset of labor. Additionally, increased blood volume can cause an increase in size of all four cardiac chambers, and the gravid uterus may cause compression of the inferior vena cava or the aorta [32]. All of these physiologic effects within the cardiovascular system have the potential to exacerbate or unmask underlying cardiac deficiencies. Inability to meet these demands may result in arrhythmia, pulmonary edema, or congestive heart failure for the mother, and uteroplacental insufficiency leading to fetal growth abnormalities or premature delivery [33]. It is reasonable to explore whether the significant cardiovascular disease present in
some patients with Noonan syndrome has an effect on their ability to achieve a successful pregnancy.

The autosomal dominant pattern of inheritance of Noonan syndrome further complicates the question of pregnancy in Noonan syndrome, as 50% of fetuses can be expected to inherit and be affected by the maternal gene mutation. Lymphatic abnormalities can occur in up to 20% of people with Noonan syndrome and contribute to the likelihood of a successful pregnancy. These abnormalities can range from self-resolving peripheral lymphedema and cystic hygroma to chyous pleural effusions and hypoplastic lymphatic vessels [34]. In particular, lymphatic abnormalities in a fetus with Noonan syndrome can pose a danger to its survival, while maternal lymphatics are less likely to affect the pregnancy. Hydrops fetalis, the accumulation of fluid in at least two fetal compartments, is a potential life-threatening complication of these lymphatic abnormalities, and is exacerbated by underlying fetal cardiac dysfunction. Polyhydramnios may also occur as a result of abnormal lymphatic flow, putting these fetuses at a higher risk for premature delivery [35].

Fetuses inheriting Noonan syndrome-related mutations may also demonstrate abnormalities in the placenta during pregnancy, as the placenta is derived primarily from embryonic cells [36]. Given the wide-ranging and multisystemic manifestations of Noonan syndrome, it is highly possible that placental manifestations, and therefore dysfunction, may occur. Such dysfunction in women with Noonan syndrome has not, to our knowledge, been previously studied, but could be expected to have significant effects on pregnancy in light of the myriad roles of the placenta and complex maternal-fetal interactions involved in placental health [37].
The study of pregnancy in the setting of congenital heart disease has been widely explored in many conditions other than Noonan syndrome with great benefit, providing some of the inspiration for this study. A brief literature search for “congenital heart disease in pregnancy” returns thousands of results studying either specific cardiac abnormalities or congenital heart disease as a whole. A study of pregnant women with uncorrected pulmonary valve stenosis found a high rate of serious complications during pregnancy, delivery, or the neonatal period, including higher than expected rates of preeclampsia, preterm birth, and offspring mortality [38]. A systemic review of 2,491 pregnancies complicated by congenital heart disease described increased rates of cardiac complications such as arrhythmias and heart failure as compared to the general population, as well as higher rates of offspring mortality (4% vs 1%) [39]. A study of 90 pregnancies in 53 women with congenital heart disease demonstrated increased rates of premature birth, pulmonary edema, and sustained arrhythmias [40]. A recent 2018 systematic review of pregnant women with Fontan circulation for congenital single ventricle demonstrated high rates of maternal cardiac complications as well as frequent miscarriage, intrauterine growth restriction, and premature delivery [41]. A general theme present throughout many studies is the importance of multidisciplinary counseling, monitoring, and treatment prior to pregnancy, with obstetricians, cardiologists, geneticists, and others involved to optimize and prepare patients for a successful pregnancy. Optimization of cardiovascular health, risk stratification, and anticipation of complications may greatly influence decision making, including mode of delivery, use of anesthesia, and even the decision of become pregnant in the first place. The strength of
this body of literature suggests that it may be useful to explore similar questions in Noonan syndrome.

We have identified a gap in the literature regarding the question of successful pregnancy in women with Noonan syndrome. The growing population of adult women with Noonan syndrome, through increased identification and prolonged survival, is one factor that has brought this question to light. Advances in the diagnosis and intervention of congenital heart disease, a common feature of Noonan syndrome, contribute an additional area of focus to our question: namely, the likelihood of a woman affected by Noonan syndrome having a successful pregnancy and delivery, and the extent to which this likelihood is affected by her cardiovascular history and present condition.
STATEMENT OF PURPOSE

Considering the potential benefit to patients with Noonan syndrome and the current lack of research in this area, our study was designed to examine a larger sample of women with Noonan syndrome who have experienced pregnancy in order to further explore patient characteristics (focusing on cardiac abnormalities) that may contribute to the likelihood of maternal-fetal complications during pregnancy, delivery, and the neonatal period.

Hypothesis

The hypothesis of this study is that women with Noonan syndrome who become pregnant are at greater risk than the general population for the development of maternal-fetal complications during pregnancy and delivery related to the extent of underlying maternal cardiac disease.

Specific Aims

Specific Aim 1: This study aims to determine the effect of cardiac health on the probability of complications during pregnancy and delivery among patients with Noonan syndrome.

Specific Aim 2: This study aims to determine which interventions, if appropriate, may limit complications during pregnancy in the case of cardiac disease prior to conception.

Specific Aim 3: This study aims to provide data on women with Noonan syndrome who have become pregnant and given birth in order to understand potential issues in maternal-fetal health for this population.
METHODS

Chart review

We performed a retrospective chart review of patients at a single center, Yale-New Haven Hospital, from 2012-2020. This time period coincides with the introduction of electronic medical records at Yale-New Haven Hospital. We utilized the services of the Yale Joint Data Analytics Team (JDAT) to compile a database including all female patients in the electronic medical record with a diagnosis of Noonan syndrome in their medical history who had been evaluated at Yale during that time period for any reason (29 records.) We reviewed these charts to include only those women who were confirmed to have either a genetic or unambiguous clinical diagnosis of Noonan syndrome. In order to be included, patients must have had genetic testing which revealed one of the genetic mutations commonly associated with Noonan syndrome [11]. Alternatively, we also included women who had not undergone genetic testing but had a phenotype consistent with Noonan syndrome as recorded in the medical record by an official genetics evaluation and a first-degree relative who had undergone genetic testing (in some cases the offspring of the patient). We then narrowed our study population to those patients who were recorded as having been pregnant at any time, as determined by a search through each record for obstetrical notes. We included subjects who were pregnant outside of the initial time period searched as long as sufficiently detailed records of the pregnancy were available. We examined these clinical records and extracted information related to medical history, obstetrical history, and outcomes of the offspring. Medical history collected included genetic testing, medical conditions, medications, and surgical history. Obstetrical history obtained included pregnancy course (medications, abnormal
findings on prenatal screening, pregnancy-related medical conditions), gestational age at
delivery, method of delivery, postpartum course (maternal and fetal), and any genetic
testing performed. We also recorded cardiac conditions and history of intervention to date
for the offspring.

Classification of Pregnancy-Related Complications

Complications were divided into those related to pregnancy, delivery, and
postpartum course. Pregnancy complications included pregnancy-related medical
conditions (preeclampsia, gestational hypertension, gestational diabetes) and abnormal
findings during prenatal screening (ultrasound, chorionic villous sampling,
amniocentesis). Delivery complications included preterm labor (defined as labor prior to
37 weeks gestation), premature rupture of membranes, and conversion to Cesarean
section. Postpartum complications included postpartum hemorrhage (maternal) and
admission to the neonatal intensive care unit (infant).

Echocardiography Image Review

To obtain quantitative cardiac information for patients meeting inclusion criteria,
echocardiography images were analyzed. When possible, the most recent echocardiogram
prior to the first pregnancy was selected for analysis. Alternatively, a recent
echocardiogram performed after the first pregnancy was accepted given the absence of
significant change in cardiac health or function in the intervening time. All raw images
were analyzed by a cardiologist experienced with congenital heart imaging, rather than
by reviewing reports made at the time of the image.
We graded pulmonary stenosis as mild, moderate, or severe based on the peak gradient across the valve as measured by Doppler ultrasound. Mild pulmonary stenosis was defined as a peak gradient less than 36 mmHg, moderate as between 36 and 64 mmHg, and severe as greater than 64 mmHg [42]. Ventricular septal thickening consistent with hypertrophic cardiomyopathy was suspected if the septum was measured to be greater than 13 mm thick in any view [43]. Presence or absence of an atrial septal defect was also specifically evaluated in these images.

Distribution of Labor

All medical record review and data collection were performed by the medical student. Interpretation of echocardiograms was performed by the thesis advisor with participation by the medical student. Data analysis and manuscript preparation were performed by the medical student with review by the thesis advisor.
RESULTS

We identified 5 women meeting inclusion criteria who had become pregnant a total of 10 times with 1 twin gestation and a total of 11 fetuses. Nine out of 10 pregnancies occurred within the 9-year period of record review, and 1 pregnancy occurred prior to that period with sufficient records for review. Because of the paucity of published cases involving this population, the cases will first be presented individually, where they may be best understood, before they are analyzed together as a study population.

Subject 1: 3 pregnancies

The patient has genetically confirmed PTPN1 mutation with a history of pulmonary stenosis. She has no history of cardiac interventions. Her most recent echo demonstrated mild pulmonary stenosis and mild aortic insufficiency. She has a remote history of self-resolving ventricular septal defect. Her most recent electrocardiogram (EKG) demonstrated sinus rhythm with premature ventricular contractions. While she had been followed by cardiologists for many years prior to becoming pregnant, she did not receive a formal diagnosis of Noonan syndrome until after her second pregnancy, when her children underwent genetic testing. Her medical history is also significant for hypothyroidism.

- The first pregnancy occurred at maternal age 32 and resulted in a late stillbirth at 36 weeks gestation. Prenatally, the fetus had bilateral pleural effusions and polyhydramnios. Fetal autopsy showed preductal coarctation of the aorta with
right ventricular hypertrophy, and a tortuous and congested left descending coronary artery. Fetal Noonan syndrome was suspected but specific genetic testing was not performed. The fetus had a normal karyotype and microarray.

- At age 36, a second pregnancy was complicated by dichorionic-diamniotic twin gestation, placenta previa hypothyroidism management, and intrauterine insemination. The twins were delivered at 33 weeks gestation via emergent Cesarean section due to bleeding secondary to placenta previa. Both infants were transferred to the neonatal intensive care unit (NICU) for prematurity. The male infant was diagnosed with Noonan syndrome with pulmonary stenosis, and he later underwent open surgical repair. The female infant was not found to be affected by Noonan syndrome.

- A third pregnancy at maternal age 37 was complicated by anti-K isoimmunization. Delivery occurred at 37 weeks gestation due to chorion/amnion separation. The mother was initially induced for trial of labor after Cesarean section (TOLAC), but transitioned to Cesarean section due to fetal breech presentation and intrapartum chorioamnionitis. The male infant was delivered successfully and later diagnosed with Noonan syndrome with moderate pulmonary stenosis. He underwent balloon dilation of the dysplastic pulmonary valve followed by surgical pulmonary valvectomy.

**Subject 2: 1 pregnancy**

The subject has an SOS1 mutation with a cardiac history of pulmonary stenosis. She underwent surgical repair at 6 months of age. During preconception counseling, she was
found to have free, severe pulmonary insufficiency related to her prior repair. She underwent pulmonary valve replacement at 35 years of age, prior to pregnancy. Her echocardiogram prior to pregnancy was significant for bioprosthetic pulmonary valve replacement that exhibited mild pulmonary regurgitation and trivial tricuspid regurgitation with good left ventricular function. EKG showed sinus rhythm. She has no other significant medical history.

- Pregnancy occurred at maternal age 36. A prenatal ultrasound at 17 weeks gestation was significant for bilateral pleural effusions, ascites, membranous ventricular septal defect, and increased nuchal thickness. The ascites resolved on subsequent scans. The patient was on metoprolol throughout pregnancy for palpitations and ventricular ectopy. A female infant was delivered at 39 weeks gestation by Cesarean section due to failure to progress in the second stage with meconium-stained fluid. The infant had a short NICU stay for increased work of breathing requiring continuous positive airway pressure (CPAP). Genetic testing revealed an SOS1 mutation (R552G) associated with Noonan syndrome. The infant has been followed for pulmonary stenosis but has not required any intervention.

Subject 3: 3 pregnancies

The subject was diagnosed with Noonan syndrome at age 11 without genetic testing due to characteristic facial features and her cardiac history significant for pulmonary stenosis, which was alleviated at age 12 years via balloon valvuloplasty. A recent echo demonstrated mild pulmonary stenosis and mild pulmonary insufficiency. Recent EKG
showed sinus rhythm. Her medical history is otherwise significant for diabetes mellitus on insulin, chronic anemia, rheumatoid arthritis, and Hashimoto’s thyroiditis. Her surgical history is significant for multiple esophageal dilation for esophageal webs.

- The first pregnancy occurred at maternal age 23. A male infant was delivered at 29 weeks gestation by Cesarean section after preterm premature rupture of membranes (PPROM). The infant stayed in the NICU for 3 months after delivery due to respiratory distress and growth issues related to prematurity. Genetic testing revealed PTPN11 with a heterogenous 8228 A-G mutation. The infant was found to have pulmonary valve stenosis and later underwent balloon valvuloplasty.

- A second pregnancy occurred at maternal age 30. The patient received progesterone injections during pregnancy for history of preterm delivery. Labor was induced at 33 weeks after PPROM. The male infant was delivered 2.5 days after induction via repeat Cesarean section for a non-reassuring fetal heart tracing. The patient reported that the delivery was complicated by postpartum hemorrhage. The infant was also found to have pulmonary valve stenosis and later underwent balloon valvuloplasty.

- Third pregnancy at maternal age 34, complicated by pregestational type 2 diabetes managed with insulin. This patient again received progesterone injections during pregnancy due to her history of preterm delivery. The female infant was delivered via Cesarean section at 32 weeks gestation following PPROM. The infant was sent to the NICU for hypertrophic cardiomyopathy and severe lymphatic
abnormalities with chronically draining chylous effusions. In spite of optimal medical therapy, the infant died at 5 weeks of age.

**Subject 4: 2 pregnancies**

The subject has confirmed RIT1 mutation without typical cardiac abnormalities. Recent echo demonstrated mild mitral valve prolapse with mild mitral regurgitation and patent foramen ovale. Medical history otherwise unremarkable.

- First pregnancy occurred at maternal age 21. The uncomplicated pregnancy resulted in normal spontaneous vaginal delivery of a healthy male infant at 39 weeks gestation. There was no known genetic testing and no phenotypic signs of Noonan syndrome.
- Second pregnancy at maternal age 23. The pregnancy was complicated by self-resolving cystic hygroma in the fetus. An elective induction of labor at 40 weeks gestation was complicated by arrest of dilation and subsequent Cesarean section. Healthy female infant was delivered with uneventful hospital stay. Subsequent testing has revealed a RIT1 variant of uncertain significance as well as mild pulmonary stenosis on echocardiogram.

**Subject 5: 1 pregnancy**

The subject has a confirmed PTPN1 mutation with otherwise unremarkable medical or cardiac history. Echocardiogram many years after pregnancy was significant for grade I diastolic dysfunction but not valvular dysfunction.
One pregnancy at maternal age 29. She had an uneventful pregnancy with delivery at term via Cesarean section for failure to progress. A healthy female infant was delivered with uneventful hospital course. Genetic testing later revealed a PTPN1 mutation as an adult. A subsequent echocardiogram did not demonstrate any abnormality. Medical history significant for mild developmental delay in childhood.

**Summative Results**

Out of 5 patients reviewed, 3 carried diagnoses of pulmonary valve stenosis (see Table 1.) One patient had undergone repair by balloon valvuloplasty and 1 had undergone open pulmonary valvotomy with closure of an ASD as a child followed by pulmonary valve replacement as an adult while the third patient had not had any intervention. At the echocardiogram closest to the time of first pregnancy, all 3 women with pulmonary valve involvement had mildly elevated peak gradients (range: 15-28 mmHg, mean: 20, SD: 7) across the pulmonary valve (Figure 1.) 0 out of 5 patients (0%) carried a diagnosis of hypertrophic cardiomyopathy. 1 out of 5 patients (20%) had a history of atrial septal defect, repaired at the time of most recent echocardiogram. 1 out of 5 patients (20%) had no appreciable history of cardiac abnormality. 0 out of 5 patients (0%) had any other known serious medical comorbidity directly or commonly associated with Noonan syndrome such as renal disease or bleeding diathesis.
<table>
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<td>3.7</td>
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Table 1: Patient Medical Characteristics
Figure 1. Representative echocardiography images from Subject 3

A. Color Doppler flow across pulmonary valve

B. 2D vs color Doppler comparison across pulmonary valve

C. Doppler gradient with velocity measurement for calculation of degree of pulmonary stenosis
Of 10 total pregnancies studied, 9 (90%) resulted in the birth of at least 1 living infant, while 1 pregnancy (10%) resulted in vaginal delivery of a stillborn infant after intrauterine fetal demise (see Table 2.) Because 1 delivery was a set of twins, the total number of living infants delivered was 10. Complications are divided into those affecting the prenatal course, delivery, and the postpartum period (see Figure 2A.)

**Prenatal Course**

No maternal patient experienced cardiac or life-threatening complications during pregnancy. 1 pregnancy resulted in intrauterine fetal demise at 36 weeks with noted significant lymphatic abnormalities suspicious for fetal Noonan syndrome. 1 pregnancy was significant for gestational hypertension. 1 pregnancy was significant for a self-resolving cystic hygroma; although this lymphatic abnormality could be indicative of a fetus affected by Noonan syndrome, it is not considered an adverse prenatal finding. No cases of pre-eclampsia, gestational diabetes, or other common significant maternal complications of pregnancy were observed.

**Delivery**

The average gestational age at delivery among the 10 pregnancies was 36 weeks (range:29-40 weeks, SD: 3.5 weeks). 5 out of 10 pregnancies (50%) resulted in term deliveries. 5 out of 10 pregnancies (50%) resulted in preterm labor, with an average gestational age among preterm deliveries of 33 weeks (range: 29-36 weeks, SD: 2.2 weeks). Of these, 4 out of 5 underwent spontaneous preterm labor, while 1 out of 5 underwent preterm operative delivery for a complication (bleeding placenta previa).
8 pregnancies (80%) were converted to Cesarean section after a trial of labor for a variety of reasons including non-reassuring fetal status and failure to progress. Every Cesarean section resulted in the birth of a living infant. No significant complications during surgery were apparent.

3 pregnancies (30%) involved maternal complications at the time of delivery – 1 bleeding placenta previa requiring emergent Cesarean section, 1 post-partum hemorrhage, and 1 case of chorioamnionitis. These events were all resolved without long-term morbidity (see Figure 2B.)

Postpartum

Out of 10 livebirths, 6 infants (60%) required care in the NICU for respiratory difficulties or prematurity with length-of-stay ranging from 3 days to 3 months. 1 infant died in the NICU at 5 weeks of age; the remaining infants were able to be discharged from the hospital. 7 infants out of 11 (64%), including the intrauterine fetal demise, received the diagnosis of Noonan syndrome after genetic testing; 3 were not felt to have Noonan syndrome and the 1 infant who had intrauterine fetal demise had highly suspicious findings for Noonan syndrome but was not formally tested. 5 out of the 6 infants who received NICU care had a diagnosis of Noonan’s syndrome (83%).
Table 2. Pregnancy Outcomes

<table>
<thead>
<tr>
<th>Subject #</th>
<th>Pregnancy complications</th>
<th>Gestational Age (weeks)</th>
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<th>Noonan syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>intrauterine fetal demise</td>
<td>36</td>
<td>NSVD</td>
<td>n/a</td>
<td>unknown</td>
</tr>
<tr>
<td>2</td>
<td>dichorionic-diamnionic twin gestation</td>
<td>33</td>
<td>Emergent CS for bleeding placenta previa</td>
<td>yes/yes</td>
<td>yes/no</td>
</tr>
<tr>
<td>3</td>
<td>anti-K isoimmunization</td>
<td>37</td>
<td>CS for breech presentation following trial of labor, chorioamnionitis</td>
<td>no</td>
<td>yes</td>
</tr>
<tr>
<td>2</td>
<td>gestational hypertension</td>
<td>39</td>
<td>CS for failure to progress in 2nd stage, meconium-stained fluid</td>
<td>yes</td>
<td>yes</td>
</tr>
<tr>
<td>3</td>
<td>none</td>
<td>29</td>
<td>CS after PPROM</td>
<td>yes</td>
<td>yes</td>
</tr>
<tr>
<td>2</td>
<td>none</td>
<td>33</td>
<td>CS after PPROM, non-reassuring FHR, Post-partum hemorrhage</td>
<td>yes</td>
<td>yes</td>
</tr>
<tr>
<td>3</td>
<td>pre-gestational diabetes, polyhydramnios</td>
<td>32</td>
<td>CS after PPROM</td>
<td>yes</td>
<td>yes</td>
</tr>
<tr>
<td>4</td>
<td>none</td>
<td>39</td>
<td>NSVD</td>
<td>no</td>
<td>no</td>
</tr>
<tr>
<td>2</td>
<td>fetal cystic hygroma</td>
<td>40</td>
<td>CS after arrest of dilation (eIOL)</td>
<td>no</td>
<td>unknown</td>
</tr>
<tr>
<td>5</td>
<td>none</td>
<td>term</td>
<td>CS after failure to progress</td>
<td>no</td>
<td>yes</td>
</tr>
</tbody>
</table>

* NSVD = normal spontaneous vaginal delivery, CS = Cesarean section, PPROM = preterm premature rupture of membranes, eIOL = elective induction of labor, NICU = neonatal intensive care unit
Figure 2. Pregnancy Complications

A

Rate of Complications

<table>
<thead>
<tr>
<th>Category of Complication</th>
<th>Percentage of pregnancies affected</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prenatal</td>
<td>100</td>
</tr>
<tr>
<td>Delivery</td>
<td>80</td>
</tr>
<tr>
<td>Postpartum</td>
<td>60</td>
</tr>
<tr>
<td>Fetal Noonan syndrome</td>
<td>40</td>
</tr>
</tbody>
</table>

B

Delivery Complications

<table>
<thead>
<tr>
<th>Category of Complication</th>
<th>Percent of pregnancies affected</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preterm labor</td>
<td>90</td>
</tr>
<tr>
<td>PPROM</td>
<td>70</td>
</tr>
<tr>
<td>Conversion to Cesarean section</td>
<td>50</td>
</tr>
<tr>
<td>Maternal event</td>
<td>30</td>
</tr>
</tbody>
</table>
DISCUSSION

The study of rare diseases in general is often extremely challenging because of barriers to subject recruitment and adequate funding [44]. However, findings or even mere description of these rare diseases can provide valuable guidance for future clinicians who may have little experience with a specific rare disease, such as Noonan syndrome, in a high-stakes situation, such as pregnancy. Our study sought to examine the course of pregnancy and delivery in women with Noonan syndrome in order to determine the risk of complications depending on maternal cardiac health. We were able to identify a small population of eligible subjects and demonstrated that successful pregnancy and delivery were possible for the majority of patients.

One of the accomplishments of this study was the identification and description of a group of subjects with Noonan syndrome who were able to successfully and safely become pregnant and deliver. As noted in the introduction, only a small number of case reports have previously described successful pregnancy in Noonan syndrome, and the majority of those have focused on specific elements of care, such as complicated administration of anesthesia [23-30]. Our population is the largest group of these patients described in a single study. With regards to maternal health, there were no life-threatening events or complications during the prenatal period. A number of maternal delivery complications occurred, such as bleeding placenta previa and postpartum hemorrhage; however, the rates were not noticeably higher than in the greater population and these patients did not suffer any long-term morbidity. Noticeably, there was a complete lack of concerning cardiac events, despite the presence of congenital heart disease in the majority of our sample. In this small sample, having cardiac disease related
to Noonan syndrome was not associated with maternal health and safety during the pregnancy and delivery course.

The rates of pregnancy and delivery complications in our study population were significant, particularly the rates of prematurity, preterm premature rupture of membranes, conversion to Cesarean section, and need for care in the neonatal intensive care unit. While the factors contributing to these events are complex and multiple, it is possible that these high rates may be linked to the underlying Noonan syndrome diagnosis. The high rates of abnormal findings on intrapartum fetal testing, in some cases leading to operative delivery by Cesarean section, bring into question the health of the placenta in maternal-fetal Noonan syndrome. Because many of the infants delivered in this study were affected by Noonan syndrome, the baseline function of the placenta (whose genetics are derived from the fetus) may have been compromised. Given the known deleterious cardiovascular manifestations of Noonan syndrome, it is worth questioning whether fetal Noonan syndrome could lead to reduced ability of the placenta to facilitate diffusion of oxygen and nutrients to the fetus, particularly during the stress of delivery [45]. While the effects of Noonan syndrome have been studied and described in a wide variety of organ systems, little information exists on placental health, a possible area of further exploration. The potential for uteroplacental insufficiency in the context of underlying maternal cardiovascular disease could also contribute to fetal distress and premature labor. Several subjects had mild pulmonary stenosis on echocardiogram. However, our data do not support that those with measurable cardiac disease were more likely to experience complications during pregnancy as compared to those subjects who had minimal or no cardiac history. That being said, because these echocardiograms were
not performed during pregnancy, we cannot exclude the possibility that any individual subject’s cardiac function may have worsened under the strenuous circumstances created during pregnancy.

The rate of preterm birth prompted by preterm premature rupture of membranes (PPROM) was unusually high in our population, with 4 total pregnancies resulting in PPROM. Three of these were observed in a single subject, while the fourth was prompted by a case of intrauterine fetal demise, making it difficult to generalize this observation to the Noonan syndrome population. However, this high rate does raise the possibility of the influence of unknown factors related to Noonan syndrome, in addition to cardiac and lymphatic abnormalities, that could be contributing to this event. A variety of risk factors have been described as contributing to the likelihood of PPROM, such as infection, behavioral factors (e.g., tobacco use), obstetric complications, and genetic predisposition [46]. These may affect several pathophysiological pathways that may lead to PPROM, including oxidative stress, excessive collagenolysis, and apoptosis of fetal membranes. While oxidative stress and buildup reactive oxidative species may be a signal for initiation of labor in normal pregnancy, PPROM in Noonan syndrome could be an indicator of unusually high oxidative stress. A link between Noonan syndrome and collagen dysfunction has not been previously described, although some of the phenotypical manifestations of Noonan syndrome occur in collagen-rich environments, such as spinal deformity, synovitis, and disordered lymphangiogenesis, a process which relies heavily on the extracellular matrix [47]. While these connections are merely speculative at this time, further study may provide insight both into the pathophysiology of Noonan syndrome as well as pathophysiological factors influencing PPROM.
While we cannot directly conclude that worse cardiac function contributed to pregnancy complications, our study does reinforce the importance for patients with high risk of cardiac disease to seek multidisciplinary preconception counseling. In fact, one of the patients in our study (patient 2) presented pre-pregnancy for a cardiac evaluation and at the time was found to have severe pulmonary insufficiency and significant right ventricular dilation. She was advised and ultimately went for surgical pulmonary valve replacement with appropriate recovery and right ventricular remodeling prior to her pregnancy, which likely resulted in less hemodynamic burden and a better tolerated pregnancy. This recommendation for pre-conception evaluation is relevant to all women with Noonan syndrome who wish to become pregnant, particularly if there has been a prior cardiac history or procedure. Our study population may be selectively biased towards those patients who had been deemed healthy enough to attempt pregnancy based on consultation with cardiologists and obstetricians. Several subjects had also undergone substantial interventional procedures either in childhood or later in life that attempted to correct previously severe cardiac disease. We can expect that, left uncorrected, severe cardiac disease would leave patients more vulnerable to complications for the patient and the fetus. While current recommendations for adults with Noonan syndrome suggest regular cardiac monitoring, the frequency of such monitoring might reasonably be increased in the event that a patient wishes to become pregnant.

We observed in our study population that members of the same family demonstrated significantly different phenotypes despite carrying the same gene mutation. While not surprising, given our knowledge of Noonan syndrome, we still found the phenotypic heterogeneity to be striking. For example, several mothers with little to mild
history of cardiac disease gave birth to infants with significant cardiac disease requiring early intervention. Similarly, the medical course of siblings with Noonan syndrome was rarely identical, with some displaying very mild disease and others having Noonan phenotypes leading to severe and life-threatening neonatal courses. These cases serve as a reminder of the complexity of inheritance and gene expression, even for a single-gene autosomal dominant condition. Clinically, affected mothers should be counseled and monitored closely for every pregnancy, regardless of her own phenotype or the presence of a previous successful pregnancy. They should be advised explicitly on the meaning of an autosomal dominant pattern of inheritance, and their attitudes regarding heritability of a phenotypically diverse syndrome should be explored in depth.

The greatest limitation of our study is the small sample size. While we understood going into this project that studying a specific subset of a rare disease would make it difficult to identify a large number of subjects, the eventual number of subjects included still did not match our expectations of 10-20 subjects based on anecdotal clinical experience. Some potential subjects could not be included because of a lack of genetic testing, even if there was strong suspicion that the person likely had Noonan syndrome; however, due to the already low number of subjects we elected not to include these subjects in order to avoid diluting any possible conclusions that we might draw. Our analysis was also restricted to electronic medical records due to their ease of access and searchability; however, it is possible that more subjects could be located from records before the widespread use of electronic medical records. The rarity of suitable study candidates also made it difficult to identify a suitable control group. Ideally, we would be able to stratify patients based on the extent of their cardiac disease in order to make
meaningful comparisons between groups. In future studies, it would be beneficial to expand our population to multiple centers in order to capture a larger study population. While we did consider this approach for the current study, it unfortunately was not immediately possible for logistical and administrative reasons.

One effect of our small sample size is that it is more difficult to control for major factors influencing pregnancy outcomes. For example, one of the pregnancies included in our study was a twin gestation. Twin gestations are already known to carry higher risk for certain pregnancy complications, particularly premature labor and PPROM, and thus it is more difficult to attribute the events of this pregnancy to Noonan syndrome specifically. As another example, several occurrences of PPROM in our population were attributed to a single subject, making it difficult to determine whether these events are attributable to Noonan syndrome, another genetic factor, or an environmental factor. Ideally, in a larger study, adequate power would enable us to draw more specific conclusions.

Another limitation of our study is its retrospective nature. While we were able to obtain relevant obstetrical, cardiac, and medical data from reviewing patient charts, this information is not always complete or as detailed as we may hope. For example, although we were able to generate quantitative data by directly analyzing patient echocardiograms, it would have been beneficial to have had additional images from just prior to and throughout pregnancy as well. Unfortunately, a prospective study capturing many time points and studies beyond the standard-of-care may be costly and time consuming, especially considering the difficulty of identifying eligible subjects.

We have succeeded in identifying and describing a small sample of rare patients with significant health needs. We found that, in our sample, women with Noonan
syndrome were able to become pregnant and deliver infants, albeit not without complications among mothers and infants. We hope that this study may contribute to guidance for future patients and clinicians, as well as act as a foundation for future study of this condition.
REFERENCES


