Down syndrome (DS), caused by a trisomy 21, is the most common chromosomal aneuploidy occurring in approximately 1 of 750 live births. Individuals with DS exhibit craniofacial dysmorphology, cardiac defects, gastrointestinal problems, and cognitive impairment, although these phenotypes vary in incidence and severity. Common cardiac defects are usually recognized in young infants with DS and include atrial septal anomalies, ventricular septal abnormalities, atrioventricular canal defects, and patent ductus arteriosus. Additional abnormalities may also affect infants with DS, but not be identified until later in life. Since multiple phenotypes are found in these individuals, we hypothesize that children with a severe congenital heart defect may be at increased risk for additional medical issues. To investigate this hypothesis, we performed a retrospective chart review of 170 infants with DS between birth and 6 months of age who were referred to the Down Syndrome Program at Riley Hospital for Children from August 2005 to July 2010. We analyzed comorbidity in infants with upper airway obstruction (UAO) or a feeding problem with and without a severe congenital heart defect. Our data show that 33% of infants without a cardiac defect have identified UAO while 44% with a severe cardiac defect have identified UAO. Additionally, 59% of infants without a cardiac defect compared to 49% with a severe cardiac defect have a feeding problem. With the knowledge of these comorbid clinical features in DS, healthcare providers may be able to identify potential complications affecting infants with DS earlier in life.