OBSTETRICS

Prenatal vs postnatal diagnosis of 22q11.2 deletion syndrome: cardiac and noncardiac outcomes through 1 year of age

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BACKGROUND: The 22q11.2 deletion syndrome is the most common microdeletion syndrome and is frequently associated with congenital heart disease. Prenatal diagnosis of 22q11.2 deletion syndrome is increasingly offered. It is unknown whether there is a clinical benefit to prenatal detection as compared with postnatal diagnosis.

OBJECTIVE: This study aimed to determine differences in perinatal and infant outcomes between patients with prenatal and postnatal diagnosis of 22q11.2 deletion syndrome.

STUDY DESIGN: This was a retrospective cohort study across multiple international centers (30 sites, 4 continents) from 2006 to 2019. Participants were fetuses, neonates, or infants with a genetic diagnosis of 22q11.2 deletion syndrome by 1 year of age with or without congenital heart disease; those with prenatal diagnosis or suspicion (suggestive ultrasound findings and/or high-risk cell-free fetal DNA screen for 22q11.2 deletion syndrome with postnatal confirmation) were compared with those with postnatal diagnosis. Perinatal management, cardiac and noncardiac morbidity, and mortality by 1 year were assessed. Outcomes were adjusted for presence of critical congenital heart disease, gestational age at birth, and site.

RESULTS: A total of 625 fetuses, neonates, or infants with 22q11.2 deletion syndrome (53.4% male) were included: 259 fetuses were prenatally diagnosed (156 [60.2%] were live-born) and 122 neonates were prenatally suspected with postnatal confirmation, whereas 244 infants were postnatally diagnosed. In the live-born cohort (n=522), 1-year mortality was 5.9%, which did not differ between groups but differed by the presence of critical congenital heart disease (hazard ratio, 4.18; 95% confidence interval, 1.56–11.18; $P<.001$) and gestational age at birth (hazard ratio, 0.78 per week; 95% confidence interval, 0.69–0.89; $P<.001$). Adjusting for critical congenital heart disease and gestational age at birth, the prenatal cohort was less likely to deliver at a local community hospital (5.1% vs 38.2%; odds ratio, 0.11; 95% confidence interval, 0.06–0.23; $P<.001$), experience neonatal cardiac decompensation (1.3% vs 5.0%; odds ratio, 0.11; 95% confidence interval, 0.03–0.49; $P=.004$), or have failure to thrive by 1 year (43.4% vs 50.3%; odds ratio, 0.58; 95% confidence interval, 0.36–0.91; $P=.019$).

CONCLUSION: Prenatal detection of 22q11.2 deletion syndrome was associated with improved delivery management and less cardiac and noncardiac morbidity, but not mortality, compared with postnatal detection.

Key words: 22q11.2 deletion syndrome, congenital heart disease, genetic syndrome, infant morbidity, infant mortality, perinatal outcome, prenatal diagnosis

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Introduction

Chromosome 22q11.2 deletion syndrome (22qDS), also known as DiGeorge, velocardiofacial, and conotruncal anomaly face syndrome, has an estimated prevalence of 1 per 2148 live births.[1] The prevalence has been estimated to be as high as 1 per 1000 to 1500 in prenatal series.[2,3] The condition has a highly variable phenotype, but most affected individuals identified early in life have cardiac or aortic arch anomalies.[4] Typical indications for prenatal testing for 22qDS have included the ultrasound detection of conotruncal congenital heart disease (CHD) or a noncardiac anomaly, such as cleft lip or palate,[5] or family history. The evolving availability of targeted cell-free fetal DNA (cfDNA) screening for 22qDS[6,7] has begun to alter the landscape of prenatal screening and detection, but it is not yet recommended

AJOG at a Glance

Why was this study conducted?

Prenatal testing is increasingly offered for 22q11.2 deletion syndrome, the most common microdeletion syndrome, which is frequently associated with congenital heart disease. It is unknown whether there is a clinical benefit to prenatal detection as compared with postnatal diagnosis.

Key findings

In this international retrospective study, the presence of critical congenital heart disease, not time of diagnosis, affected 1-year mortality. In adjusted analyses, prenatally diagnosed patients were less likely to deliver at a local community hospital, experience neonatal cardiac decompensation, or have failure to thrive by 1 year of age.

What does this add to what is known?

Prenatal detection of 22q11.2 deletion syndrome led to improved delivery management and less neonatal and infant cardiac and noncardiac morbidity, but not mortality.

by professional societies.[8] In the absence of prenatal diagnosis or suspicion, postnatal testing may be prompted by dysmorphic features, organ system anomalies, or newborn screening for severe combined immunodeficiency (SCID). Other clues, such as difficulty feeding, failure to thrive, or developmental delay, are non-specific and may not lead to early diagnosis.

Neonates and infants with 22qDS often require comprehensive, multidisciplinary care.[9] Neonates with critical CHD require cardiac intervention shortly after birth, which necessitates careful delivery planning and perinatal care at a tertiary care center to manage transitional physiology and prevent hemodynamic decompensation. Complications from cardiac surgery may be higher in patients with 22qDS, leading to increased length of hospital stay.[10,11] Noncardiac morbidities, such as hypocalcemia, immunodeficiency, and thrombocytopenia are important to recognize and treat as early as possible. Neonatal hypocalcemia, in particular, may influence later neurodevelopmental outcome.[12,13] Additional important issues may arise throughout the first year of life, including feeding challenges, which may be associated with an underlying palatal disorder, and developmental delay.[4,9]

Prenatal detection of 22qDS may allow for more comprehensive perinatal management with delivery at a tertiary care center and improved neonatal and infant outcomes. However, the potential benefit of prenatal detection of 22qDS, as compared with postnatal diagnosis, has not yet been studied. Using a collaborative approach across multiple institutions, differences in management and cardiac and noncardiac outcomes were explored between contemporaneous cohorts of pre- and postnatally diagnosed patients through 1 year of age.

Materials and Methods

An international multicenter, retrospective study across 30 sites on 4 continents was performed from 2006 to 2019. The cohort was predominantly drawn from sites in the National Perinatal Research Consortium and/or the International 22q11.2DS Modifier Gene Consortium. The consortia were used as a means to identify sites that provide care for patients with 22qDS, regardless of outcome. Data collection was specific to the current study. Each site obtained local ethics board approval with a waiver of informed consent.

All fetuses, neonates, and infants were required to have genetic test confirmation of a 22q11.2 deletion using standard methods, including fluorescence in situ hybridization (FISH), quantitative polymerase chain reaction (qPCR), multiplex ligation-dependent probe amplification (MLPA), or comparative genome hybridization or single-nucleotide polymorphism microarray. Cases with deletions extending beyond the "DiGeorge critical region" (outside of low copy repeat 22A-22D), more complex rearrangements, and those with 22q11.2 duplication were excluded. Prenatally diagnosed patients without known pregnancy outcome were also excluded. The prenatal cohort refers to fetuses in either of the following categories: (1) fetuses with confirmatory prenatal genetic testing through chorionic villus sampling, amniocentesis, fetal blood sampling, or autopsy (prenatal diagnosis); or (2) those with suspected 22qDS based on sonographic or echocardiographic findings consistent with 22qDS and/or high-risk cfDNA screen *and* for whom confirmatory prenatal genetic testing was declined because of parental preference (prenatal suspicion). The prenatally suspected patients were managed as if the diagnosis was present while awaiting postnatal testing; postnatal genetic test confirmation of a 22q11.2 deletion was required within the first week of life or before neonatal hospital discharge. The postnatal cohort refers to postnatally diagnosed patients who had no prenatal diagnosis or suspicion of 22qDS but had genetic test confirmation of the diagnosis by 1 year of age.

A standardized data extraction form was completed locally for each case and entered into a central REDCap (Research Electronic Data Capture; Vanderbilt University, Nashville, TN) database. Maternal, paternal, and fetal/child demographics were obtained. Indications for genetic testing, pre- and postnatal findings, management, and outcomes were collected.

If any type of CHD was identified prenatally or postnatally, it was categorized by a pediatric cardiologist (L.R.F.) as critical (defined as needing cardiac intervention at $\leq$30 days of age, ie, tetralogy of Fallot with pulmonary atresia, interrupted aortic arch with ventricular septal defect, truncus arteriosus) or

noncritical (cardiac intervention at >30 days of age, ie, tetralogy of Fallot with pulmonary stenosis, or other findings warranting surveillance by a cardiologist, ie, ventricular septal defect, right aortic arch with vascular ring). Prematurity was defined as <37 weeks of gestational age (GA), intrauterine growth restriction as estimated fetal weight <10th percentile by ultrasound, and small for GA as sex-based birthweight <10th percentile. The neonatal period was defined as ≤30 days or the period before neonatal hospital discharge, whichever was longer. A tertiary care center was defined as having an intensive care unit with pediatric subspecialists available. Delivery complication included the need for respiratory support or resuscitation in the delivery room. Cardiac decompensation was defined as cardiogenic shock requiring prostaglandin therapy or inotropic support, cardiac arrest, or extracorporeal membrane oxygenation in the preoperative period. Major infection or sepsis was defined as treatment with antibiotics ≥7 days or associated hemodynamic instability, respectively; seizure secondary to hypocalcemia was defined as clinical or electroencephalographic seizure with serum calcium <7 mg/dL (or equivalent). Failure to thrive was defined as weight/length below the fifth percentile, and developmental delay as any documented gross motor, fine motor, or speech delay.

Variables are presented as prevalence (percentage) or median (interquartile range [IQR]) due to nonnormative distributions, where appropriate. Baseline characteristics were assessed. The prenatally diagnosed or suspected patients did not have meaningful clinical differences (Supplemental Table 1); therefore, they were grouped together into the prenatal cohort. Outcomes were evaluated between the prenatal and postnatal cohorts using chi-square, Fisher exact, or Wilcoxon rank-sum test, as appropriate.

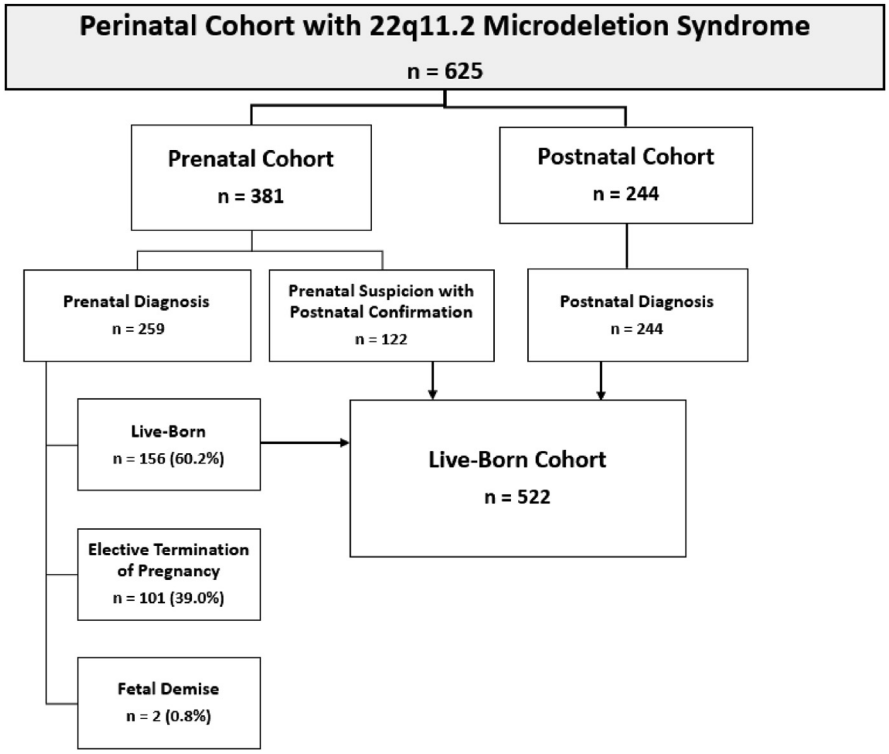
Analyses of time to mortality and time to major morbidity (cardiac decompensation, major infection/sepsis, or seizure) were performed with Cox proportional hazards models with adjustment for presence of critical CHD (vs no or noncritical CHD) as a time-dependent covariate (based on time of diagnosis), as well as GA at birth and site (US vs non-US). For all analyses, birth was time zero. In the mortality analysis, left truncation methods were used to account for the diagnosis of 22qDS after birth in the postnatally diagnosed group. In the morbidity analysis, because postnatally diagnosed patients could progress to an event before diagnosis, 22qDS time was treated as another time-dependent covariate. Patients with any missing data point were excluded from the models, and all patients were administratively censored at 1 year of age. Post hoc analyses were performed by site. Logistic regression modeling was also performed to examine discrete neonatal and infant outcomes, adjusting for the presence of critical CHD, GA at birth, and site. Hazard ratios (HRs) and odds ratios (ORs) with 95% confidence intervals (CIs) are reported. *P* values <.05 were considered statistically significant. Analyses were performed with R, version 4.0.0 (R Core Team, Vienna, Austria).

Results

In total, 625 fetuses, neonates, or infants with 22qDS were included. Of the 620 with known sex, 331 were male (53.4%). Figure 1 depicts the study population.

The prenatal cohort comprised 381 patients: 259 were prenatally diagnosed with 22qDS at a median GA of 21+2/7 (IQR, 20+0/7−24+4/7) weeks. There were 101 elective terminations of pregnancy (39.0%) at a median GA of 22+2/7 (IQR, 20+1/7−23+5/7) weeks and 2 fetal demises (0.8%) at 33+4/7 and 29+1/7 weeks. Both demises occurred in fetuses with CHD; one had additional noncardiac anomalies and intrauterine growth restriction. Therefore, 156 (60.2%) of prenatally

FIGURE 1
Flowchart of perinatal 22qDS study population



The present study focuses on the live-born cohort of 522 patients.

22qDS, 22q11.2 deletion syndrome.

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TABLE 1
Characteristics of live-born cohort by time of diagnosis of 22q11.2 deletion syndrome (n=522)

Characteristics	Prenatally diagnosed or suspected n=278[a]	Postnatally diagnosed n=244[a]	*P* value
Genetics			
22q11.2 deletion extent (by flanking LCR)			.68
A-D	145 (90.06)	155 (91.72)	
A-B	8 (4.97)	5 (2.96)	
A-C	3 (1.86)	5 (2.96)	
B-D	2 (1.24)	3 (1.78)	
C-D	3 (1.86)	1 (0.59)	
Initially detected by FISH targeted test[b]	123 (46.59)	102 (42.68)	.38
22q11.2 deletion inherited from an affected parent[c]	56 (26.05)	19 (13.67)	.005
Identification of a previously undiagnosed parent	24 (9.80)	7 (3.04)	.003
Maternal factors			
Median maternal age (y)	28 (24–33)	28 (24–33)	.86
Maternal education			.11
High school or less	43 (39.81)	30 (30.61)	
College/trade school or bachelor's degree	39 (36.11)	36 (36.73)	
Graduate degree	26 (24.07)	32 (32.65)	
Birth and delivery			
Vaginal delivery	159 (60.00)	141 (63.51)	.43
Gestational age at birth (wk)	38.7 (37.1–39.1)	38.7 (37.0–39.6)	.32
Preterm birth (<37 wk)	55 (20.15)	41 (17.67)	.48
Birthweight (g)	2840 (2580–3265)	2900 (2596–3250)	.48
Small for gestational age (birthweight <10th percentile)	34 (13.08)	33 (16.84)	.67
Apgar score <3 at 1 min	9 (4.05)	2 (1.70)	.34
Apgar score <5 at 5 min	2 (0.90)	1 (0.83)	1.00
Fetal features and postnatal management			
Male sex	146 (53.09)	133 (54.51)	.75
Any congenital heart disease	263 (92.65)	172 (70.49)	<.001
Critical congenital heart disease	177 (63.90)	77 (31.56)	<.001
Neonatal cardiac procedure	149 (55.60)	75 (36.94)	<.001
Median number of cardiac procedures	1 (0–2)	0 (0–1)	<.001
Neonatal noncardiac procedure	54 (22.04)	35 (18.72)	.40
Median number of noncardiac procedures	0 (0–1)	0 (0–1)	.23

Values are presented as prevalence (percentage) or median (interquartile range), as appropriate.

FISH, fluorescence in situ hybridization; *LCR*, low copy repeats.

[a] Maximum sample size (missing data for individual variables); [b] FISH targeted test detects standard A-D and proximal A-B, A-C (but not distal B-D, C-D) 22q11.2 deletions; [c] Excludes known affected parents before pregnancy.

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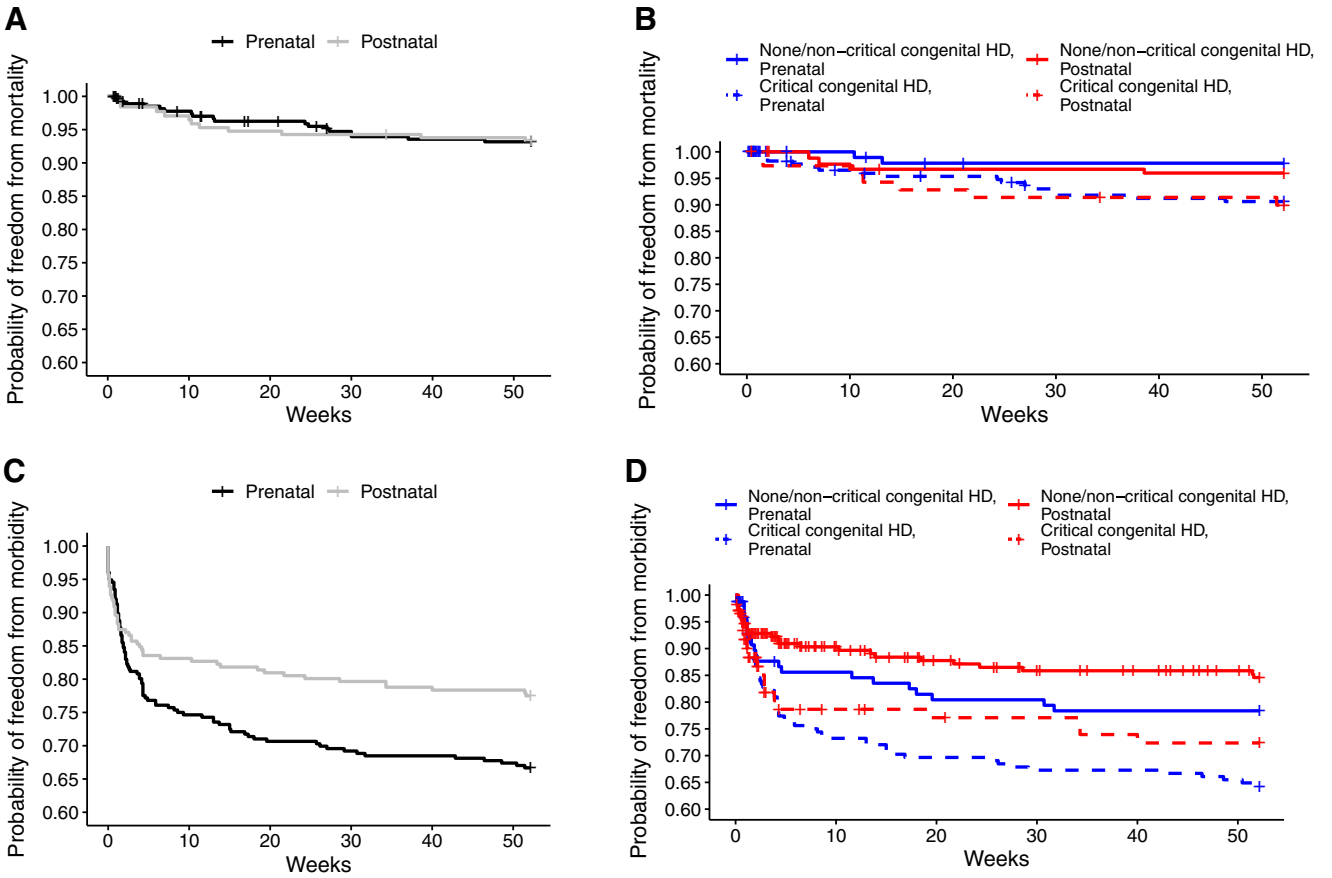
diagnosed pregnancies resulted in live birth. An additional 122 pregnancies had prenatal suspicion of 22qDS with postnatal confirmation at 8 (4–17) days of age. The postnatal cohort comprised 244 patients diagnosed at 28 (9–86) days of age. Thus, the total live-born cohort, which is the focus of the present study, consisted of 522 patients.

Table 1 compares the baseline characteristics of the live-born prenatal and

FIGURE 2
Cox proportional hazards models of freedom from mortality and morbidity



A, Freedom from mortality at 1 year of age in the 22qDS cohorts by time of diagnosis (prenatal vs postnatal); **B,** freedom from mortality by time of diagnosis and presence of critical CHD (vs no or noncritical CHD); **C,** freedom from major morbidity at 1 year of age by time of diagnosis; and **D,** freedom from major morbidity by time of diagnosis and presence of critical CHD. Major morbidity included cardiac decompensation, major infection/sepsis, or seizure. Analyses were adjusted for gestational age at birth and site.

22qDS, 22q11.2 deletion syndrome; *CHD*, congenital heart disease; *HD*, heart disease.

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postnatal cohorts. The most common indication for genetic testing in both cohorts was the detection of CHD. In the prenatal cohort, detection of a noncardiac anomaly (10.0%), most commonly absent or hypoplastic thymus or renal anomalies, also prompted genetic testing. A total of 37 patients (13.3%) had a high-risk cfDNA screening result for 22qDS at 26+3/7 (20+5/7−30+4/7) weeks, 5 of whom had no echocardiographic or sonographic findings or family history. Indications for postnatal testing for 22qDS beyond CHD included dysmorphic features (36.5%); noncardiac anomaly (14.5%), most commonly craniofacial/palatal; developmental delay (7.5%); abnormal newborn screen for SCID (4.6%); and/or failed pulse oximetry testing for CHD (4.2%).

By 1 year of age, 31 infants died, yielding all-cause mortality of 5.9%. The median age of death was 72 (29−181) days. All but 1 patient (96.8%) had CHD, and most (n=19; 61.3%) had critical CHD. Of the 20 patients with known cause of death, 14 (70.0%) died of cardiac causes, 5 (25.0%) of sepsis, and 1 of respiratory failure in the context of severe immunodeficiency.

There was no significant between-group difference in freedom from mortality at 1 year by time of diagnosis (Figure 2, A), but there was a significant difference based on the presence of critical CHD (HR, 4.18; 95% CI, 1.56−11.18; P=.004) (Figure 2, B; Table 2). There was also no significant between-group difference in freedom from major morbidity at 1 year by time of diagnosis (Figure 2, C), but there was a significant difference based on the presence of critical CHD (HR, 2.29; 95% CI, 1.52−3.45; P<.001) (Figure 2, D; Table 2). Advancing GA at birth was associated with less mortality (HR, 0.78 per advancing week in gestation; 95% CI, 0.69−0.89), and US site was

TABLE 2
Cox proportional hazards models for infant mortality and major morbidity among live births with 22q11.2 deletion syndrome

Infant mortality (n=488)[a]	Hazard ratio with 95% CI	*P* value
Postnatal diagnosis of 22qDS	1.28 (0.54–3.04)	.57
Critical congenital heart disease (time-dependent)	4.18 (1.56–11.18)	.004
Gestational age at birth (per advancing wk)	0.78 (0.69–0.89)	<.001
US site	0.39 (0.18–0.88)	.02
Major morbidity[b] (n=469)[a]	Hazard ratio with 95% CI	*P* value
Postnatal diagnosis of 22qDS	0.69 (0.41–1.18)	.18
22qDS diagnosis (time-dependent)	0.90 (0.47–1.75)	.76
Critical congenital heart disease (time-dependent)	2.29 (1.52–3.45)	<.001
Gestational age at birth (per advancing wk)	0.95 (0.89–1.03)	.21
US site	0.45 (0.31–0.65)	<.001

Supplemental Table 2 includes additional analyses.

22qDS, 22q11.2 deletion syndrome; *CI*, confidence interval; *US*, United States.

[a] Only patients with data available for all covariates were included in the model (sample sizes are less than n=522 because of missing data on type and/or timing of congenital heart disease diagnosis and gestational age at birth); [b] Cardiac decompensation, major infection/sepsis, or seizures.

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associated with less mortality (HR, 0.39; 95% CI, 0.18–0.88) and less morbidity (HR, 0.45; 95% CI, 0.31–0.65). Among US sites, mortality, but not morbidity, was attenuated for patients with critical CHD (Supplemental Table 2).

Perinatal and infant outcomes, adjusted for the presence of critical CHD, GA at birth, and site are depicted in Table 3 and Figure 3. The prenatal cohort patients were significantly less likely to deliver at a local community hospital (OR, 0.11; 95% CI, 0.06–0.23; *P*<.001). They were also less likely to experience cardiac decompensation in the neonatal period (OR, 0.11; 95% CI, 0.03–0.49; *P*=.004). Stated differently, the prenatal cohort patients were over 9 times more likely to deliver at a tertiary care center or higher level of care (OR, 9.09; 95% CI, 4.35–16.67) and over 9 times less likely to experience neonatal cardiac decompensation (OR, 9.09; 95% CI, 2.04–33.33). Patients in the prenatal cohort were also less likely to have a delivery complication (OR, 0.56; 95% CI, 0.33–0.95; *P*=.03) and to have mechanical ventilation unrelated to a cardiac procedure (OR, 0.48; 95% CI, 0.24–0.95; *P*=.04). Half of the prenatally detected patients (139/278) were documented to have a change in their delivery plan to a higher level of care, and 49 (17.6%) were scheduled for induction of labor or cesarean delivery.

By 1 year of age, patients in the prenatal cohort were less likely to have failure to thrive (OR, 0.58; 95% CI, 0.36–0.91; *P*=.02). There were no significant between-group differences for other major neonatal events, length of hospitalization(s) ≥30 days through 1 year of age, or neonatal/infant death.

Comment

Principal findings

In the present study, prenatal vs postnatal diagnosis of 22qDS and perinatal and infant outcomes were assessed in a large cohort of live-born fetuses, neonates, and infants with confirmed deletion status. In both the prenatal and postnatal cohorts, the presence of critical CHD was the driver of both mortality and major morbidity by 1 year of age. Although there was no difference in survival based on time of diagnosis, prenatal detection yielded important benefits that may affect long-term outcomes of patients with 22qDS. Prenatal detection was associated with improved perinatal management with more deliveries at a tertiary care center, fewer delivery complications, and less cardiac decompensation and need for mechanical ventilation in the neonatal period. Notably, prenatal detection was also associated with less failure to thrive in infancy, which underscores the advantage of an earlier genetic diagnosis beyond the identification of CHD.

Results in the context of what is known

The impact of prenatal detection of 22qDS on perinatal and infant outcomes has not yet been explored and has important clinical and research implications.

Clinical implications

Prenatal diagnosis affords multiple potential benefits, including delivery planning for optimal perinatal management. In the setting of critical CHD, which was present in nearly half of the live-born 22qDS cohort, delivery closer to a cardiac surgical center is associated with decreased neonatal mortality.[14] Specialized delivery room planning for specific lesions can also optimize perinatal outcomes.[15] Neonatal cardiac decompensation, that is, cardiogenic shock requiring initiation of prostaglandin therapy, was less frequent in the prenatal cohort of this study. Improved hemodynamics in the neonatal period as a result of prenatal diagnosis may also result in less end-organ system dysfunction, including less preoperative brain injury[16] and better neurodevelopment[17] compared with postnatal diagnosis. In keeping with the finding that other neonatal risk factors, such as hypocalcemia and seizure activity, have been associated with intellectual disability in adults with 22qDS,[12] hemodynamic stability in the neonatal period may be an additional modifiable risk factor that influences the long-term

TABLE 3
Perinatal and infant outcomes for 22q11.2 deletion syndrome by time of diagnosis (n = 522)

Outcomes	Prenatally diagnosed or suspected n=278[a]	Postnatally diagnosed n=244[a]	Unadjusted *P* value	Multivariable analysis[b] Adjusted *P* value	Odds ratio	95% confidence interval
Delivery outcomes						
Delivery at local community hospital (nontertiary center)	13 (5.14)	58 (38.16)	<.001	<.001	0.11	(0.06–0.23)
Delivery complication	46 (18.47)	43 (24.43)	.14	.03	0.56	(0.33–0.95)
Neonatal outcomes						
Cardiac decompensation	3 (1.31)	7 (4.96)	.05	.004	0.11	(0.03–0.49)
Mechanical ventilation unrelated to cardiac procedure	41 (17.52)	23 (16.55)	.81	.04	0.48	(0.24–0.95)
Major infection or sepsis	45 (17.93)	22 (12.43)	.12	.78	0.92	(0.50–1.69)
Kidney failure	5 (2.01)	2 (1.09)	.70	.45	1.97	(0.34–11.26)
Hypocalcemia	117 (45.53)	71 (37.77)	.10	.58	0.89	(0.58–1.36)
Seizure	19 (7.63)	15 (8.02)	.88	.41	0.72	(0.34–1.56)
Stroke	7 (2.79)	0 (0)	.04	.11	6.80	(0.70–919.73)
Infant outcomes						
Live vaccines not withheld for immunodeficiency concerns	115 (59.28)	114 (72.15)	.01	.36	0.79	(0.48–1.31)
Failure to thrive	88 (43.35)	92 (50.27)	.17	.02	0.58	(0.36–0.91)
Developmental delay	143 (84.12)	134 (85.35)	.76	.09	0.55	(0.28–1.10)
Length of hospitalization(s) ≥30 d	151 (54.32)	104 (42.62)	.01	.74	0.93	(0.62–1.41)
Death	19 (7.22)	12 (5.02)	.31	.77	0.88	(0.38–2.04)

Values are presented as prevalence (percentage).

[a] Maximum sample sizes per 22q11.2 deletion syndrome subgroup; some patients had missing data; [b] Multivariable analysis was adjusted for presence of critical congenital heart disease, gestational age at birth, and site. Figure 3 depicts a forest plot of selected variables.

Freud. Perinatal outcomes of 22q11.2 deletion syndrome. Am J Obstet Gynecol 2024.

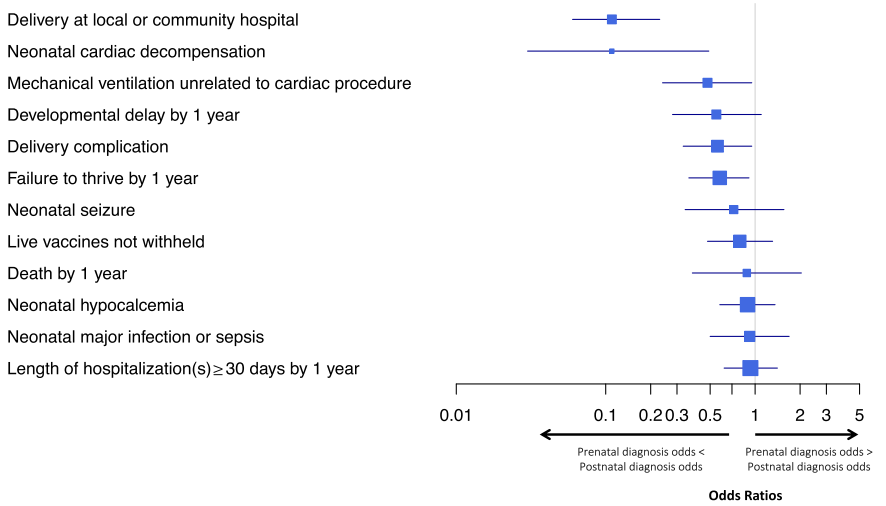
neurocognitive profile of patients with 22qDS.

Beyond the perinatal period, the prenatal cohort with 22qDS had less failure to thrive by 1 year of age in analyses adjusted for critical CHD and GA at birth. This finding may be related to a shortened diagnostic odyssey with earlier genetic diagnosis,[18] and thus the potential for more comprehensive, multidisciplinary care in infancy. For example, more timely diagnosis of palatal abnormalities and attention to feeding difficulties and nutritional status with earlier referral for surgery, feeding therapy, and dietitian support[9] may have mitigated poor growth by 1 year.

The all-cause mortality rate in the cohort by 1 year of age was 5.9%, which is slightly higher than previously reported in a large single-center cohort of patients with 22qDS (4%).[19] There were no significant differences in mortality or major morbidity by 1 year of age between the prenatal and postnatal cohorts. Rather, the presence of critical CHD played a significant role. This phenomenon has been well-described in the context of increasing complexity of cardiac surgery,[20] and our findings demonstrate that these important effects persist in the 22qDS population. The difference between US and non-US sites, which was not driven by any particular center, may be related to distinct models of care, infrastructure and availability of resources, case-mix and center-volumes, or other factors that are worthy of future multinational investigation.

Of note, despite prenatal diagnosis or suspicion being associated with more critical CHD, which would be expected to be associated with worse outcomes, there were no significant differences in mortality, major morbidity, or length of hospital stay in comparison with the postnatally diagnosed cohort. Perhaps the mortality and morbidities associated with critical CHD in the prenatal group were "offset" by enhanced perinatal planning and multidisciplinary care provided at tertiary care centers to patients known to have 22qDS. For example, there may have been greater attention paid to delivery planning, hemodynamic monitoring, airway management without the need for mechanical ventilation, perioperative calcium handling,[21] or infection

FIGURE 3
Forest plot of outcomes by time of 22qDS diagnosis



Odds ratios (ORs) were adjusted for presence of critical congenital heart disease, gestational age at birth, and site; all analyzed outcomes are shown in Table 2. The vertical gray line represents OR=1. The horizontal blue lines represent the confidence intervals (CIs); box size is inversely proportional to CI, that is, larger box denotes narrower CI. To the left of the gray line, prenatal diagnosis was associated with less likelihood of the outcome (protective) compared with postnatal diagnosis.

22qDS, 22q11.2 deletion syndrome.

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precautions. This is speculative but raises important questions about the potential effect of earlier genetic diagnosis of 22qDS on both cardiac and noncardiac outcomes, which merits prospective evaluation.

There are additional potential benefits of prenatal detection of 22qDS beyond the clinical outcomes investigated in the present study. This series demonstrates that there is substantial morbidity among infants with 22qDS: approximately half had failure to thrive and nearly 85% had documented delayed development by 1 year of age. These findings are helpful for counseling of expecting parents to allow for decision-making, optimal pregnancy management, and preparation for their journey. Health care for children with 22qDS has been demonstrated to be costly.[22,23] Analyses comparing cohorts of prenatally vs postnatally ascertained patients, including costs incurred by emergency transportation for neonatal cardiac decompensation due to critical CHD, diagnostic odysseys, and other morbidities, have not been conducted. Finally, the long-term association of timing of diagnosis and outcome, particularly from a neurocognitive perspective, has not been studied.

Research implications

The present findings are salient in the context of increasing availability and improving sensitivity and specificity of cfDNA screening for the prenatal detection of 22qDS.[24–26] In the SMART (SNP-based Microdeletion and Aneuploidy RegisTry) study, sensitivity of cfDNA for 22qDS was 75.0% with positive predictive value (PPV) of 23.7%, which improved with an updated algorithm to sensitivity of 83.3% and PPV of 52.6%.[3] Although few patients in this retrospective cohort had cfDNA screening for 22qDS, screening may move to the first trimester in the future, which will require careful prospective evaluation. Furthermore, although our results highlight that prenatal detection of 22qDS may allow for enhanced counseling, planning, and early comprehensive care, it is critical that both the option of cfDNA screening and the screening results be delivered by an informed health care provider given the current screening test performance.

A high-risk cfDNA screen for 22qDS should prompt not only confirmation by genetic testing (prenatally or postnatally depending on parental preference), but also referral for a detailed obstetrical ultrasound and fetal echocardiogram to screen for CHD. It is noteworthy that, in the postnatal cohort, over two-thirds had CHD and nearly one-third had critical CHD. This finding underscores the fact that prenatal diagnosis of CHD by ultrasound screening remains suboptimal and that other markers of fetuses at risk for CHD are necessary, largely to ensure appropriate delivery location. Further investigations are necessary to explore the performance, clinical utility, and cost-effectiveness of cfDNA screening for 22qDS as the technology evolves in accordance with guidelines from professional societies.[27]

Strengths and limitations

The present study describes a large series of fetuses, neonates, and infants with 22qDS, and explores the clinical benefit of prenatal detection. To amass this cohort, it was necessary to include patients from different sites, countries, and continents that have distinct models of prenatal and postnatal care, infrastructure, and patient volumes. As a result, site differences inevitably arose, for which adjusted analyses were performed. The present study focuses mainly on the live-born cohort; subsequent studies will explore in greater detail all cases with prenatal diagnosis or suspicion of 22qDS and changes in prenatal management, regardless of pregnancy outcome. Because all patients were diagnosed prenatally or within the first year of life, there was high reliance on organ anomalies, mainly CHD, recognized as likely 22qDS[18] or a family history, which may have led to selection bias. Early miscarriages and elective terminations of pregnancy may not have been referred for further prenatal evaluation, and

postnatal deaths before arrival at a referral center were not captured. The latter cases would almost invariably have been due to critical CHD, and inclusion would have strengthened the observed association in the present study. Finally, it is important to acknowledge that development was ascertained by chart review and not by validated assessments. It will be critical to evaluate long-term neurodevelopmental, cognitive, and psychiatric profiles in a more rigorous manner as the cohort ages.

Conclusion

Prenatal detection of 22qDS was associated with improved delivery management and less cardiac and noncardiac morbidity, but not mortality, in comparison with postnatal detection. ■

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SUPPLEMENTAL TABLE 1

Characteristics of prenatally diagnosed or suspected groups by timing of confirmed 22q11.2 deletion syndrome diagnosis (n = 278)

Characteristics	Prenatally diagnosed n=156[a]	Prenatally suspected, postnatally confirmed n=122[a]
22q11.2 deletion extent (by flanking LCR)		
A-D	76 (84.44)	69 (95.83)
A-B	5 (5.56)	3 (4.17)
A-C	3 (3.33)	0 (0)
B-D	2 (2.22)	0 (0)
C-D	3 (3.33)	0 (0)
Maternal age (y)	29 (25–34)	28 (24–32)
Gestational age at birth (wk)	38.7 (37.0–39.1)	38.6 (37.3–39.1)
Birthweight (g)	2835 (2480–3290)	2845 (2619–3236)
Male sex	80 (51.95)	66 (54.54)
Any congenital heart disease	147 (94.23)	116 (95.08)
Critical congenital heart disease	95 (65.07)	82 (70.69)
Neonatal cardiac procedure	84 (56.76)	65 (54.17)
Median number of cardiac procedures	1 (0–2)	1 (1–1)
Neonatal noncardiac procedure	31 (23.31)	23 (20.54)
Median number of noncardiac procedures	0 (0–1)	0 (0–1)

Values are presented as prevalence (percentage) or median (interquartile range), as appropriate.

LCR, low copy repeats.

[a] Maximum sample size (missing data for individual variables).

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SUPPLEMENTAL TABLE 2

Cox proportional hazards models for infant mortality and major morbidity among live births with 22q11.2 deletion syndrome by US and non-US site

US site		
Infant mortality (n=276)[a]	**Hazard ratio with 95% CI**	***P* value**
Postnatal diagnosis of 22qDS	1.10 (0.30–4.03)	.89
Critical congenital heart disease (time-dependent)	0.94 (0.27–3.34	.93
Gestational age at birth (per advancing wk)	0.72 (0.59–0.88)	.001
Major morbidity[b] (n=275)[a]	**Hazard ratio with 95% CI**	***P* value**
Postnatal diagnosis of 22qDS	0.46 (0.20–1.03)	.06
22qDS diagnosis (time-dependent)	0.47 (0.15–1.51)	.21
Critical congenital heart disease (time-dependent)	2.17 (1.15–4.09)	<.001
Gestational age at birth (per advancing wk)	0.85 (0.30–0.63)	<.001
Non-US site		
Infant mortality (n=212)[a]	**Hazard ratio with 95% CI**	***P* value**
Postnatal diagnosis of 22qDS	1.52 (0.49–4.74)	.47
Critical congenital heart disease (time-dependent)	22.73 (2.83–182.65)	.003
Gestational age at birth (per advancing wk)	0.82 (0.68–0.98)	.031
Major morbidity[b] (n=194)[a]	**Hazard ratio with 95% CI**	***P* value**
Postnatal diagnosis of 22qDS	1.13 (0.55–2.35)	.74
22qDS diagnosis (time-dependent)	1.51 (0.65–3.51)	.33
Critical congenital heart disease (time-dependent)	2.56 (1.49–4.41)	<.001
Gestational age at birth (per advancing wk	1.05 (0.94–1.17)	.40

22qDS, 22q11.2 deletion syndrome; *CI*, confidence interval, *US*, United States.

[a] Only patients with data available for all covariates were included in the model (sample sizes are less than n=522 because of missing data on type and/or timing of congenital heart disease diagnosis and gestational age at birth as in Table 2); [b] Cardiac decompensation, major infection/sepsis, or seizures.

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