201 Fetal skeletal disorders: what is our overall diagnostic capability using phenotype and molecular laboratory tests currently available in clinical practice?

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OBJECTIVE: Recent advances in molecular technology and fetal ultrasound have improved the ability to identify the genetic etiology of fetal anomalies. This is particularly true for fetal skeletal disorders, visualized by prenatal ultrasound. We sought to determine our current diagnostic capability for diagnosing fetal skeletal disorders encountered at a tertiary referral center.

STUDY DESIGN: This is a retrospective cohort of singleton fetuses with sonographically detected skeletal disorders identified between December 1, 2014 and April 1, 2016. Cases with significant anomalies of other organ systems, isolated polydactyly and isolated clubfeet were excluded. The following were ascertained: fetal phenotype, genetic testing performed, pregnancy outcome and neonatal phenotype when available.

RESULTS: Of 3863 fetuses evaluated by prenatal ultrasonography over the study period, skeletal findings were ascertained in 88 (2.3%). 59 were excluded for multi-system manifestations, isolated clubfoot or polydactyly. A molecular genetic diagnosis was made in 8 (27.5%) of the remaining 29 cases (Table), including 1 case by whole exome sequencing (WES). A clinical diagnosis was made in 5 (17.2%) additional cases: methotrexate teratogenicity, Russell Silver, pseudoachrondroplasia, achondroplasia and hypophosphatasia (confirmatory testing is pending for the last 2 cases). No clinical or molecular diagnosis was reached for the remaining 16 (55.5%) subjects.

CONCLUSION: The availability of multiple diagnostic laboratory analyses including: karyotype, microarray, single gene mutation analysis, and multi-gene platforms yields a diagnosis rate of approximately 50% for fetal skeletal anomalies while furthering our clinical acumen in the recognition of phenotypic hallmarks of specific skeletal disorders. A substantial percentage of fetal skeletal disorders, however, remain undiagnosed from a clinical and molecular perspective. Clinical WES, in a variety of formats, is now available. The additive diagnostic performance of clinical WES in the prenatal arena is unclear. Prospective studies with more aggressive molecular evaluation which includes WES are needed to elucidate its role and additive benefit in the workup of fetal skeletal anomalies.

Fetal genotype/phenotype

Prenatal Skeletal Findings	Invasive procedure	Pregnancy Outcome	Postnatal Findings	Molecular results/diagnosis	Inheritance pattern
Cloverleaf skull, short long bones, echogentic intracardiac focus	Amnio	TAB/D&E	None	Array: Triple X, Trisomy 9/9p mosaicism	De novo, AD
Prominent coronal sutures, flattened profile, long philtrum, micrognathia, urinary tract dilation	Amnio	TAB/D&E	None	Array: Deletion 3p21.31-p14.3 (7.6 Mb)	De novo, AD
Brachycephaly, midline cleft lip and palate, abnormal sacral spine, right echogenic kidney	Amnio	TAB/IOL	Midline cleft lip and palate, posterior rotation of left ear, overriding 5th toe, protuberance of distal sacral spine	*MASP1* mutation 3MC syndrome	AR
Bilateral clubfeet, joint deformities, abduction of knees bilateral syndactyly of hands, hitchhiker thumbs, abnormal curvature of the spine (kyphosis/lordosis).	CVS	TAB/D&E	None	*CANT1* mutation, Dabuquios syndrome	AR
Bilateral clubfeet, non-immune hydrops	Amnio	Fetal demise D&E	None	*GUSB* mutation, MPS VII	AR
Bilateral clubfeet, micromelia, small chest, small stomach, polyhydramnios	Amnio	Neonatal demise	Narrow chest, protuberant abdomen, short long bones, metaphyseal cupping and splaying, hypoplasia of the pelvis and platyspondyly	*COL2A1* mutation	De novo, AD
Multiple fractures of the long bones consistent with OI type III	Declined	Neonatal demise	Multiple fractures of the long bones of the extremities which are short, broad and demineralized	*COL1A1* mutation OI type II/III	De novo, AD
Multiple joint contractures, arms and legs fixed in extended position, clenched hands with overlapping fingers, dorsiflexion of right foot, deviation of the great toe and 5th toe	Declined	Live born	Neonatal seizures	WES: *SCN8A* c.718A>G	De novo, AD

202 Down syndrome births in the United States: What are the trends?

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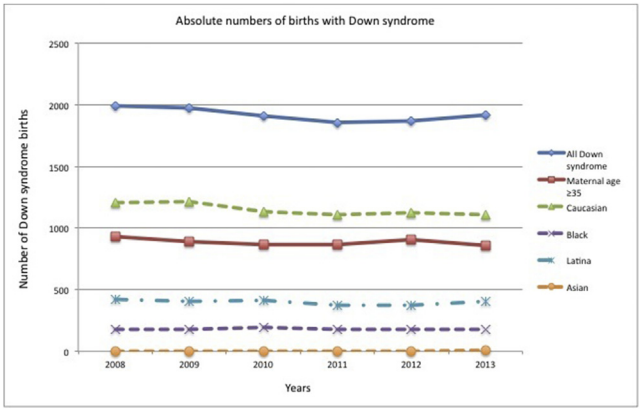
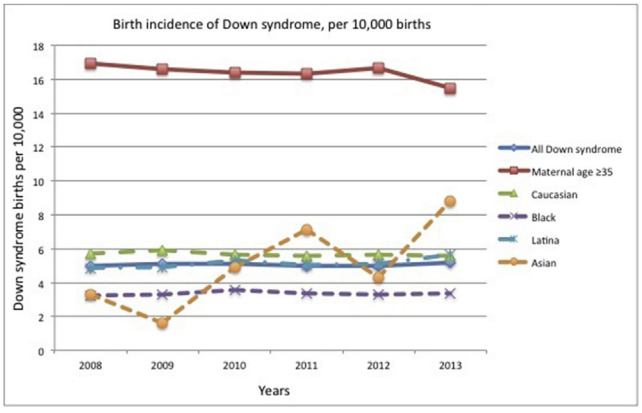
OBJECTIVE: To examine the birth incidence of Down syndrome in the United States at late preterm and term gestational ages, across time as well as by demographic subgroups.

STUDY DESIGN: Retrospective cohort study of singleton pregnancies in the United States from 2008 to 2013, using linked live birth and infant death cohort data from the National Center for Health Statistics (NCHS). Data sets for 2008 to 2010 and 2011 to 2013 were linked, and temporal trends in the birth incidence of Down syndrome were examined. Stratified analyses evaluated trends by maternal age and race/ethnicity subgroups. Down syndrome cases were confirmed by the NCHS through review of infants' karyotype results, and we identified cases via a unique coded variable. Analyses included all births whether the outcome was survival or death, and were limited to late preterm and term gestational ages ($\geq$34 through 42 weeks). The chi square test compared proportions.

RESULTS: A total of 22,805,529 births occurred during the study time period, 11,533 (0.05%) of which were infants with Down syndrome. The first image displays the absolute numbers of Down syndrome births per year, and the second displays the birth incidence of Down syndrome per 10,000 births. Over time, the birth incidence of Down syndrome decreased for the maternal age $\geq$35 years and increased for the Asian race/ethnicity subgroup, with several variations by ethnicity.

CONCLUSION: A decreasing birth incidence of Down syndrome was observed across time for maternal ages $\geq$35 years, and an increased incidence for the Asian race/ethnicity subgroup. Further research is indicated to investigate reasons for these trends, including the application of new prenatal genetic screening tests, as well as termination and stillbirth.





203 A contemporary amniotic fluid volume standard for the United States: the NICHD fetal growth studies-singletons

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OBJECTIVE: To develop a contemporary amniotic fluid volume (AFV) standard for the U.S. and assess racial/ethnic differences.

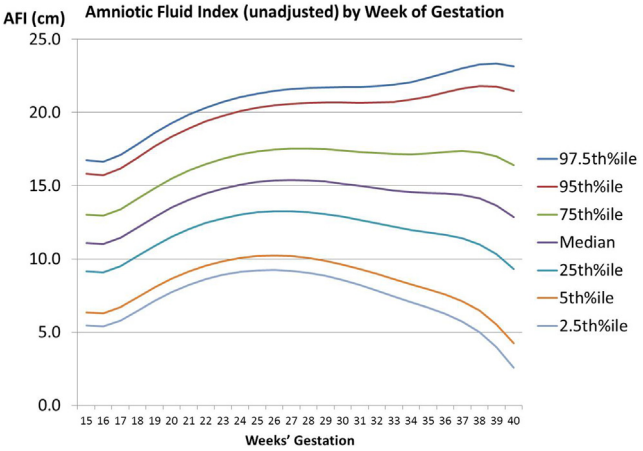
STUDY DESIGN: 1,719 low-risk gravidas of 4 self-reported racial/ethnic groups, carrying singletons, had serial (q 4 wk) sonograms at 12 U.S. sites, 2010-2013. Low-risk was defined: age 18-40 yr, BMI 19-29.9 kg/m^2, healthy lifestyle, normal obstetric history and uncomplicated pregnancy. Protocol trained, credentialed sonographers measured the 4-quadrant amniotic fluid index (AFI) at each scan, 15-40 wks' gestation (GA), as determined by a certain LMP, confirmed by first-trimester biometry. Women were randomly assigned to 1 of 4 sonography groups to ensure that each GA week was sampled. AFI trajectories were estimated using linear mixed models with cubic splines as fixed effects and cubic terms as random effects. AFI values were compared by race/ethnicity after adjusting for age, height, weight, parity, employment, marital status, insurance, income and education. We further adjusted for estimated fetal weight (EFW).

RESULTS: 480 non-Hispanic white (NHW), 418 non-Hispanic black (NHB), 485 Hispanics and 366 Asians underwent 7,177 scans. The population median AFI & percentiles are shown in the figure. Median AFI peaked at 27 wks (15.4 cm) falling to 12.9 cm by 40 wks. At 40 wks the population 2.5th %ile was 2.6 cm versus 97.5th %ile, 23.1 cm (table). Significant differences were observed among racial/ethnic groups from 18-21 and 26-40 wks ($p<0.001$): at 40 wks NHW had the largest and NHB the smallest median (delta=1.5cm; $p<0.001$). Racial/ethnic differences persisted after adjusting for EFW.

CONCLUSION: We present a contemporary AFV standard for the U.S. based on a large, low-risk multi-racial/ethnic population, evaluated serially by credentialed sonographers at 12 U.S. centers. Statistically significant racial/ethnic differences were observed. This information may help inform future clinical studies of amniotic fluid volume assessment and obstetric management.

Table. Population AFI values (unadjusted) by weeks' gestation

Gestational Age (weeks)													
AFI (cm)	16	18	20	22	24	26	28	30	32	34	36	38	40
Median	11.1	12.1	13.5	14.5	15.1	11.1	15.4	15.1	14.8	14.6	14.5	14.1	12.9
2.5th %ile	5.4	6.5	7.7	8.6	9.1	9.2	9.1	8.6	7.8	7.1	6.3	5.0	2.6
5th %ile	6.3	7.4	8.7	9.5	10.1	10.2	10.1	9.6	9.0	8.3	7.6	6.5	4.2
25th %ile	9.1	10.2	11.5	12.5	13.0	13.3	13.2	12.9	12.4	12.0	11.7	11.0	9.3
75th %ile	12.9	14.1	15.5	16.5	17.1	17.5	17.5	17.4	17.2	17.2	17.3	17.3	16.4
95th %ile	15.7	16.9	18.3	19.4	20.1	20.5	20.7	20.7	20.7	20.9	21.4	21.8	21.5
97.5th %ile	16.6	17.8	19.3	20.3	21.0	21.5	21.7	21.7	21.8	22.1	23.0	23.3	23.1



204 First trimester supratentorial and infratentorial abnormalities in fetuses with open spina bifida

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OBJECTIVE: To examine whether supratentorial, infratentorial, and calvarial manifestations of open spina bifida (OSB)occur in the first trimester.