

Expressive and Receptive Communication Development and Interventions in Prenatally Identified Children with Klinefelter Syndrome (XXY): 36 Month Analysis of the eXtraordinary Babies Study

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PURPOSE: Klinefelter Syndrome (47,XXY) is a common chromosomal condition defined by the presence of an additional X chromosome in males occurring in approximately 1 in 650 males. Features of Klinefelter syndrome typically include hypogonadism with primary testicular insufficiency, infertility, and tall stature. Infants and young children with Klinefelter syndrome may also have speech and language delays, motor delays, or learning difficulties. Advances in noninvasive prenatal screening (NIPS) have increased the identification of Klinefelter syndrome prenatally. The eXtraordinary Babies Study is a natural history study of prenatally-identified children with sex chromosome trisomies, including Klinefelter syndrome, aiming to characterize health and neurodevelopment from infancy and identify predictors of outcomes. This project aimed to: (1) Describe the utilization of early intervention speech therapy services in infants and toddlers with Klinefelter syndrome through 36 months of age, and (2) compare language development and outcomes of those with and without speech therapy.

METHODS: Infants with a prenatally identified diagnosis of Klinefelter syndrome were enrolled in the study prior to 12 months of age. Data collected at the 12, 24, and 36 month visits were analyzed for this project. Detailed demographic information, medical history and developmental history was collected at each visit, including data regarding speech therapy services. Speech and language development was directly assessed using the Bayley Scales of Infant and Toddler Development, Third Edition, specifically scaled scores and growth scale values (GSV) of receptive and expressive language domains. Interviews at each study visit recorded if speech therapy was being received (Yes or No). If Yes, then reason for initiation of therapy was coded as either proactive due to concerns of potential speech and language delays associated with Klinefelter syndrome, or reactive due to identified speech and language delays. Hollingshead 4 factor index was surveyed for socioeconomic status at enrollment. Descriptive statistics were used to describe the demographics of the cohort. Participants were categorized based on speech therapy (ST) experience as “never received,” or initial indications with “proactive” or “reactive.” Analysis utilizing t-Tests, chi square tests and ANOVA compared both the standard score (SS) and Growth Scale Value (GSV) scores between participant categories

RESULTS:

80 children with Klinefelter syndrome had completed a 36-month research visit.

Participants with Klinefelter syndrome and a 36m Completed Visit (n=80)			
	Received ST (n=49)	Never Received ST (n=31)	p
Race (%)			0.385
White	43 (87.76)	25 (80.65)	
Black	1 (2.04)	0	
Asian	0	1 (3.23)	
More Than One Race	5 (10.20)	5 (16.13)	
Ethnicity (%)			0.676
Not Hispanic or Latino	41 (83.67)	27 (87.10)	
Hispanic or Latino	8 (16.33)	4 (12.90)	
Hollingshead 4 factor index mean (SD)	53.5 (10.4)	52.8 (9.8)	0.278
Underrepresented (%) ¹	13 (26.53)	8 (25.80)	0.943

¹ Underrepresented includes non-white, Hispanic, and/or family income <\$50K USD/year

Utilizing the Hollingshead 4 factor index, participants in the proactive ST cohort had a mean score of 51.7, participants in the reactive ST cohort had a mean score of 58.8 and participants who did not receive ST had a mean score of 52.8, with no statistically significant difference between groups.

46 participants had direct assessment of receptive and expressive speech using the Bayley Scales of Infant and Toddler Development at 36 months of age (proactive n=15, reactive n=13, never received n=18). During the COVID-19 pandemic, study visits transitioned to telehealth, leaving only a subset of the sample with data from direct developmental assessment with the Bayley.

Bayley Scores for Participants with Klinefelter Syndrome at 36 month visit Stratified by Speech Therapy Intervention Category (n=46)				
	Proactive (n=15)	Reactive (n=13)	Never Received (n=18)	p Value
Receptive μ (SD)				
GSV	652.33 (18.11)	622.4 (72.08)	649.94 (14.90)	0.181
Scaled Score	10.75 (1.35)	9.20 (3.40)	9.83 (2.53)	0.362
Expressive μ (SD)				
GSV	650.75 (26.63)	602.70 (66.78)	643.11 (40.88)	0.052
Scaled score	10.08 (2.09)	7.40 (3.28)	9.38 (2.97)	0.098

39 participants had direct assessment of speech using the Bayley Scales of Infant and Toddler Development completed at both the 12-month and 36-month visits. 26 participants had direct

assessment of speech using the Bayley Scales of Infant and Toddler Development completed at all three time points, including 12-month, 24-months, and 36-month visits. Comparison of both SS and GSV scores between intervention groups (Proactive, Reactive, and Never Received) demonstrated significantly lower receptive (SS: $p=0.04$; GSV: $p=0.03$) and expressive (SS: $p=0.01$; GSV: $p=0.005$) language scores in the Reactive group at the 12-month assessment compared to the other two groups. Participants from the Reactive group also demonstrated significantly lower scaled scores in expressive language at the 36-month visit (SS: $p=0.007$; GSV: 0.013). There was no statistical difference between the three groups in receptive or expressive scaled scores at 24 months nor receptive scaled scores at 36 months. There was no statistical difference in the change in scaled scores between 12-36 months between the three groups.

When comparing participants who received speech therapy for any indication (proactive or reactive, $n=25$) to never received ($n=14$), there was no statistical difference between the two groups in SS or GSV at the 12-month, 24-month, or 36-month visit or in changes in SS or GSV between 12-24 months, 24-36 months, or 12-36 months.

CONCLUSION: This study describing speech therapy interventions in young children with XXY can help guide genetic counseling and medical care recommendations for the growing population of infants with a prenatal diagnosis of XXY. Importantly, ~61% of the total cohort received early intervention speech therapy services prior to 36 months of age, and 21% of the cohort initiating therapy due to the presence of language delays. We observed that participants who reactively qualified for speech therapy interventions demonstrated statistically lower receptive and expressive language scores at 12 months and statistically lower expressive scores at 36 months. Speech therapy did not significantly impact the change in GSV scores between timepoints compared to the group that did not receive therapy. When therapy is initiated due to the presence of a developmental delay, it is reasonable to predict language scores in this subgroup to be lower than those without developmental delays. Future analyses will model and compare longitudinal trajectories of change between the three groups, and also take into consideration the age that speech therapy was initiated and duration of therapy.