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# Prenatal phenotype of 47, XXY (Klinefelter syndrome)

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## Abstract

**Objective:** There is a paucity of knowledge regarding the prenatal presentation of Klinefelter syndrome, or 47, XXY. Accurate prenatal counseling is critical and in utero diagnosis is currently limited by a poor understanding of the prenatal phenotype of this condition.

**Methods:** This is a case series of fetuses with cytogenetically confirmed 47, XXY in the prenatal period or up to age 5 years, with prenatal records available for review from four academic institutions between 2006 and 2019. Ultrasound reports were reviewed in detail to assess for increased nuchal translucency and structural abnormalities. Additionally, we reviewed results of cell-free DNA and serum analyte testing when performed to inform our understanding of the detection of fetal 47, XXY through standard genetic screening tests.

**Results:** Forty-one cases with confirmed cytogenetic diagnosis of 47, XXY and prenatal records available for review were identified: 37 had a prenatal diagnosis and 4 had a postnatal diagnosis. Nuchal translucency was increased ≥3.0 mm in 23.1% (6/26) of cases with a documented

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CONFLICTS OF INTEREST

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measurement. In 29.2% (7/24) of cases with a second trimester anatomical ultrasound available for review, a fetal abnormality was identified (3 brain anomalies, 1 cardiac abnormality, 1 echogenic bowel, and 2 limb abnormalities). Among those who had cell-free DNA and serum analytes performed, 92.6% (25/27) and 36.3% (4/11) had an abnormal result respectively.

**Conclusion:** This case series expands our knowledge of the prenatal presentation of 47, XXY by identifying first and second trimester fetal sonographic abnormalities. Prenatal identification of this condition enables accurate counseling, focused prenatal management, and early postnatal interventions to ameliorate some of the known complications.

## 1 | INTRODUCTION

Klinefelter syndrome (KS), or 47, XXY, is the most commonly occurring sex chromosome aneuploidy, with an estimated incidence of approximately 1 in 660 live male births.[1] KS can present in childhood with developmental delay, learning disability, and behavioral disturbances, and in adulthood with infertility and osteoporosis.[1,2] Studies have suggested that prenatal diagnosis is associated with a less severe phenotype than postnatal diagnosis,[3] perhaps related to the role of early intervention and treatment in ameliorating some of the known complications.[4] Further, achieving a prenatal diagnosis enables more opportunities for parental education and focused counseling as well as prenatal management.

Prenatal diagnosis of KS is relatively infrequent, with approximately 10%–13% of patients with KS diagnosed prenatally.[1,5,6] This can be attributed to an absence or incomplete understanding of prenatal ultrasound findings, and limited data on the prenatal phenotype of pregnancies with KS.[3] Additionally, reported positive predictive values of cell-free DNA for detecting KS are less than optimal, ranging from 67% to 91%.[7–9] For patients considering diagnostic testing, a better understanding of the prenatal phenotype may help inform decision making.

In light of the potential benefits of early diagnosis and limitations of genetic screening in detecting this condition, our objective was to characterize the frequency of abnormal ultrasonographic findings in pregnancies with KS, the specific prenatal phenotypic features, and the performance of genetic screening tests for detecting it. We hypothesize that a significant proportion of pregnancies with fetal KS will have associated sonographic findings that might raise suspicion for this diagnosis.

## 2 | MATERIALS AND METHODS

This case series includes pregnancies from 4 institutions over years 2006 to 2019 in which the fetus had KS. Those eligible for inclusion were pregnancies in which diagnostic testing with karyotype or chromosomal microarray confirmed the diagnosis of KS, or cases in which the diagnosis was confirmed by the time the child was 5 years of age and had prenatal records available for review. Cases that resulted in pregnancy termination were still included to capture as much phenotypic data as possible. Cases with mosaic KS were excluded from analysis, as were cases in which diagnostic testing to confirm the results of cell free DNA was not performed.

We defined the primary outcome as the overall frequency of abnormal ultrasound findings in cases with a prenatal diagnosis of KS. Secondary outcomes were the types of abnormal ultrasound findings in cases with a prenatal diagnosis of KS, as well as the sensitivity of cell-free DNA and serum analytes for detection of fetal KS.

Among those with nuchal translucency (NT) measured, an NT ≥ 3.0 mm was considered abnormal, recognizing that the risk of any chromosome abnormality is increased with an NT measuring 3.0 mm or more.[10] All prenatal ultrasound examinations were performed by certified ultrasonographers and interpreted by Maternal-Fetal Medicine specialists. NT measurements were obtained by Nuchal Translucency Quality Review (NTQR) certified sonographers and interpreted by NTQR certified Maternal-Fetal Medicine physicians between 10 weeks 3 days gestation and 13 weeks 6 days gestation. The frequency and types of structural abnormalities were also assessed from records of second trimester anatomy ultrasounds, which are typically performed at 18 to 20 weeks gestation. Third trimester ultrasound were not routinely performed at our institutions for the diagnosis of fetal KS, and therefore were not available for review. Serum analytes were performed in the first trimester, second trimester, or both, depending on timing of patient presentation to care, patient preference, and provider preference. Similarly, cell free DNA was pursued at the discretion of patients and their providers. Cytogenetic diagnosis of 47, XXY was confirmed through either karyotype or chromosomal microarray, depending on institutional practice.

Data on ultrasound reports, including specific findings, were abstracted from the electronic medical records at each site. Additionally, maternal demographic information, genetic screening results, indication for genetic testing, pregnancy complications, and pregnancy outcomes were abstracted from the electronic medical records.

The primary and secondary outcomes related to ultrasound abnormalities were reported as proportions. The secondary outcome of the sensitivity of genetic screening tests for detecting KS was reported as a percentage. Stata version 15.1 (StataCorp, College Station TX;2019) was used for statistical analyses. This study was approved by the individual Institutional Review Boards at each institution.

## 3 | RESULTS

A total of 56 cases with cytogenetic diagnosis of KS during the study period were identified: 38 in the prenatal period and 18 in the postnatal period. One case with prenatally-identified mosaicism for KS was excluded. Fourteen subjects with postnatal diagnoses had no prenatal records available for review, and were therefore excluded. This left a total of 41 cases that were ultimately included. Of the 37 prenatally-identified affected pregnancies, 16 (43.2%) resulted in live births, 14 (37.8%) ended in pregnancy termination, and 7 (18.9%) were lost to follow up. Demographic characteristics of women whose pregnancies were complicated by fetal KS are described in Table 1. Notably, the median maternal age was 36 years (IQR 32–39), the majority of women identified as non-Hispanic White, and cases were enrolled from across all 4 institutions.

Among the 37 prenatally-identified cases, 15 (40.5%) had diagnosis via chorionic villus sampling and 22 (59.5%) via amniocentesis. The most common indication for prenatal diagnostic genetic testing was abnormal cell-free DNA ($n$ = 21, 56.8%). Of these, 3 had findings on second trimester anatomy ultrasound, 7 had no findings on second trimester anatomy ultrasound, and 11 had no second trimester anatomy ultrasound performed. Eight participants (21.6%) underwent elective prenatal diagnostic genetic testing, 6 of whom had maternal age greater than 35. Two participants (5.4%) underwent testing for each of the following indications: abnormal serum analytes, enlarged NT, both abnormal serum analytes and enlarged NT, and identification of a structural anomaly. All four of the postnatal cases declined prenatal testing and underwent genetic testing in the immediate neonatal period following abnormal cell-free DNA in the index pregnancy.

A total of 26/41 cases had NT measured. Of these, 23.1% (6/26) had enlarged NT measuring 3.0 mm or more, with a median NT measurement of 2.1 mm and range of 0.7–3.9. Of the 24 cases with an anatomy ultrasound performed, 7 (29.2%) had abnormal ultrasound findings. These included 3 intracranial abnormalities (1 isolated ventriculomegaly, 1 ventriculomegaly and vermian hypoplasia, and 1 semilobar holoprosencephaly), 2 skeletal abnormalities (1 unilateral clubbed foot and 1 bilateral shortened femurs and humeri), 1 cardiothoracic abnormality (deviated cardiac axis and cardiomegaly), and 1 gastrointestinal abnormality (echogenic bowel) (Table 2). No additional genetic evaluation was performed in these cases. Twenty-seven subjects underwent cell-free DNA testing. In 25/27 (92.6%), cell-free DNA was positive for KS; the other two subjects (7.4%) had a false negative result. Eleven subjects had serum analytes performed; of those, 4 (36.3%) had abnormal results.

NT measurement was not different among those who terminated or continued the pregnancy, with median values of 2.2 and 2.1 mm respectively ($p$ = 0.8). Three of the patients who terminated had second trimester anatomy ultrasound performed. There were no anomalies noted in this cohort.

## 4 | COMMENT

In this case series, we identified 41 pregnancies in which KS was diagnosed in the prenatal or postnatal period, and prenatal records were available for review. Cell-free DNA frequently, but not universally, identified these pregnancies, with a false negative frequency of 7.4%. In pregnancies complicated by fetal KS, 23.1% of those who had NT measured were found to have an enlarged NT ≥ 3.0 mm. Among those that had a second trimester anatomy ultrasound performed, 29.2% had an abnormal finding, most commonly intracranial abnormalities.

Overall these findings suggest that ultrasound abnormalities are more frequent in patients with a prenatal diagnosis of KS than has been previously suspected. Our finding of increased NT is consistent with previously reported findings; a prior similarly sized study reported that 26% of subjects with prenatally diagnosed KS had NT in the 99th percentile.[5] Another study found that 40% of fetuses with sex chromosome abnormalities (including KS, as well as 47, XXX and 47, XXY, but not Turner syndrome) had NT measuring above the 95th percentile.[11] A finding of increased NT should prompt a clinician to consider KS in

the differential diagnosis. Additionally, approximately one third of subjects in our study had abnormalities noted on second trimester anatomy scan, though these involved multiple organ systems, and beyond cerebral ventriculomegaly, no specific anomaly impacted more than one pregnancy. Interestingly, these findings have not been routinely reported in the postnatal setting, though evaluation that might identify these findings (i.e. brain imaging or echo-cardiography) is likely not regularly performed. While most of these ultrasound findings are non-specific, and may not be directly related to the underlying diagnosis of KS, the overall frequency of ultrasound findings in this cohort was significantly higher than anticipated. As other authors have previously noted, embryogenesis may be different in these pregnancies and may underlie this higher frequency of ultrasound abnormalities.[5]

The findings in this study may be useful in helping to identify pregnancies at risk of fetal KS. In this study, approximately one third of pregnancies resulted in termination. Reported frequency of pregnancy termination with a prenatal diagnosis of KS have ranged widely, from 17% to 85%, depending on the location and the year.[3] This variation is likely related to differences in legal access to pregnancy termination as well as patient preferences and prenatal genetic counseling practices. However, the high frequency of termination is concordant with other studies suggesting its importance in patient autonomy, as it may impact decision making regarding pregnancy continuation.

Additionally, should pregnancy continuation be desired, prenatal diagnosis of KS provides an opportunity to families to receive prognostic counseling prior to delivery and to identify a multispecialty team of health care providers to assist in future care. While treatment options at this time remain largely supportive, close surveil-lance and early intervention for issues related to testicular development, neurocognitive and behavioral development, and bone development are recommended for children with KS.[12] Retrospective data has also suggested that testosterone supplementation during the first 1–2 years of life may improve neurocognitive outcomes in these patients; while this data has not yet changed management guidelines, research in this field is ongoing, and may ultimately highlight the importance of early diagnosis.[13]

A unique finding in this study is the high frequency of false negative cell-free DNA. While this was significantly higher than anticipated, the true false negative frequency is largely unknown. Several large studies assessing the test performance of cell-free DNA for the diagnosis of KS lacked ability to report the false negative frequency, as cytogenetic testing was not routinely performed on those with negative cell-free DNA.[7–9,14–16] While this cohort is too small to draw large conclusions about the true false negative frequency of cell-free DNA for detection of KS, additional information on the test performance characteristics is warranted to better inform interpretation of results and patient counseling. If indeed the false negative frequency is as high as our study suggests, the importance of understanding the prenatal phenotype of this condition is even more significant.

This study has several strengths. We assessed the commonly espoused idea that KS is not associated with ultrasound abnormalities, and found conversely that ultrasound abnormalities (particularly enlarged NT) were common in this cohort. As a multicenter study, we included subjects from across the country, which may increase generalizability.

We also sought to include subjects with a postnatal diagnosis to minimize ascertainment bias, as patients with ultrasound abnormalities may be more likely to undergo prenatal genetic diagnostic testing.

This study also has several limitations. Perhaps most notably, patients with 47, XXY are more likely to be identified prenatally when sonographic findings are present. While a majority of subjects in this case series underwent diagnostic testing either electively or for abnormal screening (either cell-free DNA or serum analytes), 4 specifically underwent diagnostic genetic testing for abnormal ultrasound findings. This likely enriched the percentage of anomalies in our cohort. In light of this, and the small number of subjects included, our findings may not represent the true incidence of ultrasound abnormalities in all patients with 47, XXY; rather, these findings may inform future research on the subject. While we did include postnatally identified cases for whom prenatal records were available, we were unable to include cases that were identified at older ages, as we did not have prenatal records available for review. There are likely differences between patients with KS identified in the prenatal or immediate postnatal period compared with those identified later in life. Additionally, while our case series includes subjects from four different institutions, as referral centers, our patients' findings may not be generalizable to those at other institutions.

In conclusion, we found that ultrasound abnormalities, particularly enlarged NT, were common in a cohort of pregnancies complicated by prenatally diagnosed KS. As early diagnosis may provide an opportunity to improve outcomes of children with this condition, understanding the fetal phenotype is particularly important. KS should be considered when there is an enlarged NT or other sonographic findings; this may inform further testing strategies. Further research on larger cohorts is warranted to better refine this understanding.

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## DATA AVAILABILITY STATEMENT

Data can be made available upon request to the corresponding author.

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**Key points What is already known about this topic?**

- While prenatal diagnosis of 47, XXY is associated with improved outcomes, few cases of 47, XXY are diagnosed prenatally, in part due to limited understanding of the prenatal phenotype.

**What does this study add?**

- This large multicenter cohort provides significant insight into the prenatal phenotype of 47, XXY. Approximately one quarter of fetuses with 47, XXY had enlarged nuchal translucency, and nearly one third had structural abnormalities at the time of anatomic survey.

**TABLE 1**

Demographic characteristics of women with pregnancies complicated by fetal 47, XXY

| | **Prenatal diagnoses** ***n*** **= 37** | **Postnatal diagnosis** ***n*** **= 4** | **All** ***n*** **= 41** |
|---|---|---|---|
| Median maternal age at delivery (IQR) | 36 (32–40) | 37 (34–38.5) | 36 (32–39) |
| Median body mass index (IQR) | 25.6 (23.2–30.2) | 25.5 (20.3–30.5) | 25.6 (22.7–30.2) |
| Race/ethnicity – no. (%) | | | |
| Non-hispanic white | 26 (70.3) | 2 (50.0) | 28 (68.3) |
| Non-hispanic black | 1 (2.7) | 0 (0) | 1 (2.4) |
| Hispanic or Latina | 3 (8.1) | 0 (0) | 3 (7.3) |
| Asian/Pacific islander | 6 (16.2) | 2 (50.0) | 8 (19.5) |
| Unknown | 1 (2.7) | 0 (0) | 1 (2.4) |
| Pre-existing diabetes - no. (%) | 1 (2.7) | 0 (0) | 1 (2.4) |
| Chronic hypertension - no. (%) | 2 (5.4) | 1 (25.0) | 3 (7.3) |
| Substance use - no. (%) | 2 (5.4) | 0 (0) | 2 (4.9) |
| IVF conception - no. (%) | 6 (16.2) | 0 (0) | 6 (14.6) |
| Study site - no. (%) | | | |
| University of California, San Francisco | 16 (43.2) | 2 (50.0) | 18 (43.9) |
| Johns Hopkins | 7 (18.9) | 2 (50.0) | 9 (21.9) |
| University of North Carolina | 7 (18.9) | 0 (0) | 7 (17.1) |
| Thomas Jefferson University | 7 (18.9) | 0 (0) | 7 (17.1) |

**TABLE 2**

Sonographic findings of anatomy scan and NT in patients with prenatal diagnosis of 47, XXY

| | ***n* = 24** | **Specific finding** | **Gestational age at anatomy ultrasound** | **NT measurement** |
|---|---|---|---|---|
| Normal | 17 (70.8) | Normal anatomy | 19 weeks 4 days[a] | 2.1 mm[a,b] |
| Intracranial | 3 (12.5) | 1 vermian hypoplasia with ventriculomegaly[c] | 18 weeks 2 days | 3.9 mm |
| | | 1 mild bilateral intracerebral ventriculomegaly[d] | 20 weeks 5 days | -- |
| | | 1 semilobar holoprosencephaly | 20 weeks 4 days | -- |
| Skeletal | 2 (8.3) | 1 unilateral (right) clubbed foot | 20 weeks 6 days | -- |
| | | 1 bilateral shortened femurs and humeri[e] | 19 weeks 5 days | 2.1 mm |
| Cardiothoracic | 1 (4.2) | 1 deviated cardiac axis and cardiomegaly | 16 weeks 6 days | -- |
| Gastrointestinal | 1 (4.2) | 1 echogenic bowel | 20 weeks 3 days | -- |

*Note*: Data presented as *n* (%).

Abbreviations: NT, Nuchal translucency, (--) NT ultrasound not performed.

[a]Median value presented for subjects with no second trimester anomalies.

[b]NT not measured in 7 subjects with no ultrasound abnormalities on second trimester ultrasound.

[c]Largest lateral ventricle measurement at second trimester anatomy ultrasound 12 mm.

[d]Largest lateral ventricle measurement at second trimester anatomy ultrasound 11.6 mm.

[e]Measuring <10%ile at the second trimester anatomy ultrasound and <5%ile in a follow up third trimester ultrasound.