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The Dichotomy of Medical Ethics in the Field of Fetal Medicine

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Abstract

Noninvasive prenatal screening (NIPS) by cell-free DNA (cfDNA) in maternal blood is increasingly being used for screening for common aneuploidies due to its high sensitivity and specificity. The increased uptake of this noninvasive test has also increased the prenatal detection of sex chromosome aneuploidies (SCA) which is usually an unexpected finding for parents and clinicians alike, especially when the ultrasound does not report any abnormal finding. One such condition being increasingly diagnosed prenatally is the triple X syndrome (47,XXX) which has a reported incidence of 1 in 1000. Since the outcome of this condition is highly variable, with a large majority thought to remain undiagnosed, counselling parents can be difficult for healthcare professionals. This paper highlights the challenges of providing non-directive, evidence-based counselling, the ethical dilemmas, and the contrasting outcomes depending on parents' choices when confronted with this unexpected diagnosis.

Keywords: Noninvasive prenatal screening, prenatal diagnosis, sex chromosome aneuploidy (SCA), triple X syndrome, 47XXX

Introduction

Noninvasive prenatal screening (NIPS) by cell-free DNA (cfDNA) in maternal blood is currently recommended as the best screening test for detection of the common aneuploidies in both singleton and twin pregnancies (Dungan et al., 2023). The increased uptake of this noninvasive test has also increased the prenatal detection of sex chromosome aneuploidies (SCA) that are reported to affect 1 in 400 newborns making these the most common chromosomal abnormalities (Hui et al., 2023). One such condition is the triple X syndrome (47,XXX) which has a reported incidence of 1 in 1000 in the general population. Triple X can be associated with orofacial clefts, cardiac abnormalities, and clubfoot which are usually detectable at prenatal ultrasound. In the absence of congenital abnormalities, triple X fetuses are not known to be at increased risk of other antenatal or postnatal complications compared to the general population, and women who opt to continue their pregnancies should receive standard obstetric care (Reimers et al., 2023).

Individuals with triple X are reported to be at increased risk of developmental delay, learning disabilities, and mental health disorders as compared to the general population, but these findings are variable and not present in every case (Tartaglia et al., 2020). There is also a difference in outcomes of prenatal versus postnatal diagnoses, with Wigby et al suggesting that children diagnosed with triple X prenatally may have a higher intelligence quotient (IQ) and adaptive skills though the risk for speech delay or learning disability still remains. However, accurate counselling regarding expected outcomes is difficult because only 10% of affected triple X individuals are ever clinically diagnosed (Wigby et al., 2016). A recent publication states that the reported data on medical and neurodevelopmental differences in individuals with triple X syndrome should be interpreted with caution because of the ascertainment bias that would be inherent to a condition that is diagnosed in only 10% of cases (Reimers et al., 2023). Since the outcome of this condition is highly variable, counselling parents can be difficult for healthcare professionals (Fisher et al., 2023). This paper aims to highlight this ethical conundrum by presenting three clinically similar cases that had different outcomes, thus highlighting the divergent ethical ramifications of these unexpected diagnoses.

Patient 1: A 36-year-old G3P1 with no live issue (first miscarriage, second unexplained intrauterine

fetal demise at 26 weeks gestation) consulted us in her third pregnancy for the isolated finding of aberrant right subclavian artery (ARSA) at the anomaly scan. Her triple marker showed low risk for Down syndrome. The options of noninvasive prenatal screening (NIPS) and diagnostic test, i.e. amniocentesis were discussed with the couple. The couple was counselled that NIPS remains a screening test despite its high detection rate and that a high-risk report will need confirmation with amniocentesis. Considering the bad obstetric history and the 1% risk of miscarriage associated with invasive testing, the couple opted for NIPS. NIPS reported 'low risk' for trisomy 21,18, and 13 but gave 'high risk' for triple X (XXX). The result was discussed with the couple, and they were offered amniocentesis. The couple was also given relevant clinical information regarding triple X (https://rarediseases.org/rare-diseases/trisomy-x/). After counselling, the couple opted against invasive testing as they felt they were okay to have a baby with triple X. They opted to do their karyotypes, and interestingly, the mother herself had a triple X karyotype. She went on to have a normal delivery of a healthy baby girl at term.

Patient 2*:* A 42-year-old primigravida who conceived naturally came to us at 14 weeks and 3 days with a high risk for Down syndrome on dual marker test. The risk was in the screen positive range (cut off of 1 in 250 used to define 'high risk') but it was actually reduced compared to the age-related background risk. An ultrasound was performed, and there were no structural abnormalities nor any markers for chromosomal abnormalities detectable at that gestation. The options of noninvasive prenatal screening (NIPS) vis a vis invasive testing, i.e., amniocentesis were discussed with the couple. This couple was also counselled that NIPS remains a screening test, and a high-risk result will need confirmation with amniocentesis. NIPS can be done at any gestational age between 9-24 weeks, whereas amniocentesis is best performed at or after 16 weeks. The couple opted for NIPS which was given the same day. The NIPS report came eight days later and reported 'low risk' for trisomy 21,18, and 13 but gave 'high risk' for triple X (XXX). The report was shared with the couple, and they were asked to come back for a consultation. The patient requested our team to speak to her sister, who happened to be a genetic counsellor, and we discussed this result with her. Since the positive predictive value of NIPS for sex chromosomal abnormalities is only about 50% (Kornman et al., 2018), amniocentesis was offered. The couple was agreeable, and an uneventful procedure was done the same day. The quantitative fluorescent polymerase chain reaction (QFPCR) report also reported triple X in the fetus. The couple was asked to consult the medical geneticist soon after the reports came. The expectant mother came for the consultation accompanied by her sister and was counselled regarding the possible outcomes of this condition. A non-directive counselling was done, and recent literature was shared with the mother. The mother and her sister expressed their wish to continue the pregnancy as she had conceived with difficulty. A day after this consultation, we started receiving disturbing, lengthy emails, calls and WhatsApp messages from the patient's husband accusing us of encouraging his wife to have an 'abnormal' baby. He was outraged at how could a consultation be done for his wife with his sister-in-law in his absence. This was when we realized that there was a difference of opinion between the couple regarding the continuation of pregnancy. We replied to the first mail addressing his concerns, and we reiterated that as clinicians, we could only provide correct information. Prompt genetic counselling was provided as soon as the diagnosis was confirmed. The decision to continue (or discontinue) the pregnancy is a prerogative of the couple, and we as clinicians would provide support in whatever decision they take. The husband sent a legal notice to his wife with a copy to our team that he will not be responsible for the upkeep of the 'abnormal' baby if she continued with the pregnancy. Eventually, the patient wrote a mail to the hospital administration that the fetal medicine team had spoken to her sister at her request and that she had no complaint regarding the clinicians dealing with her case. The hospital administration requested the husband to come for a meeting in which it was conveyed to him that an internal inquiry of the hospital did not find any 'malpractice' in handling this case. The couple filed for mutual divorce and the expectant mother chose to carry on with her antenatal care in another place.

Patient 3: A 39-year-old G3A2 came for a fetal medicine consultation at ten weeks gestation as she herself was diagnosed with a triple X karyotype on undergoing investigations for her previous two miscarriages. This lady has a postgraduate degree and is working at a senior position in a multinational company and has no history

of any significant medical or surgical history. The possibility of having a fetus with normal karyotype, triple X karyotype or XXY was discussed with the couple. Both parents were unanimous in their opinion that they would continue with the pregnancy in case the fetus turned out to have a triple X karyotype. An amniocentesis was performed at 17 weeks, and the fetal karyotype was normal. She went on to have a normal delivery of a healthy baby boy at term.

Discussion

It is difficult to define what constitutes 'ethics'. A combination of one's values, belief systems, and experience(s) shapes every individual's unique code of ethics. Society, in general, gives us a broad background of what constitutes 'right', but there remains plenty of room for variation within this framework. Fetal medicine is a particularly vulnerable branch as it deals with something that is partly unknown. An ultrasound done halfway through pregnancy at around 18-20 weeks is expected to predict how the fetus will evolve over the next 20 weeks and presumably even for the first two years after birth. Subtle findings or the so-called 'soft markers' generate a lot of anxiety when mentioned to expecting parents. As per standard clinical guidelines and recommendations, a fetal medicine specialist is expected to look for these and discuss the uncertainty of 'screening tests' vis a vis the certainty of diagnostic but invasive tests with an inherent albeit small risk of miscarriage (ACOG Practice Bulletin; 2020). Thus, the fetal medicine specialist walks a tightrope between flagging up findings and not alarming the parents enough to make pregnancy an arduous journey.

Add to it the recognition of newer findings where the outcome is highly variable. This dilemma was presented strikingly in these three cases where there was no 'structural' abnormality in the fetus but we, both the clinicians and parents, were faced with a diagnosis with no certain answers. These cases with similar test results also illustrate the dramatically different 'ethical' repercussions despite our best intentions of providing the most up-to-date, accurate information to parents in a timely manner and with nondirective counselling. We believe that there is no 'correct' way of dealing with these sensitive issues, and as clinicians, one can only take solace in the fact that one acted to the best of their capabilities and as per current guidelines. But does that absolve us from the upheaval that we create in our patients' lives, however unintentional that might be? The purpose of sharing these cases with the medical fraternity is to sensitize our colleagues to the vagaries of this specialty that has more unknowns than knowns.

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