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Ethics Case: When is Non-Invasive Prenatal Diagnostic Testing Beneficial?

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Commentary Article

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Abstract

Recommended for antepartum screening in pregnancies of high-risk women, non-invasive prenatal testing (NIPT) is poised for wider use. A holistic approach to pregnancy requires that paternal genetic contribution be considered when evaluating genetic risk. High-risk male contribution to a pregnancy from advanced paternal age may be best screened for by NIPT. Given subtly older maternal ages, NIPT also provides a means for non-communicable disease early diagnosis.

Keywords: Advanced Paternal Age; Advanced Maternal Age; Aneuploidy Screening; Antepartum Screening; Autonomy; Beneficence; Cell-Free Fetal DNA; Choriocarcinoma; Cost-Effectiveness; Down's Syndrome; Egalitarianism; Informed Consent; Libertarianism; Non-Invasive Prenatal Testing; Nonmaleficence; Single-Base Substitutions; Trisomy 13; Trisomy 18; Trisomy 21; Utilitarianism.

The Patient Scenario

Thirty-year-old Felicia has alpha thalassemia trait. Felicia's forty-five-year-old partner Jorge has sickle-cell trait. Felicia is nine weeks pregnant with their first child. Felicia is already experiencing breast tenderness, fatigue, nausea, and vomiting. Her initial laboratory tests showed that she is hyperthyroid. Felicia's parents Gina and Giuseppe, neither of whom have a history of thyroid dysfunction, have suggested that Felicia have antepartum genetics screening done. Felicia and Jorge believe that antepartum screening is unnecessary as irrespective of whether the baby has a hemoglobinopathy, they will continue with the pregnancy.

One week later, Felicia and Jorge have their second antepartum visit with Dr. Wong, their obstetrician. Dr. Wong introduces the concept that willingness to end a pregnancy is not prerequisite for antepartum genetics testing. She explains that many parents appreciate being able to prepare for the child they will bring home. Dr. Wong communicates that there are several antepartum genetics screening and confirmatory testing options, each with unique timing windows and applicability. Following a genetics consultation Felicia and Jorge consent to non-invasive prenatal diagnostic testing (NIPT), to be done at the same appointment as by an ultrasound for dating and initial fetal structural abnormalities at 12 weeks estimated gestational age. Dr. Wong encourages antepartum genetic testing as given Jorge's age, Felicia and Jorge's risks of having a baby with any genetic anomaly are greater than obvious.

Three weeks later, the pregnant couple and the future maternal-grandparents have an unscheduled results counseling visit with Dr. Wong. Neither

maternal ovary was visualized on the ultrasound. NIPT showed that the baby does not have a hemoglobinopathy. However, based on NIPT and nuchal translucency, the baby has been identified as most probably having Trisomy 21 (T21). NIPT indicated a second worrisome finding: Trisomy 18 (T18) and monosomy 13 (M13). Jorge is stunned, disbelieving that T21 is possible since Felicia is younger than thirty-five-years old. Dr. Wong and the geneticist recommend invasive fetal diagnostic testing to confirm the diagnosis of T21, for which a warm hand-off is given to the maternal-fetal-medicine team.

Dr. Wong also recommended that Felicia undergo abdominal and pelvic magnetic resonance imaging (MRI) for ovarian visualization. A week later the foursome return to see Dr. Wong. Felicia is given a diagnosis of unilateral dermoid tumor, possibly Struma ovarii consistent with antepartum hyperthyroidism, and a possible contralateral ovarian choriocarcinoma. Felicia is given a warm hand-off to the gynecology-oncology service for second trimester cytoreductive surgery followed by chemotherapy as needed. Felicia is urged to return to see Dr. Wong within three days.

Commentary

Applicability of various antepartum screening modalities is central to antepartum care. Felicia's presentation – breast tenderness, fatigue, gastrointestinal changes, and thyroid dysfunction-may be mistakenly attributed to the pregnancy, when in fact, there is an underlying malignancy [1-3]. While advanced maternal age is an established eligibility criteria for antepartum genetic testing, advanced paternal age (APA) should also be considered. APA of forty-years-old or greater is associated with genetic single-base substitutions found in achondroplasia, Apert syndrome, Crouzon syndrome, multiple endocrine neoplasia 2A and 2B, Pfeiffer syndrome, and thanatophoric dysplasia [4,5]. Autism, bipolar disorder, Hutchinson-Gilford progeria, neurofibromatosis I, Noonan syndrome, retinoblastoma, tracheoesophageal fistula, and trisomy 21 are also associated with APA [4,5]. Beneficence and nonmaleficence required that Dr. Wong offer antepartum genetic testing. Autonomy indicates that Felicia and Jorge should freely decide whether to pursue any antepartum genetic testing.

Cell-free fetal deoxyribonucleic acid (DNA), forming up to 15% of cell-free maternal DNA from 10 weeks estimated gestational age, enables NIPT [6,7]. Cell-free DNA testing reveals chromosomal trisomies, aneuploidy, microdeletions, paternity, and biologic sex [6,8]. In the high-risk population cost modeling shows NIPT at a unit cost of USD 795 or less, to be a cost-effective primary screen for trisomy 21 [9]. Cost modeling has found NIPT to be a cost-effective primary screen for trisomy 13, 18, and 21 in the general pregnancy population at a NIPT unit cost of USD 665 or less [10]. Two clinical series, totaling 21,955 consecutive pregnancies validated NIPT for screening for trisomies 13, 18, and 21, with a greater than 99% detection rate for trisomy 21, compared to a 73% - 78.9% detection rate with first trimester screening [11,12]. Antepartum screen acceptors and decliners will have opinions as to the applicability of NIPT as an antepartum screen and as a maternal cancer screen. Maternal cancer patients can adopt the libertarian argument that NIPT cost is worth it to them, as NIPT provides fairness in maternal cancer screening that has hitherto been absent [13]. NIPT affords maternal cancer patients an opportunity to choose early cancer treatment, which resounds with antepartum screen acceptors wish to make their own decisions [14].

Uninterpretable positive NIPT results may indicate maternal cancer [7]. In the presented case while T21 was confirmed, T18 and M13 were not. Evaluation of 3,757 positive NIPT samples detected 10 maternal cancers [15]. Simultaneously three maternal cancers cases occurred in a prospective NIPT study of 4,000 pregnancies [16]. Safety of sufficient chemotherapeutics and supportive therapies in the second and third trimesters contributed to recommendations not to delay cancer treatment in pregnancy [2,17-19]. Knowing that the placenta is not a barrier to maternal-fetal cancer transmission, gives maternal cancer detection and treatment added urgency [18,20]. While ultrasound is the preferred abdominopelvic imaging method in pregnancy, MRI at 3.0 tesla or less may be performed in the second and third trimesters [21]. Gadolinium contrast can be used in pregnancy if the benefits outweigh the risks [21].

Gestational ovarian choriocarcinomas affect 1 in 369 million pregnancies [22]. A heterotophic pregnancy phenomenon makes concurrent intrauterine gestation and ovarian choriocarcinoma biologically plausible. In fact, ovarian choriocarcinomas may present as ectopic pregnancies [22]. Ovarian choriocarcinomas are aggressive; therefore treatment should not be delayed [22]. Ovarian choriocarcinoma may be initially treated with cytoreductive surgery [22]. Systemic chemotherapy may follow cytoreductive surgery [22]. Systemic

etoposide-methotrexate-actinomycin D-cyclophosphamide-vincristine has been tolerated antepartum for treatment of metastatic choriocarcinoma, with preterm delivery at 32 week gestation [23]. If a non-pelvic malignancy had been found, antenatal treatment would be recommended as chemotherapy and radiation are generally safe when performed after the first trimester, and when radiation does not target the uterus [18,24,25]. Preterm birth occurs up to nine times more frequently when maternal chemoradiation is performed [24]. Preterm birth affects cognitive outcomes of children exposed to chemoradiation in utero [24]. All preterm newborns have hepatic and renal immaturity, requiring a 2-week delay between the last course of maternal chemotherapy and delivery to facilitate placental drug excretion [18]. If preterm birth is maternal chemoradiation's primary fetal risk, a risk affecting benign pregnancies, maternal cancer screening should be recommended and performed.

Beneficence demands that what benefits the mother and the fetus is done [13,18]. Prenatal NIPT should be performed; abnormal NIPT results evaluated, and if maternal cancer is detected, timely treatment be performed. This permits maternal survival, possibly sparing the fetus from transplacentally inherited cancer, and permits the newborn the benefit of a living biological mother. The risks to the fetus of preterm birth are worth the benefit of maternal survival.

Failure to diagnose maternal cancer, and thus, failure to treat otherwise treatable maternal cancer is to do harm, whereas physicians are sworn to nonmaleficence [13]. Pregnant women retain autonomy over the fetus (American College of Obstetrics and Gynecology Committee on Ethics [26]. Kantian autonomy and consequentially, informed consent require that a pregnant woman choose from available diagnostics and treatments, which includes antepartum NIPT and MRI [13,26]. Bentham and Mill derived utilitarianism argues that NIPT's overall sequela take priority over maternal beneficence [13, 27].

Arguably, the fetus does not have independent moral status. Ethically, to preserve access to care pregnant women are not to be held at fault for adverse perinatal outcomes, including preterm birth [26]. If the fetus had a right to prevent preterm birth, NIPT for maternal cancer screening could be withheld, precluding maternal chemoradiation, maternal surgery, and fetal preterm birth. However, if the fetus has independent moral status, the fetus would probably prefer not to be born full term and lose their mother, instead preferring to be born preterm, enjoying the benefits of their biological mother for years to come. The fetus with independent moral status may also be assuaged by the knowledge that an elevated fetal cell-free DNA fraction drawn from 14 to 20 weeks gestation indicates an increased risk of preterm birth, which may be prepared for [28].

Conclusion

Irrespective of maternal age and other maternal risk factors, NIPT should be considered in all pregnancies affected by APA. Either maternal or paternal considerations should be sufficient to trigger NIPT for a given pregnancy. Irrespective of antepartum screening needs, NIPT technology will be developed for cancer detection in asymptomatic, non-pregnant persons [3]. NIPT allows early maternal cancer diagnosis, early second trimester treatment, minimizing or removing treatment delays, and possibly preventing tragic peripartum maternal cancer deaths that render newborns motherless [29]. In the milieu of delayed childbearing and concomitant increased maternal cancer incidence, maternal cancer screening and antepartum testing via NIPT affords fetal and maternal beneficence [15]. Utilitarianism allows delayed maternal cancer diagnosis and subsequent maternal death depriving newborns of their mothers. However, autonomy, beneficence, egalitarianism, informed consent, libertarianism, and non maleficence, submit that NIPT for antepartum fetal screening and thereby maternal cancer screening should be the 21st century maternal-fetal care standard. Nonetheless, qualitative studies on parents' opinions of expanded scope NIPT use for reasons other than fetal diagnostics are warranted.

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