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Title: Attitudes towards non-invasive prenatal diagnosis among obstetricians in Pakistan: a developing, Islamic country

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Attitudes towards non-invasive prenatal diagnosis among obstetricians in Pakistan: a developing, Islamic country

Abstract

Objectives: Stakeholders' views are essential for informing implementation strategies for non-invasive prenatal testing (NIPT). Little is known about such views in developing countries. We explored attitudes toward NIPT among obstetricians in Pakistan, a developing Islamic country.

Methods: A 35-item questionnaire was distributed and collected at eight events (a national conference and seven workshops in five cities) for obstetric professionals on advances in fetal medicine.

Results: Responses from 113 obstetrician show positive attitudes towards implementation of NIPT: 95% agreed prevention of genetic conditions was a necessity and 97% agreed public hospitals should provide prenatal screening tests. However, participants also agreed the availability of NIPT would increase social pressure on women to have prenatal screening tests and to terminate an affected pregnancy (53% and 63%, respectively). Most participants would not offer NIPT for sex determination (55%), although 31% would. The most valued aspects of NIPT was its safety, followed by its utility, then accuracy.

Conclusion: Participants generally supported the implementation of NIPT, but raised concerns about social implications. Therefore, national policy is needed to regulate the implementation of NIPT, and pre-test information and post-test genetic counselling is needed to mitigate social pressure and support parents to make informed decisions.

What's Already Known About This Topic?

- Non-invasive prenatal testing (NIPT) is being introduced into private prenatal healthcare in developing countries.
- **S**takeholders’ views are essential for informing implementation strategies for NIPT.
- Little is known about stakeholders’ views in developing countries.

What Does This Study Add?

- There is a need for a national policy on prenatal screening to regulate the implementation of NIPT.
- Pre-test information and post-test genetic counselling is essential to help mitigate social pressure and support parents to make informed decisions.

Introduction

Non-invasive prenatal testing (NIPT) utilizing cell-free fetal DNA in maternal plasma can be used to test for fetal trisomies, fetal Rhesus status, sex chromosome disorders and fetal sex and some micodeletions. Advances in NIPT technologies are resulting in a rapidly expanding range of testable conditions.[1] NIPT is used mainly to test for the common trisomies, particularly trisomy 21 (Down syndrome), either as the initial screening test, in addition to or instead of combined screening, or as a more accurate test after a high-risk combined screening result (known as contingent screening).[2] Using cell-free fetal DNA, NIPT has high sensitivity and specificity for Down syndrome, and slightly lower sensitivity for Edwards, and Patau syndrome.[3] However, it is not considered diagnostic because it has a positive predictive value (the chance that the child will have Down syndrome) of approximately 80%.[3,4] Furthermore, the performance of cfDNA screening tests is depended on fetal fraction (the amount of the cell-free DNA in the maternal blood that is of fetal origin) and sampling. For example, uninterpretable and non-reportable CfDNA test results due to low fetal fraction in patients carrying aneuploid foetuses can range from 1% to 5%, and sampling errors are reported in 3% and 7% of patients.[5] There is also limited evidence about the performance of cfDNA screening for women of different ethnic origins.[6] Therefore, a positive NIPT result would require confirmatory invasive testing.

NIPT has been commercially available in the USA, parts of Europe, Asia, Africa, Australia and the Middle East for a number of years.[6] It is widely accepted that implementation strategies for NIPT should be based on stakeholders' views, and there is much research on the ethical, legal and social implication (ELSIs) of NIPT,[7] generally showing that it is acceptable to various stakeholder.[8,9] However, the simplicity, safety, accuracy and availability of NIPT early in pregnancy raises a number of ethical and social concerns. These include higher uptake of testing and without sufficient consideration,[10,11] women feeling pressured to terminate affected pregnancies and normalisation of selective abortions,[12,13] potential misuse of the technology for less serious or non-medical conditions,[14] and diminishing acceptance of people with disabilities.[15-17]

Doctors are now introducing NIPT into private prenatal healthcare in developing countries, including the Islamic republic of Pakistan, where there is comparatively little research on the ELSIs of NIPT to inform implementation.[6,18] Pakistan has a population of over 190 million and is the sixth most populous country in the world.[19] Genetic conditions are common in Pakistan predominantly because of the favoured custom of consanguineous marriages.[20] Research on the prevalence of genetic conditions is lacking in Pakistan, although beta-thalassaemia major is common.[21,22] In Pakistan, only basic prenatal healthcare is provided through public hospitals, where consultations with doctors are free of charge, but patients may have to pay for medication and tests, such as routine ultrasound scans (approximately one US Dollar), and there is no provision of prenatal screening tests. Down syndrome screening is only offered privately by specifically trained obstetricians (approximately 15-30 US Dollars). Screening involves a nuchal translucency scan for soft markers, such as, fetal nuchal fold thickness, femur length and absence of nasal bone, without any biomarkers. Screening is followed by amniocentesis or chorionic villus sampling for patients considered at high risk of having a child with the condition. The availability of NIPT enables providers to offer an additional test that is technically more advanced and accurate to those who can afford it (between 480-900 US Dollars). Prenatal screening services have been available in Pakistan's private sector for over two decades, but there is no national policy governing these services. However, there are fatwas (religious rulings) placing responsibility on health professionals to determine conditions for which termination of pregnancy should be offered, albeit privately.[23]

Furthermore, research shows that there are differences in stakeholders' (women's and HPs') preferences for prenatal screening tests between countries, suggesting the need for country specific approaches to implementing NIPT.[24] Research within developing countries is essential because the implementation of NIPT is likely to be affected by factors such as low priority at policy level, limited health resources, competing health priorities, lack of trained health professionals, low literacy rates, and cultural and religious factors.[15,25] Health professionals' views are particularly important because of their role in developing policy and practice guidelines, introducing new technologies into clinical practice, and supporting patient choices.[13] Given the paucity of research on stakeholders' views about NIPT in developing countries,[26] and the recent commercial availability of NIPT in Pakistan, this study aimed to explore the views of obstetricians in Pakistan about NIPT.

Materials and methods

Questionnaire

A self-completion, structured questionnaire developed by Sayres et al. (2011) to explore the views of obstetricians' attitudes toward implementing NIPT in the United States was adapted for this study.[27] Items unlikely to work in Pakistan were excluded, such as, "Insurance companies have an obligation to fund prenatal testing…" because of the lack of availability of such insurance companies in Pakistan and items specific to Pakistan were added (sixth to eighth item on Figure 1). The questionnaire was chosen because it included both attitudes towards prenatal screening tests more generally and towards NIPT, neither of which have been previously explored with obstetricians in Pakistan. Our 34-item questionnaire included eight items on participants' demographics, nine on prenatal screening tests in general (using a Likert scale to assess agreement or disagreement, see Figure 1) and seventeen on NIPT (eleven using a Likert scale – see Figures 1 and 2, and 6 using rank ordering – see Figure 3). The questionnaire was only available in English, the language in which medical degrees are taught in Pakistan, hence did not preclude any potential participants.

Data Collection

Ethical approval was granted by the Pakistan Medical Association. Participants were recruited through eight events: a two-day national conference in Lahore and seven one-day workshops (three in Lahore and one each in Islamabad, Faisalabad, Peshawar and Multan) on “Fetomaternal Medicine”, organised and hosted by the Central Park Medical College (CPMC: Lahore, Pakistan). The events were designed to update obstetricians on advances in fetal medicine and included a one-hour session on “NIPT through Cell-Free Fetal DNA” presented by GM (one of the authors, a retired Consultant in Fetal Medicine (Leeds General Infirmary, UK), currently a visiting professor at CPMC). Topics covered in the session included: an introduction to cell-free fetal DNA (cfDNA); uses of cfDNA; sequencing platform; test scope; sample requirements; reporting of results and recommended subsequent steps. None of the events were sponsored. HJ, YR and GM were present at all the events. YE was also present except for the events in Peshawar and Rawalpindi.

Following the session on NIPT at each event, attendees were informed about the study and asked to collect the study information sheet and questionnaire (both in English) from the registration table if they wished to participate. A member of the research team (HJ, a genetic counsellor at Genetech Laboratory) was available at the registration table at each event to answer potential participants’ queries about the study. Participants completed the questionnaire individually during the lunch/tea break and returned anonymously completed questionnaires by leaving them on the registration table. In total, the eight events were attended by approximately 240 doctors. We are unable to calculate the response rate for this study, because of the way in which the questionnaire was distributed.

Results

Sample Characteristics

One hundred and twenty-five participants completed the questionnaire. Twelve of these participants were excluded from the analysis because they had completed less than fifty percent of the questionnaire. The remaining 113 participants were all medically trained doctors specialising in obstetrics and gynaecology, and currently practicing in Pakistan, with characteristics comparable to the demographic of doctors in this field in Pakistan. Most participants were females (92.9%) and under the age of 36 years (55.8%). Participants' mean age was 38 ± 8 years. Most participants had been practicing medicine for ten years or less (58.4%). Participants practiced in public (46%), private (22.1%), public and private (31%), or military (0.9%) hospitals. Most participants were not currently offering any prenatal screening tests (58.4%). Participants offering prenatal screening tests offered a nuchal translucency tests using ultrasound technology (with no biomarkers), and four participants also offered NIPT. See Table 1 for a summary of participants' demographic characteristics.

[Insert Table 1]

Perceptions of Prenatal Screening Tests Generally

Most participants believed that women want as much diagnostic information as possible about their pregnancy (79%) and agreed with women receiving all available prenatal screening tests upon request (82%), although 11% of participants disagreed (see Figure 1). The majority of participants agreed that prenatal screening test results significantly affect women's decisions about whether to continue or terminate a pregnancy (96%) and that this was an appropriate consequence of testing (94%). Participants' views were divided about whether there were strong social pressures on pregnant women to have prenatal screening, where 36% of participants agreed, 38% disagreed and 26% neither agreed nor disagreed.

Most participants believed that prenatal screening was acceptable in Pakistan (82%) and prevention of genetic conditions was a necessity (95%). Ninety-seven percent of participants also believed that public hospitals should provide prenatal screening tests to pregnant women and 99% agreed that genetic counselling was a necessary component of prenatal screening.

[Insert Figure 1]

Perceptions of the Implications of NIPT

Only 27% of participants agreed they had a high level of knowledge about NIPT, 43% disagreed and 29% neither agreed nor disagreed. Nevertheless, most participants also believed NIPT offered value for money (73%), that the availability of NIPT would encourage clinicians to test more pregnant women (86%) and that they would offer it to their patients (65%). Ten percent of participants would not offer NIPT to their patients and 25% were unsure – there was no significant difference in responses between participants working in public or private hospitals. Most participants acknowledged that women were unlikely to consider the implication of NIPT at the time of testing (45%), although 31% were unsure and 20% believed they would. Most participants also believed that the availability of NIPT would increase social pressure on women to have prenatal screening and to terminate an affected pregnancy (53% and 63%, respectively).

When asked about offering NIPT for specific conditions, most participants would offer it for Down syndrome, other aneuploidy/chromosomal anomalies, and Rh blood group (93%, 90%, 86% respectively). Most participants would not offer NIPT for sex determination (55%), although almost a third of participants would (31%) and 14% were undecided (see Figure 2).

[Insert Figure 2]

Participants also ranked six key aspects of NIPT in order of their importance, with 1 being most important to 6 being least important (see Figure 3). “No risk to the fetus and mother” was ranked as the most important aspect of NIPT, with a mean ranking of 2.7 - most frequently ranked as 1 or 2 (23.7% and 36.8%, respectively). The ease of using NIPT as a “simple blood test” was ranked as the second most important aspect of NIPT, with a mean ranking of 3.1 and most frequently ranked as 1 by 25% of participants. This was followed by the high accuracy of NIPT (most frequently ranked as 3) and being able to conducted NIPT in early pregnancy (most frequently ranked as 4), both with a mean ranking of 3.2. The range of conditions testable with NIPT was most frequently ranked as 4 or 5, with a mean ranking of 4.1. The cost of NIPT was most frequently ranked as 6 and had the lowest mean ranking (4.7), although a significant minority of participants ranked this as 1 (13.2%).

[Insert Figure 3]

Discussion

Health professionals play a critical role in the clinical implementation of new technologies. Participants in our study believed that most women want as much diagnostic information as possible and that test results would significantly affect their decision about whether to continue or terminate a pregnancy, yet women should receive all available prenatal screening tests upon request. The findings suggest obstetricians support the prevention of genetic conditions. This may be due to their understanding of women's demand for prenatal screening tests for various conditions,[28] and experiences of the implications for affected families,[29] as there is no government provision of medical, social or financial support for such families.[30]

Just over half of the participants believed that there are strong social pressures on women to opt for prenatal screening tests. They also believed that women were unlikely to consider the implications of NIPT, and that the availability of NIPT would increase social pressure on women to both test and terminate an affected pregnancy. "Social pressures" are most likely to have been interpreted by participants as being due to cultural and economic implications of having a child with a disability in Pakistan.[29,31] For example, parents of children with Down syndrome may experience stigmatisation, social isolation, and rejection of themselves and/or their affected child by family and community, where negative cultural beliefs include an affected child being a divine punishment for parents.[29] Pre-test information about the condition and post-test genetic counselling could mitigate parents' feelings of pressure to opt for NIPT or termination of pregnancy.[13] However, obstetricians currently offering NIPT in Pakistan provide written information about the test, but not about the conditions tested for. Similar to others,[32-34] we acknowledge the lack of pre-test information and genetic counselling as major issues in implementing NIPT, compromising parents' autonomy. Our findings highlight the importance of clinical guidelines on how NIPT should be provided to parents, including guidance on (a) pre-test information provision so that parents understand the implications of testing,[34] and (b) provision of post-test genetic counselling for parents at high risk of having an affected child to enable them to make informed decisions about invasive testing and termination of pregnancy.

Similar to others,[35] most of the participants believed that genetic counselling is a necessary component of prenatal screening. However, we acknowledge the challenges of providing pre- and post-test genetic information for NIPT in a developing country like Pakistan, because of its low literacy rate and the lack of government funded prenatal screening or genetic services. Also, in developed countries, midwives and genetic counsellors/prenatal counselling specialists are usually responsible for the provision pre- and post-test counselling, respectively. However, in developing countries, this responsibility is most likely to be the obstetricians'. Furthermore, less than a third of the obstetricians in our study believed they had a high level of knowledge of NIPT even after a one-hour session on this topic. Whilst we acknowledge that 'a high level of knowledge' is subjective, this finding may indicate participants' perceptions of their limited ability to fully understand NIPT, which in turn may be related to poor knowledge on genetics. Therefore, there is a need for basic genetic education for obstetricians,[13,36] but also for research in developing countries to explore the most amenable and efficient means of providing pre-/post-test counselling for NIPT.

Similar to Pakistan, other developing counties are also likely to lack public hospital infrastructures for prenatal screening and genetic services. Nevertheless, given the commercial availability of NIPT, with the potential for testing for a range of conditions, and in light of other genetic technologies likely to be available in developing countries in the near future (whole genome sequencing), health professionals will need to be able to translate information for more complicated test results. Therefore, efforts should be made to ensure that obstetricians have basic genetic education and training in key aspect of genetic counselling.[13]

Moreover, participants almost unanimously agreed that public hospitals should provide prenatal screening tests to pregnant women. Overall, the interest in the prevention of genetic conditions in this Muslim country highlights the need for debate at policy level to consider (a) strategies for regulating prenatal genetic technologies in the private sector, and (b) implementing a national antenatal screening policy.[37]

The majority of doctors would offer NIPT for Down syndrome, other aneuploidy/chromosomal anomalies and Rh blood group. This may be because prenatal screening and diagnostic tests are already available privately for these conditions in Pakistan and termination of pregnancy is acceptable for various conditions.[28,29,38] Given the emphasis on doctors in Islamic states to decide the conditions for which prenatal screening, diagnostic tests and termination should be available,[23] further research should explore obstetricians' attitudes toward a larger range of conditions, including those for which prenatal screening is not currently available or conditions that could be considered less serious. Such research would inform the future implementation of more advanced genetic technologies, such as 'Genome-wide NIPT', which is likely to test for more conditions, including less serious and non-medical conditions.[39] Approximately a third of doctors were unsure or would not offer NIPT. This may be because NIPT was believed to be too expensive, and offering it to patients may make them appear interested in profit rather than patient care; and/or because NIPT would still potentially be followed by invasive diagnostic testing.[40] Further research is needed on reasons for this finding.

The availability of NIPT sex testing enables doctors to identify X-linked conditions, not to offer termination of pregnancy on the grounds of sex alone. Accordingly, most obstetricians in our study would not offer NIPT for sex determination, but a significant minority would. The latter finding may be because the preference for male children is deeply embedded in Pakistani culture,[41,42] yet doctors are not concerned about the possibility of sex selection leading to an imbalance of sex ratio to males, as observed in countries like China and India, because abortion on social grounds (including fetal sex) is illegal in Pakistan, religiously impermissible (unless the mother's life is threatened), and culturally disapproved.[42] Nevertheless, our finding raise concerns about the potential use of NIPT for sex determination and further highlight the importance of national policy to regulate the implementation of NIPT for medical purposes only.[13]

Most studies in developed countries show that health professionals value the accuracy and timing of NIPT, while women place greater emphasis on test safety and information.[24,43-46] Participants in our study emphasised test safety, similar to women in developed countries,[13,33,46,47] followed by ease of the test (simple blood test) and then accuracy. Given the differences in research in developed countries between health professionals and women, it is important to conduct similar research with women and their partners in developing countries to ensure that implementation of NIPT also incorporates their needs and preferences.

Surprisingly, the cost of the test was given little importance. This may be because the cost would be to the patient and not to health services, because women are already expected to pay for prenatal screening test, or because of the financial incentives for private prenatal services. Nevertheless, this raises concerns about the provision of inequitable health services, where only those with financial resources can afford prevention of genetic conditions using prenatal screening.[48] This further highlights the importance of national screening programmes in developing countries to ensure that less privileged families are not further disadvantaged by lack of access to genetic technologies.

The findings should be interpreted with caution as our study was conducted in a large but specific geographical area with a convenience sample of obstetricians with interest in advances in their field. Participants were self-selected, therefore, may have had a positive bias towards NIPT. Also, they completed the questionnaire after a conference/workshop which included a one-hour session on NIPT, which may have skewed the findings toward a greater interest in NIPT. A study capturing the views of participants nation-wide and in other developing countries could further enhance our understanding of the ethical and social implication of NIPT. Nevertheless, this study is the first to explore the views of obstetricians about NIPT in a developing, Islamic country. Qualitative research approaches could provide a more in-depth understanding of the reasons for the views expressed by the obstetricians in this study. Furthermore, research is needed with a wider range of stakeholders, including the views of service users and individuals responsible at a policy level for regulating and developing guidelines for the use of genetic technologies. Nevertheless, our study with obstetricians highlights the importance of various important points for implementing NIPT in developing countries.

Participants generally supported the introduction of publically funded prenatal screening and the implementation of NIPT for various conditions, but raised concerns about social implications. They also highlight the educational and training needs of obstetric professionals and the importance of developing an infrastructure for the provision of patient information and genetic counselling to mitigate social pressure and support women to make informed reproductive choices.

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