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Parental Experiences of Prenatal Whole Exome Sequencing (WES) in Cases of Ultrasound Diagnosed Fetal Structural Anomaly

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Conflict of interest

The authors are unaware of any potential conflict of interest.

What is already known about this topic?

- Prenatal WES for genetic diagnosis is possible, but little is known regarding parental experiences of prenatal sequencing

What does this study add?

- Parents require specific information to help them decide whether to undergo WES for prenatal diagnosis
- Appropriate counselling is essential for informed consent
- Parents require explanation about what WES might identify, and how and when findings are returned

Abstract

Objective

To explore parental experiences of WES for prenatal diagnosis, and ascertain what influenced their decision-making to undergo testing.

Method

Twelve women comprised a purposeful sample in a series of semi-structured interviews. All had received a fetal anomaly diagnosis on ultrasound. A topic guide was used, and transcripts were thematically analysed to elicit key themes.

Results

Five main themes (parental experiences of prenatal WES, need for information, consent/reasons for prenatal WES, sources of support for prenatal WES, and return of WES findings to families) emerged, some with multiple sub-themes.

Conclusions

Parents desired as much information as possible and appreciated information being repeated, and provided in various formats. Many struggled with clinical uncertainty relating to the cause and prognosis following a fetal anomaly diagnosis, and found it difficult to balance the risks of invasive testing against their need for more definitive information. Parents trusted their clinicians and valued their support with decisions in pregnancy. Testing was sometimes pursued to reassure parents that their baby was 'normal' rather than to confirm an underlying genetic problem. Parents were motivated to undergo WES for personal and altruistic reasons but disliked waiting times for results, and were uncertain about what findings might be returned.

Key words: Prenatal; whole exome sequencing; parents views

Introduction

Structural anomalies are diagnosed by ultrasound in up to 3% of pregnancies[1]. Fetal outcome is variable depending on the type of abnormalities identified, and the underlying genetic aetiology[2]. Determining the potential cause of fetal anomalies enables a more accurate diagnosis and provides prognostic information relating to

the pregnancy and the likely risk of recurrence [2]. Genetic testing is available for parents following the identification of a fetal anomaly and recent advances in molecular genetics are enabling increasingly detailed prenatal genetic investigation[3]. Prenatal genetic diagnosis is of significant value to parents and can assist with prospective planning for optimal perinatal management[4]. It may also provide a means to inform parental decisions regarding the continuation or termination of an affected pregnancy. Currently in the UK prenatal genetic testing involves increasingly routine QF-PCR (Quantitative Fluorescence-Polymerase Chain Reaction) and CMA (Chromosomal Microarray) to identify chromosomal differences and variations in copy number (CNVs). Targeted genetic sequencing of exonic regions is used to detect single nucleotide variants (SNVs) associated with various single gene disorders, but this modality has limited potential to identify CNVs. Whole genome sequencing (WGS) approaches are beginning to be used and have the ability to detect CNVs.

Next-Generation Sequencing (NGS) and the Prenatal Application of Whole Exome Sequencing (WES) Approaches

NGS applications are broadening the scope of prenatal diagnosis to identify the genetic aetiology of sporadic and inherited disease[5] and are revolutionising current practice in prenatal diagnostics[6]. Sequencing analysis of trio (fetal and biparental) DNA can identify genetic alterations that are potentially causative of fetal abnormalities, but this technology is only recently being evaluated within prenatal medicine. WES captures the majority of regions that encode proteins to identify SNVs and small insertions and deletions (indels)[5]. As a technique it has proved useful to the diagnosis of known genetic disease and to the discovery of novel

disorder genes,[7] and is increasingly being used to diagnose rare Mendelian conditions (when standard tests are uninformative)[8]. The use of WES in prenatal diagnosis is potentially advantageous as its accuracy enables personalised care, prospective risk assessment and preventative fertility treatment, reproductive genetic counselling and family planning[9]. As such, if a definitive diagnosis is made this testing may aid understanding of aetiology, potential co-morbidities and risk of recurrence. However, NGS, in the prenatal setting, presents potential challenges around the interpretation of results, especially if positive results are not thought to be 'causative' or are of unknown significance. The detection of these secondary and/or incidental findings (ICFs), may have significant and morbid emotional effects on the parents and also impact negatively on parental decision making in the prenatal setting.

Several studies involving WES in patients with Mendelian disease have demonstrated a diagnostic yield in the order of 25%[10-11]. This indicates that WES is complementary to conventional prenatal diagnostic techniques[12]. Research relating to the use of genetic sequencing for prenatal diagnosis in on-going pregnancy is limited,[4] however, the feasibility of WES in prenatal diagnostics has been demonstrated in small case series[3,12,13]. Survey data involving 186 expectant parents in the USA demonstrated that 83% thought that prenatal WES should be offered,[14] and research into the views of fifteen women with non-continuing anomalous pregnancies found that they had high hopes and expectations of WES, despite testing enabling a diagnosis in only 1 in 3 (30% of cases)[15].

Successful implementation of WES for prenatal diagnosis would require rigorous health economic assessment, and would be dependent upon the development of

rapid analytical and interpretation pipelines[12]. Sequencing findings would need to be available within a timeframe that would assist parents to make informed decisions relating to the affected pregnancy, and this will only be possible when the knowledge base relating to the genetic causes of prenatal structural anomalies is significantly developed[12]. The challenge of prenatal WES will be the integration of sequencing analysis into prenatal diagnostics as part of a responsible and ethical framework for clinical practice[2]. Currently, the PAGE consortium project funded by the Department of Health/Wellcome Trust is prospectively recruiting parent/fetus trios across the UK to investigate the prenatal use of WES as a diagnostic tool in structurally abnormal fetuses[16]. The study will analyse ~1000 trio whole exomes with the aim to elucidate the relative contribution of different forms of genetic variation to prenatal structural anomalies.

As the use of WES increases, and transfers from the research setting to routine care, it will be important to ensure a streamlined approach to the integration of genomic analysis to existing prenatal care pathways. This transition will require an understanding of parental acceptability and expectations around sequencing analysis for prenatal diagnosis following discussion with parents who have personal experience of this type of genetic testing in pregnancy. These parents will provide a unique perspective on their experiences as it is important to ensure that this technology is translated into clinical care because parents consider it to be of value. The views of parents who have undergone genetic sequencing for prenatal diagnosis have not been formally explored using qualitative interview methodology. The aim of this research was to gain insight into the experience of parents who have undergone prenatal WES following a fetal anomaly diagnosis, to understand more about what

influenced their decision-making to have testing, and elicit their beliefs around how they perceived WES to be of potential benefit. Qualitative methods allow for exploration of parental experiences, beliefs and feelings around the use of prenatal WES in a way that quantitative methodology cannot. It is important to understand parental views around prenatal sequencing to inform the routine use of these technologies in the future.

Method

A purposeful sample[17] (i.e. parents who had undergone WES for prenatal diagnosis following enrolment in the PAGE Study[16]) was selected to participate in this research. All parents had received focussed pre-test counselling for approximately one hour from a fetal medicine specialist regarding standard invasive prenatal testing options (QF-PCR and CMA), non-invasive prenatal testing (NIPT) for common aneuploidy, and WES as part of the PAGE Study. All were informed prior to testing that trio analysis (biparental/fetus) would be performed and that results would not be available within the timeframe of their pregnancy. It was also explained that only pathological findings considered to have contributed to the fetal phenotype would be returned, and that no uncertain, secondary or incidental information would be reported. They were also told that WES could potentially detect up to 10% more causes for fetal structural anomalies above standard testing based on exiting evidence. Fifteen women were approached at random by EQJ (research midwife) during their appointments at the Birmingham Women's Hospital Fetal Medicine Centre and asked to participate in an interview, three of whom declined without giving a reason, thus the study sample composed twelve women (Figure 1). It was anticipated that if data saturation was not reached after twelve interviews then more

interviews would continue until data saturation was achieved. Interviews were undertaken either at the hospital or at home depending on parental preference. A topic guide was used to guide questioning, and interviews were carried out by EQJ with each interview lasting approximately 30 to 45 minutes. Development of the topic guide was informed by related focus group research with stakeholders undertaken by EQJ and others[18]. Women were interviewed alone, or with their partner/or other close family member. All women spoke English although this was not a criterion for inclusion. The timing of interviews varied, but all were carried out within two weeks of parents giving consent for WES. Issues explored with parents included their personal experience of prenatal genetic testing and diagnosis, and what they remembered and understood regarding WES. Parents were asked about their expectations and concerns relating to prenatal genetic sequencing, and about the factors that influenced them to undergo testing, including the information they required to inform their decision. Interviews were digitally recorded and transcribed. National Research Ethics Service approval to undertake this study was granted by West Midlands - South Birmingham Committee (REC Reference 14/WM/0150).

Analysis

Analysis of the interview data followed a standard thematic approach[19]. Transcripts were read by EQJ to enable familiarisation. Using an inductive process[20] the transcripts were then coded for similarities and differences in content to develop a coding frame. Encompassing key themes with underpinning sub-themes were produced by combining the identified codes. Two transcripts were independently read by SCH (clinical co-facilitator for aforementioned focus groups and interview design) who similarly used thematic analysis to elicit themes[19]. The coding frame

developed by EQJ was shared with SCH and was subsequently modified. The coding frame and agreed themes were shared with SMG (medical sociologist). Two further transcripts were analysed by SMG using the established coding frame. Further amendments to the coding frame were not thought necessary as a result of this analysis. All three researchers met to reach a consensus that the themes identified were indeed reflective of the accounts provided. A rapid analysis of the interview transcripts was then undertaken by EQJ to ensure completeness and assess for data saturation[19]. A consensus decision by the three researchers was made that data saturation had occurred and that no further interviews were required.

Results

Participants were diverse with regard to age, ethnicity, parity and gestation, and had varying diagnoses of both isolated and multiple fetal structural anomalies (Figure 1). Women were aged between 21 and 38, and identified themselves as Caucasian, Black African or Asian, with Caucasian women comprising 75% of the sample. Of the 12 women interviewed 7 (58%) were multiparous and gestational ages ranged from 12 to 38 weeks. There was an equal split between isolated and multiple structural abnormalities and the prognosis for fetuses were variable and sometimes uncertain.

Five main themes emerged some with multiple sub-themes (Figure 2).

Theme One: Parental experiences of prenatal WES

Parents sometimes struggled to balance the risks of invasive testing against the perceived benefit of receiving a genetic diagnosis, particularly if there was uncertainty relating to the ultrasound features and the prognosis for the baby (this

was especially true if there was a previous history of miscarriage and any associated traumatic memories)

> *"It was more the risk factor because I had a miscarriage last year and it was really horrible so we didn't want to go through that again, especially as I was well over 20 weeks and into my second trimester and the baby was fully formed, so that was quite worrying but it wasn't so much for the results" (Interview 4 – Mother)*

Parents felt shocked when first told that their baby had a congenital difference, but this initial shock was often replaced with on-going anxiety. Some said it felt as though a 'heavy weight' had been placed upon them, and found the experience to be extremely scary. Parents appeared to worry more about the uncertain prognosis for the baby and less about the genetic findings that testing might identify. Many remembered feeling overwhelmed by the different tests available, and felt that their worries and concerns were compounded because they had so much to think about at the time:

> *"It was scary to be honest with you, all the different tests and constant worry. It was worrying because we didn't know what she (baby) would look like or anything like that" (Interview 2 – Father)*

Self-blame that they had done something to have caused the fetal anomaly was a common parental concern, thus a desire for reassurance that this was not the case was reported. All parents described that they trusted their clinicians and valued receiving their clear explanations. Parents described that they were assisted in their decision-making when they felt supported by clinicians, and believed that any

prenatal testing options discussed by the consultant overseeing their care would be relevant and useful which reassured them:

> *"We thought that it would give us some reassurance and help us plan and prepare for the future" (Interview 4 – Father)*

Some parents described how they tried to remain hopeful for a good pregnancy outcome, but also felt that they would love the baby regardless of any disability they may have. Some remembered consciously blocking out their concerns in an attempt to keep positive, believing that searching out more information would only serve to exacerbate their worry. When faced with various options, parents felt that they could make difficult decisions if they were not pressurised and were given enough time:

> *"I think we've tried to blank quite a lot of it because we don't want to be negative. When she is here we will cross that path won't we?" (Interview 2 – Mother)*

Theme Two: Need for information

A desire for information to understand more about the anomaly affecting their baby and the different testing and treatment options available was universally reported by parents. Parents needed to ask lots of questions of their clinicians as they tried to balance the pros and cons of testing:

> *"More information is all good because it helps us understand whatever it is. You can prepare yourself and your family and do what you possibly can with the information that you are given" (Interview 1 – Father)*

A need for repetition of complex information was also evident as parents found it difficult to fully understand everything that they were told at the initial consultation. Discussion and explanation on more than one occasion was found to be helpful, and parents appreciated receiving clinical details in written format relating to the specific anomalies identified:

> *"Some things you don't understand, some of the things the doctor says" (Interview 2 – Mother)*
>
> *"But when they break it down into smaller (pieces), all these big words like, and obviously we don't know what they mean, but they do break it down" (Interview 2 – Father)*

Theme Three: Consent and reasons for prenatal WES

Desiring more information and a wish to rule out as much as possible was a key motivator for parents to undergo prenatal testing. Parents perceived WES as a more detailed assessment to find out additional genetic causes for the anomalies affecting their baby that are not tested for routinely. They considered more information to be the best thing for parents and the baby and this was often the main reason for testing:

> *"It was going to test for more than everything else, and if there was anything rare that it is more likely to pick that up, and he explained that it will take much longer" (Interview 10 – Mother)*

Parents were aware that testing involved looking for differences and similarities between their individual DNA and the DNA of their baby. It was understood that the testing would not benefit the current pregnancy (because results would not be

reported back within the timeframe of pregnancy), but thought that it may be helpful for the baby when older, or if it could provide information for future pregnancy planning:

> *"It was to try and work out if there is anything between us (parents) that has caused the anomalies. I do not know whether it searches for one or both or whatever, but just that it is trying to find out if there is anything that is within either of us that has made these things happen in the baby" (Interview 3 – Mother)*

Parents were sometimes uncertain about what was actually being tested for or ruled out and would have appreciated hearing about some example conditions. Most felt that it was better to know about any genetic causes and hoped that the testing would provide answers which would be reported back to them:

> *"I would like to know about what other things they test for because I asked them and they said they would test for over 200 things but I would have liked examples because that was still worrying me" (Interview 5 – Mother)*

Parents described their decision to have prenatal WES as an opportunity to help others in the future. Altruistic motivations involved feeling that it was important to gather more information on the genetic causes of fetal anomalies, and viewed their participation as a means to contribute to research and the progression of medical knowledge:

> *"I was kind of contributing to something really, to help others in the future. It is the only way you are going to learn and evolve in the medical field. If you can*

achieve anything with it then I would be more than happy" (Interview 7 – Mother)

Theme Four: Sources of support for prenatal WES

Electronic and written sources of support were helpful to parents when faced with the decision of whether to undergo prenatal sequencing. Many opted to avoid the internet due to a perceived risk of inaccurate information. Parents felt that some internet sources showed the extremes of disease and were not always relevant. Some accessed NHS websites and Wikipedia feeling that these were more trustworthy sources. Information leaflets on specific conditions were generally found to be helpful:

"We got advice before we came here as well to steer clear of the internet because obviously you get a lot of misinformation, so I kind of took that to heart as it sounded quite sensible so I have not really been googling" (Interview 1 – Father)

Interactive sources of support were reported to be helpful and parents valued being able to ask questions directly. One couple described that they would have liked to speak to other parents with similar experiences, suggesting that a workshop where they could find out more information and ask questions could be a forum for this:

"Maybe a workshop held by the hospital or midwife that is solely dedicated to this as part of their job, where they would have all the knowledge and can educate families, and where parents can come together and share their experiences" (Interview 4 – Father)

Theme Five: Return of prenatal WES findings to families

Presently, the prenatal WES 'clinical pipeline' within the PAGE Study[16] takes up to twelve months. The delay in receiving results was felt by some parents to have prolonged their worry and anxiety. Parents still wished to have WES even though they knew that there would be a significant wait for results believing that they would still rather know than not know about any relevant genetic findings. Many described that having this information eventually would help their understanding and better equip them to cope and prepare for any challenges ahead. Some felt that more information in time relating to the risk of recurrence was worth waiting for and would possibly assist them with future pregnancy planning:

> *"That was what I hated, just waiting (for results)" (Interview 5 – Mother)*

Some parents were uncertain regarding the process by which results would be returned and would have appreciated having this better explained to them. Some parents preferred to return to the hospital and have the results explained by familiar clinicians face-to-face. All were happy for their information to be stored and shared with other clinicians and researchers involved in prenatal diagnosis, and although some said that they preferred their personal information to be anonymised, others were less concerned about protecting their identity:

> *"If there was anything (genetic results) we would like to come back here (hospital) and sit down and discuss it face-to-face with you guys (medical team) because we are comfortable with you" (Interview I – Mother)*

Conclusions

This is the first qualitative interview study exploring parental experiences of WES for prenatal diagnosis. The findings are important because they are novel in this context

and contribute to a limited body of evidence relating to parental experiences of prenatal sequencing in structurally abnormal fetuses. Given the potential for NGS techniques to detect genetic alterations that are causative of various developmental fetal anomalies, it is likely that prenatal sequencing will be integrated into existing prenatal care pathways in the foreseeable future. Transition from the research setting to the clinic will require an assessment of the acceptability of prenatal sequencing for genetic diagnosis to evaluate if testing is desirable to parents. This research has highlighted the views of parents who have undergone WES for prenatal diagnosis, and provided insight in to their decision-making to proceed with testing, and what they perceived the potential benefits of WES to be. Facilitating appropriate consent for testing was highlighted by parents as extremely important, who felt that they needed clearer information regarding what WES might identify, and what, when and how results would be returned. If WES is to be routinely available for prenatal diagnosis this will require the development of national and international guidance that encompass the consent procedure, as well as the option for parents to opt in or out of receiving information which is not directly related to the prenatal findings (i.e. the primary indication for testing) both for the unborn baby and for themselves[13]. Inevitably, prenatal WES and the interpretation of results will become more rapid and clinical usefulness will be significantly improved. Likewise, contribution of parental views around prenatal WES will assist with streamlining the clinical use of the technology for diagnostic purposes. However, CMA research indicates that variants of uncertain significance (VUS) may continue, in a small number of cases, to have morbid emotional consequences[21,22]. The need for public debate around the use and potential benefits, as well as the drawbacks of prenatal genetic diagnosis is

clear, to facilitate the general acceptance and integration of sequencing techniques into routine prenatal care[23].

Limitations

It is acknowledged that the views expressed by some parents (such as the need for more information to balance risks, feelings of self-blame, and consciously blocking out concerns to remain positive), are likely to be applicable to any couple whose baby has ultrasonographically detected fetal anomalies irrespective of whether they decide to undergo prenatal testing (including WES). As such, these particular findings are not necessarily unique in this context. This research explored the experience of parents who underwent WES for prenatal diagnosis at one large UK fetal medicine centre and parents at other centres (within the UK or internationally) may have different views. The opinions of parents who declined WES are similarly not well represented. It cannot be assumed therefore that the findings are applicable to all parents; moreover they may not reflect the views of parents who decline genetic diagnosis using invasive methods. Further research that considers the opinions of parents who decline prenatal sequencing is needed. Ethical approval for the PAGE Study[16] only permitted the return of results to families considered to be pathogenic and contributing to the prenatal phenotype, thus it was not possible to explore parental views around the return of VUS and ICFs. Parental opinions regarding the return of VUS and ICFs will be explored in a planned further phase of work.

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