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Views of adults with 22q11 deletion syndrome on reproductive choices

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Keywords:	22q11 deletion syndrome, prenatal diagnosis, preimplantation genetic diagnosis
Search Terms:	

Table 1. Participant characteristics.

Participant identifier	Sex	Age	Parent	Phenotype
P01	F	25		Palate dysfunction, scoliosis, previous speech delay.
P02	F	28		Congenital heart disease
P03	F	40	Yes	Mild intellectual disability
P04	M	20		Cleft palate, scoliosis, mild intellectual disability
P05	F	25		Mild intellectual disability, scoliosis, short stature
P06	F	40		Congenital heart disease, arthritis
P07	F	30	Yes	Mild intellectual disability
P08	F	30	Yes	Mild intellectual disability
P09	F	30		Mild intellectual disability, congenital heart disease
P10	F	32		Intellectual disability, cleft palate, hypothyroidism, hearing impairment
P11	F	50	Yes	Hypocalcaemia, scoliosis, mild intellectual disability
P12	M	32	Yes	Hearing impairment
P13	M	50		Congenital heart disease, hypocalcaemia

Indicative qualitative interview schedule

1. Opening

(Introductions) - [Greet participant/volunteer, check environmental factors/comfort, check what they prefer to be called, introduce self and role]

I would like to ask you some questions about your 22q11DS, your understanding of genetic testing in 22q11DS, and your views about reproductive medicine options in 22q11DS. First, I will explain more about the study and this interview. Please let me know if you have questions at any point.

(Purpose) - I hope to use the information we gather as part of a research study exploring people's views and feelings about reproductive options in 22q11DS, and we hope the information we collect will feed into recommendations for 22q11DS. Therefore, it would be helpful if you could share as much as feels comfortable for you.

(Time) - My estimate is that this interview could take around 30 to 60 minutes. However, it could be more or less depending on your communication style and how much you have to say in response to each question. We can take as many breaks as you need to.

Confirm background details of interviewee – age, employment status, who in the family is affected by 22q11 deletion syndrome.

2. Main interview topics

A. I would like to start by asking you to tell me about your understanding of 22q11 deletion syndrome?
   - How did you find out you had 22q11 deletion syndrome?
   - Prompts to ask about symptoms, natural history, treatments, impact on family.

B. Can you tell me about your understanding of the genetics of 22q11 deletion syndrome? What is the genetic cause of 22q11?
   - Understanding of genes and chromosomes

C. Based upon your understanding of 22q11DS is anyone else in the family at risk of having the condition?
   - Can 22q11 deletion pass from mum/dad to child?
   - Do you know what the chance is?
   - What are your views on having a family?

D. How was the information on 22q11DS inheritance and genetics shared in your family?

   - Prompts: how did they learn about genetic inheritance of it? Have they told anyone?

E. Have you heard of any pregnancy options which can ensure that a baby is born without a specific genetic condition?
   - Prompts: have they heard of prenatal diagnosis (CVS, amniocentesis)?
   - Have they heard of non-invasive prenatal testing (NIPT)? What do they think of it.

F. Have you heard of a treatment called preimplantation genetic diagnosis?

   - Prompts: why do you find e.g. PGD acceptable/unacceptable?
   - Do you think PGD should be offered/discussed with people with 22q11DS?
   - Do you think PGD should be offered on the NHS for people with certain genetic conditions?

G. What do you think of the currently available information leaflets on PND/PGD?
   - Prompts: has PGD etc been discussed with them in the past? By whom? Have they seen any information leaflets and what did they think?

H. How would you prefer to get information on PND/PGD/NIPT?
   - What type format of leaflet would you like? Heard of infographics?
   - What is your view of internet based/smartphone based resources for information?
   - What problems accessing/understanding information do they have?

I. What information do you think people with 22q11DS should be told about their chances of passing it on to their children?

J. What are your views on people with 22q11DS being made aware of pregnancy options such as PND/PGD/NIPT?

3. Close

I have now asked all of the planned questions. Is there anything else you think would be helpful for me to know about your experiences or your views? Do you have any questions for me?

Thank you very much for taking part in our study. If you have any questions after leaving here today, please feel free to contact the study team. Our contact details are on the information leaflet that I provided.

Submitted to *American Journal of Medical Genetics Part A* as a *Research Letter*

Views of adults with 22q11 deletion syndrome on reproductive choices

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To the Editor:

The 22q11 deletion syndrome (22q11DS, OMIM 611867) is one of the most common genomic disorders, affecting 1/2500 - 1/4000 people (Bassett et al, 2005). 22q11DS is a multisystem disorder associated with neuropsychiatric features (depression, anxiety, schizophrenia), intellectual disability (85-90% of affected individuals), congenital heart disease and endocrinopathies. In 90% of people with 22q11DS the deletions have arisen *de novo*, while 10% are inherited. 22q11DS follows an autosomal dominant pattern of inheritance. Several reproductive medicine options are available for adults with 22q11DS who wish to have an unaffected child. Prenatal testing (with the option of termination of affected pregnancies) or preimplantation genetic diagnosis (PGD) are funded in the United Kingdom National Health Service (NHS). PGD involves testing an embryo (created by *in vitro* fertilization) at the blastocyst stage for the genetic variant causing a disease. Embryos which lack the genetic variant are then implanted. Around 30% of cycles will result in a live born baby free from the inherited disease in the family. Adverse pregnancy outcomes (including small for gestational age and stillbirth) have been documented in women with 22q11DS (Chan et al, 2015), but little is known about the opinions of people with 22q11DS on reproductive medicine options. The current study explored reproductive decision making and attitudes to reproductive genetic testing in adults with 22q11DS.

An inductive qualitative design using semi-structured interviews was used, to explore the views of adults with 22q11DS on reproductive medicine options. Adults (>18 years) with 22q11DS (diagnosed by comparative genomic hybridisation) were recruited from the Yorkshire and Humber Genome Medicine Service (15 were invited and 13 participated, 86% response rate). Research Ethics approval was granted by Leeds East Research Ethics Committee (16/YH/0026). The Standards for the Reporting of Qualitative Research guidelines were followed (O'Brien et al, 2014). Thirteen one-one interviews (table 1) were performed based upon a semi-structured interview guide (see supplementary data). Interviews were audio recorded (with consent) and transcribed verbatim. Nvivo 12 was used

for analysis. Framework analysis was undertaken (Gale et al, 2013). Line by line coding of the transcripts was undertaken, primarily by one author (AMcN). A second author (MF) repeated and reviewed the coding on 20% of the transcripts to achieve agreement on definition of codes. "Charting" was then performed to summarise interview data by code for each participant. Thematic saturation was reached after 13 interviews. An author with 22q11DS (RL) provided an expert by experience view on 22q11DS to comment on the face validity of the findings.

After reviewing all 13 transcripts, 3 overarching themes emerged: 1. Personal and family impact of 22q11DS, 2. Attitudes towards reproductive medicine, and 3. Lack of accessible information.

Theme 1: Personal and family impact of 22q11DS

The interviews revealed that 22q11DS has an impact on family life in ways which could influence reproductive decision making. All participants were aware of the range of clinical features associated with 22q11DS. A typical example being the statement from P4: *"it can affect all sorts…like heart conditions…learning difficulties….speech…hearing…erm kidneys….all sorts of things*". The health problems associated with 22q11DS were recognised as creating challenges for day-to-day family life. Both the intellectual disability ("*it takes 10 times longer to do everything...if I say I'll do it now I will forget about it and it can be really frustrating*" [P4]) and physical symptoms associated with 22q11DS were identified as problematic. Having 22q11DS was associated with needing significant support from family members ("*my mum literally carries me through the day sometimes*"[P5]) and the emotional strain on carers was apparent ("*it's only as I've got older that my parents have let slip about the emotional side*"[P9]).

Participants' experiences of living with 22q11DS, and the impact of 22q11DS on family life they describe, clearly influenced their reproductive decision making. Participant P2's

decision not to have children was "*defined by 22q11*" because "*I don't want my kids to go through what I've gone through*". Participants were concerned that the clinical variability of 22q11DS might result in them having a severely affected child. P8 stated: "*I would have been scared they would have been poorlier and I would have felt bad bringing in a child …that's got difficulties*" and P9 *"it is different for everybody so it is hard to sort of know what the outcome is going to be."* Participants reported additional challenges faced by people with 22q11DS in acting as parents. Physical impairments associated with 22q11DS were described as troublesome. For example, P12 stated "*it can be quite stressful because I'm hearing impaired, erm, it can be quite difficult with my hearing ….especially when I'm trying to understand my son with his speech*". P8 identified that caring for their children was "*a lot of hard work...especially when you've got it (22q11DS) yourself*". Participants were also concerned about the extra challenges of parenting a child with 22q11DS. P4 stated: "*with a normal child you can do everyday stuff but if you do have a child with 22q, you're not gonna know what type it is until they get to a certain age…they could have learning difficulties or heart problems…..literally anything*". Participants universally described the decision to have children as a highly personal one. With the health of the 22q11DS parent, their ability to function independently and the strength of their support network being seen as key factors.

Theme 2: Attitudes towards reproductive medicine

Despite the concerns about the implications of having a child with 22q11DS, there was a universal reluctance to terminate a pregnancy affected by 22q11DS. A moral argument was advanced with the presence of 22q11DS not being regarded as a valid reason to have a termination of pregnancy ("*I don't believe in aborting children because they've got a genetic condition*"[P3]), since individuals with genetic conditions should not be discriminated against. Selective termination of 22q11DS was also regarded as being potentially "*a bit designer baby*"(P5). The participants' identity as people with 22q11DS also clearly influenced their

views on termination as one reflected "*if my parents had done that with me then I would not be here*"(P5) and "*me being here I'm like "please don't do that (termination) because its my one chance at a life*"(P5).

These attitudes to termination of pregnancy were reflected in the participants' negative views on prenatal diagnostic techniques such as amniocentesis. The risks to the developing baby of inducing miscarriage was repeatedly mentioned ("*I don't agree with it because it can cause miscarriages*"[P3], "*I wouldn't have wanted it done because I had the miscarriages*"[P6]). There was also a perception that prenatal diagnostic techniques could physically damage the baby. The participants understood that prenatal diagnosis was chiefly performed to facilitate termination of foetuses with a genetic condition. The participants' opposition to terminating foetuses with 22q11DS was the principal reason for their negative views on prenatal diagnosis ("*just because of the termination side*"[P10]) with recognition of the "*emotional side effects*"[P1] and "*strain on emotional wellbeing*"[P1].

PGD was viewed more positively. Many participants stated that the main reason PGD was acceptable to them was because it did not involve termination. P10 stated: "*it is only the embryos you are creating rather than creating the child*". PGD was also felt to be acceptable because "*it's not actually affecting your baby while its inside you*"[P7] and "*If we could have a test done before pregnancy that would be better from my emotional standpoint*"[P1]. The high degree of reliability of PGD in selecting embryos without genetic disorders was also seen as attractive: "*I think that is really good I am really determined not to have a child with VCFS (velo-cardio-facial-syndrome, a synonym for 22q11DS)*."[P1]. These positive views were balanced by an understanding of the challenges of PGD. There was awareness of the limited 3-cycles of NHS funding for PGD ("*Also IVF….how much it was like £1200 for someone per cycle and the rate of conception is quite low*"[P2]). The potential health risks to the prospective mother were recognised. Concerns about whether people with 22q11DS could cope with the PGD process were also raised: "*erm it's probably be too much. Too*

much to cope with I think. It would be a lot to take in.."[P4]. In contrast to the other participants, one participant raised a moral objection to PGD ("*its wrong…why should you be bothered what condition your baby has*"[P3]). In general, participants did recognise the complexity of the different viewpoints surrounding reproductive medicine options for genetic diseases and displayed good conceptual understanding of relevant issues, with P5 stating "*it's a hard one…it's got lots of morals to it I haven't unravelled*".

Theme 3: Lack of accessible information

Currently available information resources on reproductive medicine options are not designed for people with intellectual disability or sensory impairments. The information leaflets which participants had read were "*very long…I know my attention span isn't massive and I find it challenging to understand a lot of technical information*"[P1], with "*too much to take in*"[P10] and "*they are bit rubbish for people with 22q11 deletion*"[P2]. Participants identified that they had difficulty reading long information leaflets and processing the information ("*reading documents and reading leaflets and filling out forms can be quite tricky so it takes me a lot longer to do*"[P10]) and may need help to understand the information ("*I have to ask my mum for help because it doesn't sink in*"[P3]). Lack of understanding of 22q11DS among healthcare professionals was also identified as a barrier to information. P7 stated "*actually I think doctors just need to know more about 22q*" and P5 "*they've never even heard of 22q so they wouldn't have heard of this information and therefore the chances of me thinking about a family would be even narrower*". There was strong support for the benefits of receiving information on reproductive options in 22q11DS. Having the information was seen as increasing personal choice ("*Some people might want to have a termination or get more prepared….just gather information…but others might keep going*"[P8]). Access to information was also seen as reassuring ("*a comfort almost to someone who would have been worried about whether they'd pass the condition on*"[P5]) by making people aware of their options. There was universal support for all with 22q11DS being made aware of their reproductive options. However, the age at which to receive this information was disputed.

Many felt that age 16-17 was too young since "*would they understand it at 17? I know I probably wouldn't understand it age 17*"[P2] and *"unless they want to be a parent nothing's [information] gonna go in*". The preferred means of receiving this information would be in person with information resources given after a face to face discussion. This highlights the need for referral to Clinical Genetics for genetic counselling at an appropriate age for the individual to discuss these issues and receive information on reproductive medicine options.

To our knowledge, this is the only study reporting the views of people with 22q11DS on reproductive medicine options. The views on reproductive medicine options expressed by people with 22q11DS align with those reported from people with other genetic conditions. Prenatal diagnosis with termination of selected foetuses was viewed unfavourably in our cohort. Similar findings have been reported for a range of genetic conditions including myotonic dystrophy (Faulkner and Kingston, 1998) and inherited retinal disease (Ahmed et al, 2015). In general, PGD is pursued because of the desire for an unaffected child by a methodology avoiding termination (Genoff Garzon et al, 2018). For certain conditions, couples see a moral imperative to prevent transmission of a harmful genetic condition to offspring. The attitudes of 22q11DS participants were more varied. With some participants in our study seeing 22q11DS as being an integral part of their identity (Boardman and Hale, 2018) rather than a disease *per se*, and therefore not something to be screened out. While others clearly did not want an affected child - particularly if there was the possibility of them experiencing more difficulties than they themselves did. It might be that unaffected carriers of recessive conditions are more likely to view the genetic condition in their children as a "disease" and therefore have different views, for example, on the acceptability of termination of pregnancy. Decisions around PGD use are acknowledged as complex and influenced by factors such as personal medical history, personal beliefs and personal situation (e.g. financial) (Genoff Garzon et al, 2018). People with 22q11DS face additional challenges. Lack of awareness among clinicians may result in people with 22q11DS not being informed of reproductive medicine options. The information resources available on reproductive

medicine options were not deemed suitable for people with 22q11DS by the current cohort. This will inhibit informed decision making. Our study highlights the need for health services to have strategies to offer patients with genetic conditions such as 22q11DS information on reproductive medicine options. For example, by designing accessible co-produced information resources, offering access to genetic counselling and developing an informatics infrastructure for identification of individuals with 22q11DS who may benefit from discussion of reproductive options.

Acknowledgements

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Author Roles

AM – study conceptualisation, study conduct, writing manuscript. RL – study conceptualisation, editing manuscript. MF - study conceptualisation, study conduct, writing manuscript.

References

Ahmed, K., Ahmed, M., Potrata, B., Willis, T.A., Grant, H.L., Allsop, M.J., .., McKibbin, M. (2015). Patient attitudes towards prenatal diagnostic testing for inherited retinal disease. *Prenatal Diagnosis, 35*, 913-918.

Bassett, A.S., Chow, E.W., Husted, J., Weksberg, R., Caluseriu, O., Webb, G.D., Gatzoulis, M.A. (2005). Clinical features of 78 adults with 22q11 deletion syndrome. *American Journal of Medical Genetics Part A*, *138*, 307–313.

Boardman, F.K., Hale, R. (2018). How do genetically disabled adults view selective reproduction? Impairment, identity, and genetic screening. *Molecular Genetics & Genomic Medicine, 6*, 941-956**.**

Chan, C., Costain, G., Ogura, L., Silversides, C.K., Chow, E.W.C., Bassett, A.S. (2015). Reproductive health issues for adults with a common genomic disorder:

22q11.2 deletion syndrome. *Journal of Genetic Counseling, 24*, 810-821.

Decruyenaere, M., Evers-Kiebooms, G., Boogaerts, A., Philippe, K., Demyttenaere, K., Dom, R., .., Fryns, J.P. (2007). The complexity of reproductive decision-making in asymptomatic carriers of the Huntington mutation. *European Journal of Human Genetics*, *15*, 453–462.

Faulkner, C.L., Kingston, H.M. (1998). Knowledge, views, and experience of 25 women with myotonic dystrophy. *Journal of Medical Genetics*, *35*, 1020-1025.

Gale, N.K., Heath, G., Cameron, E., Rashid, S., Redwood, S. (2013). Using the framework method for the analysis of qualitative data in multi-disciplinary health research. *BMC Medical Research Methodology*, *13*, 117.

Genoff Garzon, M.C., Rubin, L.R., Lobel, M., Stelling, J., Pastore, L.M. (2018). Review of patient decision-making factors and attitudes regarding preimplantation genetic diagnosis. *Clinical Genetics, 94,* 22–42.

O'Brien, B.C., Harris, I.B., Beckman, T.J., Reed, D.A., Cook, D.A. (2014). Standards for reporting qualitative research: a synthesis of recommendations. *Academic Medicine*, *89*, 1245-1251.

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Currently available information resources on reproductive medicine options are not designed for people with intellectual disability or sensory impairments. The information leaflets which participants had read were "*very long…I know my attention span isn't massive and I find it challenging to understand a lot of technical information*"[P1], with "*too much to take in*"[P10] and "*they are bit rubbish for people with 22q11 deletion*"[P2]. Participants identified that they had difficulty reading long information leaflets and processing the information ("*reading documents and reading leaflets and filling out forms can be quite tricky so it takes me a lot longer to do*"[P10]) and may need help to understand the information ("*I have to ask my mum for help because it doesn't sink in*"[P3]). Lack of understanding of 22q11DS among healthcare professionals was also identified as a barrier to information. P7 stated "*actually I think doctors just need to know more about 22q*" and P5 "*they've never even heard of 22q so they wouldn't have heard of this information and therefore the chances of me thinking about a family would be even narrower*". There was strong support for the benefits of receiving information on reproductive options in 22q11DS. Having the information was seen as increasing personal choice ("*Some people might want to have a termination or get more prepared….just gather information…but others might keep going*"[P8]). Access to information was also seen as reassuring ("*a comfort almost to someone who would have been worried about whether they'd pass the condition on*"[P5]) by making people aware of their options. There was universal support for all with 22q11DS being made aware of their reproductive options. However, the age at which to receive this information was disputed.

Many felt that age 16-17 was too young since "*would they understand it at 17? I know I probably wouldn't understand it age 17*"[P2] and *"unless they want to be a parent nothing's [information] gonna go in*". The preferred means of receiving this information would be in person with information resources given after a face to face discussion. This highlights the need for referral to Clinical Genetics for genetic counselling at an appropriate age for the individual to discuss these issues and receive information on reproductive medicine options.

To our knowledge, this is the only study reporting the views of people with 22q11DS on reproductive medicine options. The views on reproductive medicine options expressed by people with 22q11DS align with those reported from people with other genetic conditions. Prenatal diagnosis with termination of selected foetuses was viewed unfavourably in our cohort. Similar findings have been reported for a range of genetic conditions including myotonic dystrophy (Faulkner and Kingston, 1998) and inherited retinal disease (Ahmed et al, 2015). In general, PGD is pursued because of the desire for an unaffected child by a methodology avoiding termination (Genoff Garzon et al, 2018). For certain conditions, couples see a moral imperative to prevent transmission of a harmful genetic condition to offspring. The attitudes of 22q11DS participants were more varied. With some participants in our study seeing 22q11DS as being an integral part of their identity (Boardman and Hale, 2018) rather than a disease *per se*, and therefore not something to be screened out. While others clearly did not want an affected child - particularly if there was the possibility of them experiencing more difficulties than they themselves did. It might be that unaffected carriers of recessive conditions are more likely to view the genetic condition in their children as a "disease" and therefore have different views, for example, on the acceptability of termination of pregnancy. Decisions around PGD use are acknowledged as complex and influenced by factors such as personal medical history, personal beliefs and personal situation (e.g. financial) (Genoff Garzon et al, 2018). People with 22q11DS face additional challenges. Lack of awareness among clinicians may result in people with 22q11DS not being informed of reproductive medicine options. The information resources available on reproductive

medicine options were not deemed suitable for people with 22q11DS by the current cohort. This will inhibit informed decision making. Our study highlights the need for health services to have strategies to offer patients with genetic conditions such as 22q11DS information on reproductive medicine options. For example, by designing accessible co-produced information resources, offering access to genetic counselling and developing an informatics infrastructure for identification of individuals with 22q11DS who may benefit from discussion of reproductive options.

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Author Roles

AM – study conceptualisation, study conduct, writing manuscript. RL – study conceptualisation, editing manuscript. MF - study conceptualisation, study conduct, writing manuscript.

References

Ahmed, K., Ahmed, M., Potrata, B., Willis, T.A., Grant, H.L., Allsop, M.J., .., McKibbin, M. (2015). Patient attitudes towards prenatal diagnostic testing for inherited retinal disease. *Prenatal Diagnosis, 35*, 913-918.

Bassett, A.S., Chow, E.W., Husted, J., Weksberg, R., Caluseriu, O., Webb, G.D., Gatzoulis, M.A. (2005). Clinical features of 78 adults with 22q11 deletion syndrome. *American Journal of Medical Genetics Part A*, *138*, 307–313.

Boardman, F.K., Hale, R. (2018). How do genetically disabled adults view selective reproduction? Impairment, identity, and genetic screening. *Molecular Genetics & Genomic Medicine, 6*, 941-956**.**

Chan, C., Costain, G., Ogura, L., Silversides, C.K., Chow, E.W.C., Bassett, A.S. (2015). Reproductive health issues for adults with a common genomic disorder:

22q11.2 deletion syndrome. *Journal of Genetic Counseling, 24*, 810-821.

Decruyenaere, M., Evers-Kiebooms, G., Boogaerts, A., Philippe, K., Demyttenaere, K., Dom, R., .., Fryns, J.P. (2007). The complexity of reproductive decision-making in asymptomatic carriers of the Huntington mutation. *European Journal of Human Genetics*, *15*, 453–462.

Faulkner, C.L., Kingston, H.M. (1998). Knowledge, views, and experience of 25 women with myotonic dystrophy. *Journal of Medical Genetics*, *35*, 1020-1025.

Gale, N.K., Heath, G., Cameron, E., Rashid, S., Redwood, S. (2013). Using the framework method for the analysis of qualitative data in multi-disciplinary health research. *BMC Medical Research Methodology*, *13*, 117.

Genoff Garzon, M.C., Rubin, L.R., Lobel, M., Stelling, J., Pastore, L.M. (2018). Review of patient decision-making factors and attitudes regarding preimplantation genetic diagnosis. *Clinical Genetics, 94,* 22–42.

O'Brien, B.C., Harris, I.B., Beckman, T.J., Reed, D.A., Cook, D.A. (2014). Standards for reporting qualitative research: a synthesis of recommendations. *Academic Medicine*, *89*, 1245-1251.