

Non-invasive prenatal testing – a new dawn in antenatal care

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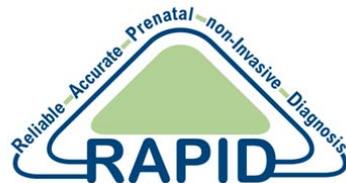
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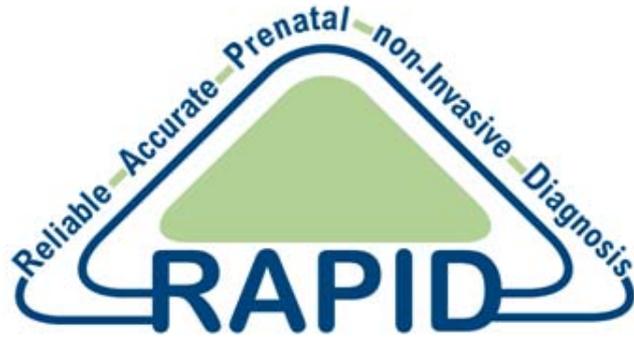
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NHS Trust



Reliable Accurate Prenatal non-Invasive Diagnosis



NIHR programme grant
RP-PG-0707-10107

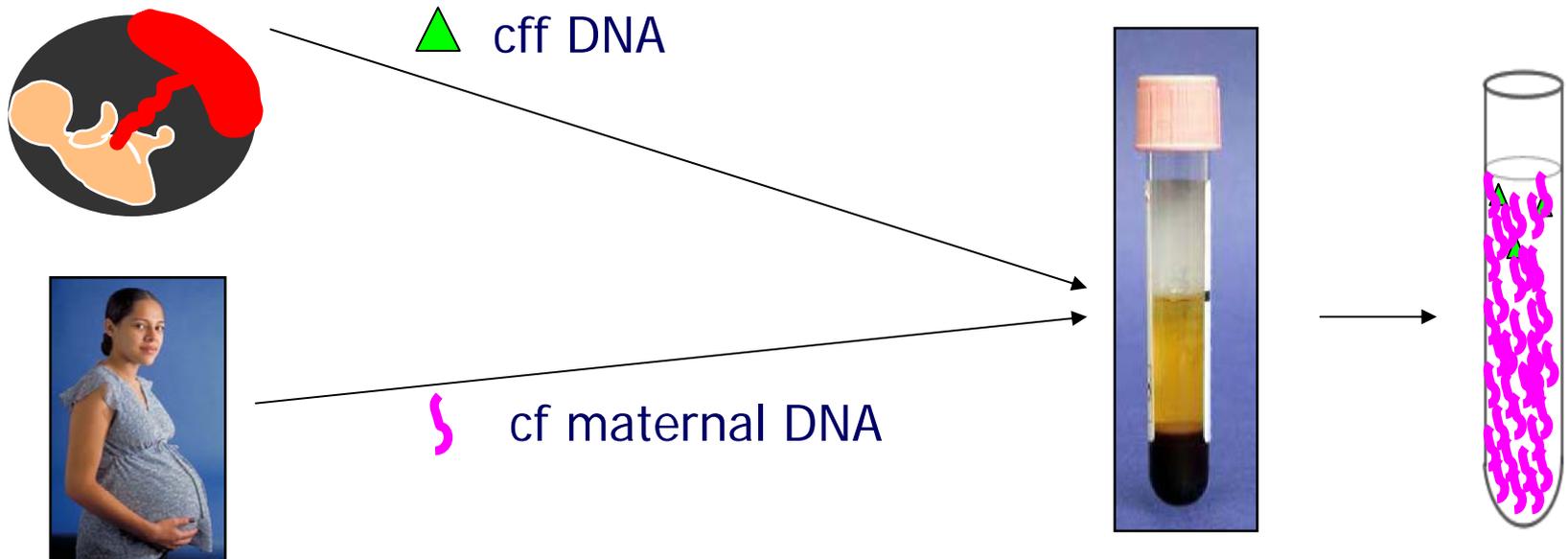
Goal: To improve the quality of NHS prenatal diagnostic services by evaluating early non-invasive prenatal diagnosis (NIPD) based on cell free fetal DNA and RNA extracted from maternal plasma.

Website: www.rapid.nhs.uk

Email: rapid@ich.ucl.ac.uk

Cell free fetal DNA

- Originates from trophoblast (placenta)
- Up to 10% of total circulating cell free DNA
- Free fetal DNA concentration increases as gestation progresses
- Detectable from 4-5 weeks (but not enough to do a test)
- Cleared from circulation within 30 minutes of delivery
- Recently shown that the entire fetal genome is represented (Lo et al 2010)



NIPD using cell free fetal DNA

Advantages over invasive testing

- No miscarriage risk
- Conducted earlier in pregnancy
- Shown to be cost neutral for X-linked conditions where invasive testing usually performed (as reduce number of invasive tests by 50%)

Potential problems

- Unreliable in multiple pregnancies (importance of ultrasound for dating and confirmation of singleton pregnancy)
- When used in early pregnancy, risks associated with 'vanishing twin'

Current applications NIPD in the UK

Current uses

- Fetal sex determination for X-linked conditions e.g. Duchenne muscular dystrophy
- RHD in Rhesus negative mothers
- De novo gene changes e.g. achondroplasia
- Dominantly inherited genes carried by an affected father e.g. Huntington's disease
- Recessively inherited genes where the parents carry different mutations e.g. some cases of cystic fibrosis

Technology in development

- Parents have same mutation e.g. CF; β -thalassaemia, sickle cell
- Down syndrome (currently available in USA, Hong Kong and China)

NIPD for fetal sex determination

- **Conditions that are X-linked**

- Serious conditions where women are likely to go on to have invasive testing e.g. Duchene muscular dystrophy (DMD)

Reduce invasive testing by up to 50%

- Haemophilia

Plan management of labour and delivery for “at risk” pregnancies

Guide the offer of invasive testing in male pregnancies

- **Conditions associated with ambiguous genitalia**

- Congenital adrenal hyperplasia (CAH): female fetuses at risk of virilisation of external genitalia and require steroid treatment

Reduce invasive testing by up to 50%

Allows early cessation of dexamethasone treatment

Aims

- Clinical value of NIPD clear. Currently no knowledge of service users' or health professionals' views and experiences of using this technology.
- Aim: Qualitative research to assess the views, experiences and preferences of:
 - Women and partners who have used NIPD for fetal sex determination or diagnosis or skeletal dysplasias
 - Health professionals who offer NIPD for fetal sexing for haemophilia
 - Carriers of single gene disorders including CF, sickle cell anaemia and beta-thalasaemia and health professionals with an interest in these conditions
 - Women who have either declined or accepted screening (and IPD) with a focus on NIPD for Down syndrome

Methods

- One-to-one qualitative interviews
- 48 women (and 6 partners) who are carriers of single gene disorders including:
 - Adrenoleukodystrophy
 - Androgen insensitivity syndrome
 - Becker muscular dystrophy
 - Charcot-Marie-Tooth disease
 - Congenital adrenal hyperplasia
 - Cystic fibrosis
 - Duchenne muscular dystrophy
 - Haemophilia
 - Pelizaeus-Merzbacher disease
 - Sickle cell anaemia
 - β -thalassaemia
 - X-linked hydrocephalus
 - X-linked mental retardation
 - X-linked severe combined immunodeficiency
- 40 health professionals (geneticists, sickle cell/thalassaemia specialists and nurses, midwives, genetic counsellors, haemophilia nurses)

Questions

- Reasons for using NIPD
 - Value of NIPD
 - Concerns about NIPD
 - Preference for how it should be offered in practice
 - Experience of using NIPD and decisions women made
 - What information is important to provide about NIPD
-
- Used thematic analysis to identify key issues



Overview

- Service users overwhelmingly positive about NIPD
- Valued a test that was early in pregnancy, safe, easy and accurate
- Highlighted importance of pre- and post test counselling by someone with specialist knowledge about the condition
- Preference for results on a range of aneuploidies including Down's syndrome



Reason for using NIPD

- Clarify need for invasive testing
- Prepare for having an affected child
- Haemophilia – majority to plan management of labour and delivery for male pregnancies
- CAH – inform need for steroid treatment in pregnancy

"I would like to know earlier so I am just that much more prepared." β -thalassaemia carrier

"Just to find out if it was a girl or a boy and if it was a boy then I knew I would have to have further tests to see if it was affected or not." DMD carrier

Value of NIPD – safe and easy

- Procedure posed no risk to mother or fetus
- Many blood tests during pregnancy
- Quick and simple procedure
- Psychologically easier than IPD or sexing scan – no visual acknowledgement of fetus during procedure

“Well because it was just a blood test, there wasn’t any risk for me or the baby.”
ALD carrier

“We asked them to turn the screen away because I didn’t want to see. I didn’t want to get emotionally attached”
Haemophilia carrier

Value of NIPD - timing

- Time to make a decision about IPD and termination
- Ensure invasive testing arranged at earliest opportunity
- Prepare mentally for possibility of having to terminate
- Prepare for having a child / another child affected by condition
- Decision-making easier in 1st trimester

"The earlier the better." CF carrier

"I think it gives you time to prepare...I feel that I had some time to go through the stage of getting upset and crying, getting emotional before the amnio and then going, no this is what I'm doing. So having those few weeks was really valuable in that way."
DMD carrier

Value of NIPD - control

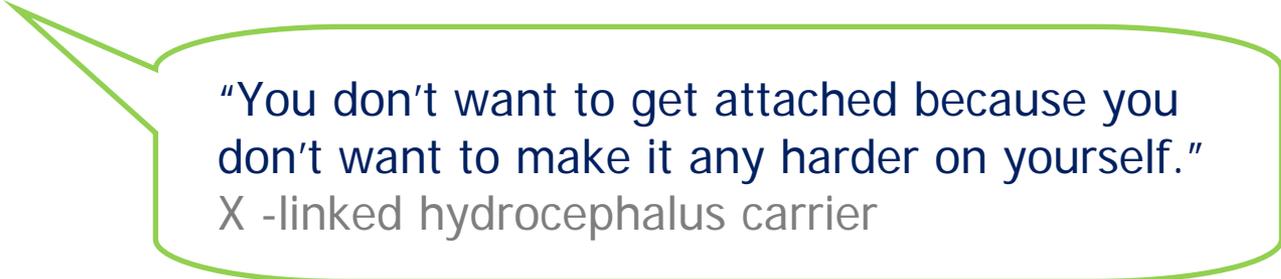
- NIPD empowered women to regain, at an early stage, sense of control over their pregnancy
 - Increased control outweighed any additional anxiety generated from information
- Unaffected sex – could relax and enjoy pregnancy
- Affected sex for those continuing pregnancy – peace of mind
 - Haemophilia carriers: reassurance around monitoring & delivery
 - CAH carriers: taking appropriate medication

"I do think you have to arm yourself with as much information as possible. Yes its unbearable, but at least you know as much as you can possibly know at that time" ALD carrier

"I suppose that one of the things that you feel, it's almost like you feel you've got a bit more control, you haven't got control, but you're not waiting for months." DMD carrier

Value of NIPD – early reengagement with pregnancy

- Mixed emotions for some women – excitement but awareness may not end in having a baby
- Some women actively disengaged with pregnancy as a form of self protection

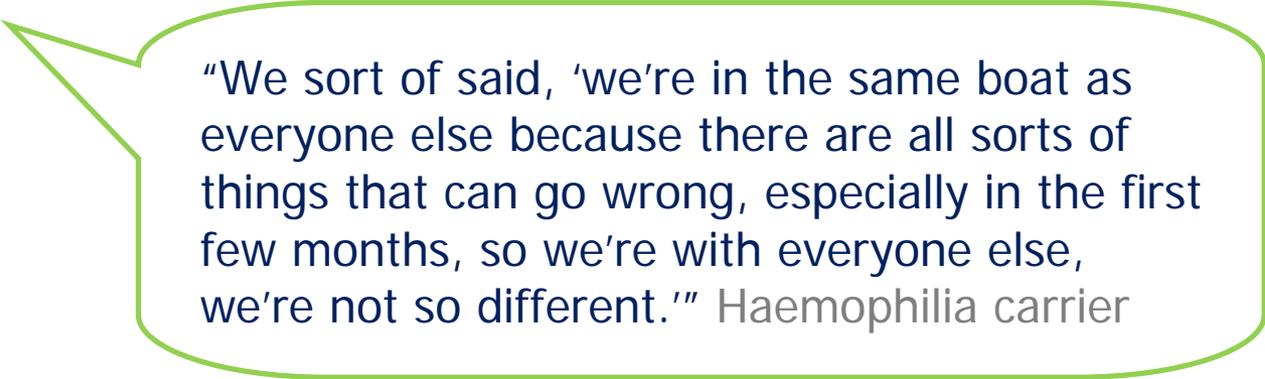


“You don’t want to get attached because you don’t want to make it any harder on yourself.”
X -linked hydrocephalus carrier

- Where fetus was of unaffected sex, participants were able to re-engage with pregnancy at an earlier stage (before 12 week period) then if having sexing scan or invasive testing
- Where fetus was of affected sex - disengagement prolonged

Value for NIPD – normalisation of pregnancy

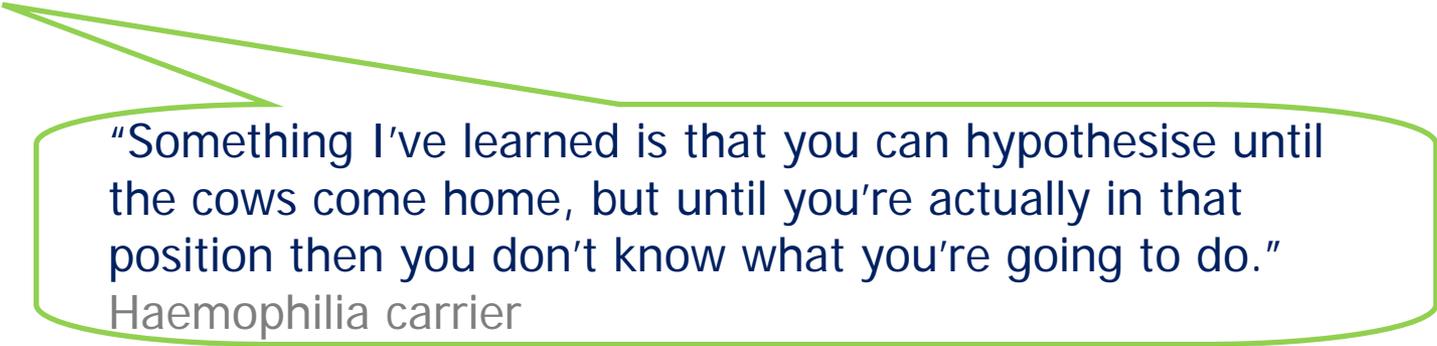
- All pregnancies increased risk within 1st trimester
- Where fetus was of unaffected sex individual was able to continue pregnancy after 1st trimester in a 'normal' way, e.g. tell friends and family
- Where fetus was of affected sex anxiety prolonged – increased awareness that pregnancy was not 'normal'



"We sort of said, 'we're in the same boat as everyone else because there are all sorts of things that can go wrong, especially in the first few months, so we're with everyone else, we're not so different.'" Haemophilia carrier

Value of NIPD – facilitate decision-making

- Participants broadly fell into 1 of 3 categories
 1. Already decided would continue without further testing (H, CAH)
 2. Already decided would undergo IPD and termination if necessary (H [severe], DMD, ALD, X-linked hydrocephalus etc)
 3. Undecided about IPD (H [severe and moderate], BMD, CMT)
- Reasons for decisional delay
 - Difference in opinion between partners
 - Pressure from family member conflicting with participants views
 - Awareness that feelings might change during course of pregnancy



“Something I’ve learned is that you can hypothesise until the cows come home, but until you’re actually in that position then you don’t know what you’re going to do.”

Haemophilia carrier

Value of NIPD – facilitate decision-making

- Value of NIPD: facilitates 'step-wise' approach to decision-making
- Enables participants to manipulate time by dividing it into manageable 'chunks' and focus on immediate future

"And I think that's the key is that once you know the sex you can either put it to the back of your mind or think right now I've got to go through the next stage and I think you can take it more in bits and pieces rather than all in one go."

DMD carrier

- Psychological coping mechanism enabling women to retain sense of control over pregnancy

Concerns about NIPD

- Miscarriage risk
 - Knowing sex early on created connection with fetus. Fetus had more of an identity. Loss through miscarriage more traumatic

“The only disadvantage I can think of from personal experience is because we lost the girl that we were carrying. Obviously I’d started to bond and we had a name and it seemed much more real and we could imagine more about what was coming ahead.” Haemophilia carrier

- Connection to a fetus that may be terminated
- Concerns about technology being used inappropriately
- Concerns about potential impact on disabled community

“There are some cultures where they want to have a boy...if its very early on they might terminate” partner

Clinical service preferences

- Preference for pre-test counselling and results delivered through specialist team e.g. geneticist, genetic counsellor, specialist haemophilia nurse.
- Trusting relationship
- Specialist knows most about the condition
- Best placed to advice on all possible options
- Can offer support
- GP's found to know very little about genetic conditions

"I think finding out from somebody who knows what they're talking about and knows the condition and knows genetics, how it works and can explain it to you. She was there to answer any question as well as talking about the test and the results and everything." ALD carrier

- Preference to receive results by telephone

Health professional perspective

- Perceived similar benefits to that of women
- Concern that women may not think through possible implications of test as just a blood test. Therefore vital to ensure informed consent is given
- Concern about use of NIPD in the private sector or direct to consumer testing which could leave the NHS “picking up the pieces”
- Minor modifications to counselling approach required to incorporate NIPD into current practice

“Because it’s so simple to administer it means that the weight of whatever information is coming from it could be trivialised .”Midwife

Prenatal care for haemophilia

- Differences in who is offered invasive testing and termination, with some offering it to all and some just to carriers of the severe type.
- Health professionals agreed that NIPD should be available to women who are considering invasive testing and termination of pregnancy
- Opinions varied on whether NIPD should be offered to all carriers of haemophilia to inform care during delivery

“You don’t need to know at nine weeks if it is not going to change things for you because you will find out at some point in the pregnancy with a scan.” Geneticist

- Our findings show NIPD can have practical and psychological benefits for women who are undecided as well as those who would not terminate
- Should be offered in a standardised way to ensure equality of access to all

NIPD for Down's syndrome study

- Results of interviews with women after their 20 weeks scan to assess:
 - Why people accept and decline the various available tests
 - Whether women who currently decline screening or are HR and decline IPD would be likely to use NIPD in a future pregnancy
 - Preferences for how NIPD should be offered in clinical practice
- Do far conducted 18 interviews:
 - 7 screening decliners
 - 5 HR IPD accepters
 - 6 HR IPD decliners

NIPD for Down's syndrome – preliminary findings

Women positive towards an early test with no risk to fetus

Mixed views reported from women who declined screening or invasive testing on the grounds that they would not terminate an affected fetus.

"It wouldn't make any difference about how I felt. So why know and put that extra concern on myself?"

Screening decliner

" Making a decision on just a high risk, low risk outcome from a screening test is not something I could have taken lightly. Whereas if there was a blood test that said you know yes or no then you can make a firm decision on solid information and work from there."

Screening decliner

NIPD for Down's syndrome – preliminary findings

- A number of women commented that a benefit of early NIPD would be easier decision-making around ToP

"I'm very pro-choice, but I think there is a certain cut off point where it becomes very muddy ethically... So I think if there is something earlier, it would make that decision making far easier and the earlier you can do it, I think more comfortable it is for everybody ethically and otherwise. The later you leave it you start feeling like you're playing God" HR- had invasive testing

- Women valued a test with a yes/no result rather than a high risk / low risk result as decision-making was considered to be much easier
- A number of women found to be high risk were not prepared for result and had not thought through decision around IPD. Is a concern as may not be prepared for a result through NIPD

Publications

- Lewis C, Hill M, Skirton H, et al. Non-invasive prenatal diagnosis for fetal sex determination – benefits and disadvantages from the service users' perspective. *Eur J Hum Genet*. In press.
- Lewis C, Hill M, Skirton H, et al. Fetal sex determination using free fetal DNA: Service users' experiences and preferences for how the service should be offered in clinical practice. *Prenat. Diagnosis*. In press.
- Hill M, Compton C, Lewis C, *et al*. Determination of fetal sex in pregnancies at risk of haemophilia: a qualitative study exploring the clinical practices and attitudes of health professionals in the United Kingdom. *Haemophilia*. Sep 23 2011.

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