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My healthy future: preconception to neonatal

New technologies are transforming reproduction, pregnancy and parenting, with a rapidly expanding toolkit for parents-to-be to utilise in order to maximise the chances of a healthy pregnancy and a healthy child. Below we offer some ideas for discussion on what future care could like. In three case studies, each looking at a different stage of the reproductive journey, we present a handful of technologies - some already available, others still in development - that could make an impact on the next generation of parenting. The case studies are based on literature reviews and conversations with experts working in related clinical and research fields.

Emerging developments in preconception care

Fertility

Emerging developments to help women achieve pregnancy include:

- Fertility tracking by app integration with microscopic implantable biosensors which monitor body temperature and hormone levels to accurately predict ovulation

- The London Women's Clinic currently offers 'fertility 'MOTs' (for £370) that women could use to to inform timing of pregnancy attempts and, if necessary, egg freezing

  Will women - and men - be opting to have fertility assessments at a younger age to find out the feasibility of having children in the future?

> **People no longer accept that being infertile is just one of those things**

Assessing endometrial function

A healthy endometrium (the cells that line the uterus) is essential for a healthy pregnancy as it allows for implantation, and helps to form the placenta. Could a technique be developed to assess endometrial function and thereby predict endometrial receptivity? Ideally, it would be non-invasive and easily performed within the daily clinical routine.

It may be possible to artificially create artificial mini-organs (organoids) to assess how an individual's endometrium is functioning. Do the cells respond to hormones in the same way? Do they grow normally and respond to the same sort of growth factors?

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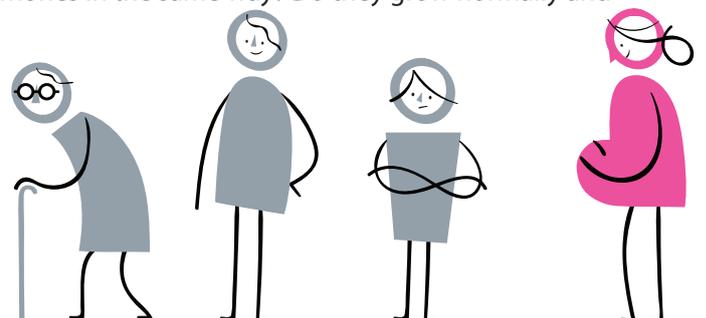
mHealth

General health preconception is crucial: potential parents should be a healthy weight, stop smoking, avoid alcohol, and follow a balanced diet. We already know that good maternal nutrition helps optimise fetal metabolic status. Pregnancy can be a motivator for change. How might digital technologies support behaviour change?

- mHealth platforms such as 'Smarter Pregnancy' offer individual coaching and information to improve nutrition and lifestyle during the preconception period for both mothers and fathers

- Could digital platforms like the one above be developed to interact with monitors and sensors?

- Ambitions for mHealth platforms include addressing other population health needs such as mental health support, and may be offered as part of a life course clinic

  How will mHealth programmes could become more personalised? Will they be measuring biomarkers and using genetic profiling to personalise advice?

Personalising nutrition advice

Existing practice provides generic advice, but future folic acid supplementation could be based on understanding of genetics. The gene *MTHFR* is responsible for converting folic acid into 5-methyl folate (the active form); mutations in this gene can result in a decrease in this activity.

  In the future could women trying to conceive be offered a portable bioassay to continuously assess folate status from urine? Intake of folic acid could then be amended if the monitor senses too much or too little folate

Looking for risk of genetic disease

Carrier testing might become common practice, to check whether an individual carries a genetic mutation that could cause a serious inherited disorder in their baby such as cystic fibrosis or sickle cell disease.

  Which conditions should be tested for? Should a carrier of a known genetic risk be obliged to tell his or her relatives?

Spotlight

We are gradually improving our understanding of how the placenta supports a healthy pregnancy, and the potential interactions between the body's immune system, the placenta, and the developing baby.

For example, uterine natural killer cells (uNK) have an important role in healthy placental implantation and growth. They are a unique population of immune cells that reside in the lining of the uterus. Evidence strongly suggests that the relationship between these immune cells and the placental cells (trophoblast) influences the way in which the placenta develops and consequently how well the baby grows. In the future, parents could be offered a test to determine the likely compatibility between these two cell types, which will be determined largely by the maternal and paternal genomes respectively.

With this information, it may be possible to identify 'risky' combinations that might predispose women to inadequate development of the placenta and associated disorders of pregnancy.

Male preconception health

Historically, family planning and fertility counselling have focused heavily on female fertility. This is likely to change with the recognition that the number, fitness and health of the man's sperm are significant factors in a couple's fertility, and that the long term health of the child is determined by the genomic contribution of both parents.

The contribution from the father determines the sex of the infant (the X or Y chromosome) and half of the rest of the genetic material, not including the mitochondrial genome.

It has recently been shown that:

- Sperm carry important epigenetic information in the form of methylation markers and microRNAs. These may affect the health of the child by influencing gene activity and may be transmissible through generations. This epigenetic information may be influenced by male health and lifestyle factors

- Everyday consumables such as cigarettes negatively affect sperm number and fitness, potentially leading to reduced fertility

In the future, men may receive personalised fertility counselling prior to conception attempts. This might include:

- Computer-assisted sperm analysis to provide an indication of overall sperm number and motility; and testing for abnormal number or composition of chromosomes

- Sperm health assessments could provide the basis for personalised general health and lifestyle advice, with the psychological impacts of fertility issues in men more readily taken in to account

- Aneuploidy testing and fitness-based sperm selection may also become more common prior to attempted IVF to improve fertility outcomes for potential parents
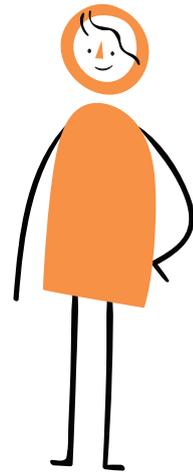
Will there be more emphasis on paternal preconception reproductive health?

Will men be treated as equal partners in ante and neonatal care, with equal attention paid to their independent physical and psychological needs?

Discussion - Lisa

Lisa has had fertility testing regularly since the age of 25 to ensure that she knows her fertility status and can use this to inform when she chooses to have a baby. At 35 she has decided that she is now financially stable and ready for the time commitment involved in starting a family. She is not in a relationship and wishes to have the healthiest baby possible through selecting genetically compatible sperm from a donor.

Having had carrier testing in her 20s, Lisa is aware that she is a genetic carrier for cystic fibrosis. Legally, all sperm donors must undergo extensive genetic screening for hundreds of different diseases and so Lisa plans to avoid CF carriers to ensure there is no chance that her baby will inherit the condition. It is also particularly important to her that she selects male DNA that provides a different variation of the *HLA* gene to her own in order to maximise her future offspring's immune responses.

Having selected her sperm she aims to optimise her health before becoming pregnant through intrauterine insemination (IUI). She has subscribed to a six month mHealth preconception care programme which promotes health through genetic profiling so as to identify and intervene on modifiable nutritional and lifestyle risk factors. Although she doesn't smoke and eats a relatively healthy diet, her baseline screening (informed by nutrigenomics) detects that she consumes too much alcohol and is lacking in iron and vitamin B12. Each week she receives texts with tips, vouchers or recipes in order to help her modify these behaviours. Home monitors and portable bioassays feed data on behavioural and chemical changes back into the platform which interacts with her electronic health record.

How much time of the user and health staff will be used up by these devices?

Will these devices ease or exacerbate worry and pressure for the user?
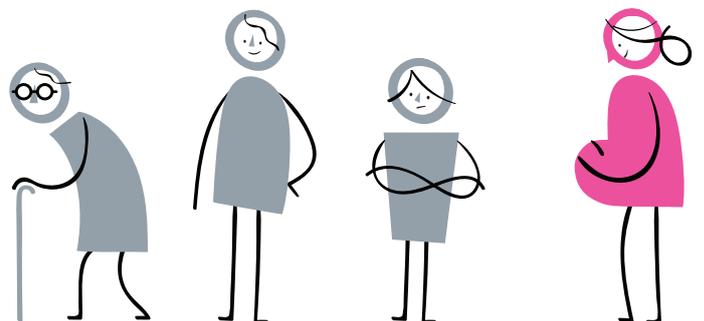
My healthy future: antenatal

Antenatal care in the future will focus on ensuring the healthy development of the fetus and placenta, with increasing weight being given to the crucial first trimester. At this stage the placenta will be monitored for healthy size/vascularity/endocrine function. Options for the continuous monitoring of the health of mother and fetus are expected to become more mainstream.

Emerging developments in antenatal care

Endometrial function

Comparisons between biopsies of women who have a normal pregnancy and those who have a pre-eclamptic pregnancy indicate the problem is with the endometrium rather than the placenta. As yet, there is no clear idea of what a healthy endometrium looks like but it is likely that reproductive health will emphasise endometrial health.

Placental function

The effectiveness of the placenta in transporting nutrients and oxygen to the fetus is important in determining fetal growth.

In the future placental function could be assessed through placental ultrasound conducted early in pregnancy, using imaging to get a 3D appreciation of the placenta, the embryo and the uterine vasculature, or examining placental function by assessing hormone concentrations through a simple blood test. An example of this imaging technique is the Barco I Space Virtual Reality Environment.

> **I would put my money on some sort of test of endometrial function**
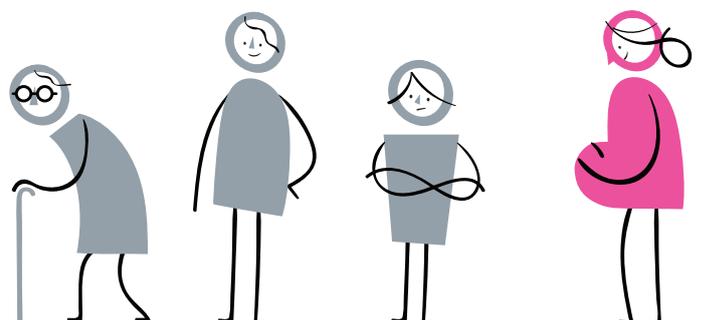
Embryonic testing

Non-invasive testing using cell free fetal DNA could be used more widely; eventually non-invasive testing for Down's syndrome is likely to be taken up by the population as a whole rather than just those identified as high risk through the current antenatal screening programme. Non-invasive testing is likely to expand from Down syndrome to detecting single gene defects as well.

Prenatal Whole Genome Sequencing (at 11 weeks) may become more commonplace. This allows the entire DNA profile of an unborn child to be mapped from a mother's blood sample, allowing genetic conditions to be screened for. As genetic research improves whole genomce sequencing could be used to obtain information on the risk of the child developing diseases such as cancer or heart disease later in life.

> Will widespread availability of prenatal WGS mean that parents will be expected to use it and act upon the information it provides?

Monitoring throughout pregnancy

Predicting risk

It is anticipated that a variety of biomarkers will be identified that can alert for risk of the major obstetric syndromes - miscarriage, early onset pre-eclampsia, stillbirth, premature rupture of the membranes, preterm delivery and fetal growth restriction.

> How far could antenatal care be modified according to individual risk profile?

> If possible, should all women be screened for biomarkers in early pregnancy for risk of pre-eclampsia, with those at high risk being offered tailored interventions?

> **Screening using biomarkers for pre-eclampsia risk, and modifying care based on the risk profile, is absolutely something that you would expect to become part of care in the future**

Spotlight

One of the main biomarkers for pre-eclampsia (the 'sFlt-1 to PlGF' ratio) has now been developed as a triage test. When a woman has clinical signs suggestive of pre-eclampsia, a normal ratio has a very high negative predictive value (i.e. the woman is very unlikely to progress to severe pre-eclampsia in the next week).

The placenta releases lots of DNA and RNA into the maternal circulation and in the future it may be possible to use cell free DNA/RNA in the mother's plasma to try and derive information about the placenta – as a way of trying to risk stratify and target assessment.

We may be able to identify women earlier in pregnancy (than the current 28 week test), who are at risk of developing gestational diabetes. A 12 week test to identify high risk women would enable earlier detection and monitoring.
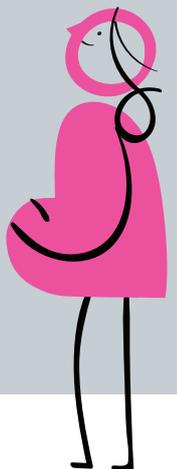
Monitoring the baby

New technologies might be combined to allow closer monitoring of the growing baby. For example

- The Intelligent Fetal Imaging and Diagnosis (iFIND) project aims to improve the accuracy of routine 18-20 week screening in pregnancy, by bringing together advanced ultrasound and MRI techniques, robotics and computer aided diagnostics to create a multiprobe system for automated ultrasound imaging

- The cause of Fetal Growth Restriction (FGR) is often maternal (e.g. smoking, pre-eclampsia) or placental (e.g. compromised supply of nutrients and oxygen to the fetus). Potentially maternal blood biomarkers, such as the sFlt-1 to PlGF ratio could be incorporated as a diagnostic criterion of FGR. Will it be feasible to combine this with ultrasound measurement to identify early potential complications from FGR?

Monitoring the mother

Apps using artificial intelligence could offer evolving personalised healthcare guidance. mHealth technologies and portable diagnostic bioassays could help women to monitor their vital signs, track their exercise and dietary requirements (based on nutrigenomics), and facilitate online pregnancy communities. Whilst women will be in constant contact with the healthcare system, might they see less of their midwives face to face - women could visit their hospital and have ultrasounds conducted in an automated machine for example? Other monitoring devices include:

- 'Salurate' bioassay test is a home kit that checks the uric acid levels in saliva in order to monitor for signs of pre-eclampsia, from 20 weeks

- Smart watches/contact lenses can monitor glucose levels to prevent and manage gestational diabetes

- Electronic tattoos/smart skin are sensors that adhere like a plaster to parts of the body and monitors vital signs like heart rate, blood pressure and breathing

- QUiPP is an app that uses an algorithm which combines the gestation of previous pregnancies and the length of the cervix with levels of fetal fibronectin to classify a woman's risk of preterm labour

- Bloomlife 'Belli Sensor' is a wearable monitor which measures electrical signals from the uterus to help parents tell the difference between normal abdominal cramps and contractions. Duration and frequency of the contractions are recorded in an app. The technology has potential to help pick up early labour in high-risk mothers since it can detect contractions that the woman can't even feel. Developments in the pipeline include monitoring fetal movement and heart rate and aspects of maternal health, all through the same sensors

Will direct to consumer technologies take the place of regular medical checkups?

Discussion - Hannah and Ray

Hannah and Ray are pregnant with their first child and are keen to use the recommended monitors and tests to ensure that any health risk to Hannah or the baby is identified and addressed early. After an initial online consultation they have been advised to buy a home kit to detect early signs of pre-eclampsia, and a smartwatch to non-invasively monitor blood glucose levels to help prevent gestational diabetes. Hannah has been advised that data collected from the watch will be sent securely to her clinician. All her data is available to her, but Hannah has chosen only to receive weekly summaries and notifications if actionable dietary changes are required.

Neither Hannah nor Ray are aware of any family history of genetic disorder and decide not to have their fetus' genome sequenced at 11 weeks. This decision has been met by surprise from many of the women in Hannah's antenatal class, most of whom have opted to have the sequencing done. They ask Hannah how she would feel if something was wrong with the fetus that could have been prevented.

As her pregnancy progresses Hannah has been advised to focus on her nutrition and ensure that she visits her GP surgery regularly for automated ultrasound scans. She is reassured to hear that intelligent fetal 3D imaging doesn't detect any abnormalities and shows good fetal growth, nor does placental imaging show any problems with placental size or vascularity. Although she has hardly seen her obstetrician, he has been in frequent contact through texts and apps such as 'BabySteps', relaying test results to her and making adjustments to her diet and folic acid intake.

Although she is not high risk, in her third trimester she rents a Belli Sensor; a lightweight device that attaches to her stomach and monitors for preterm labour. She is relieved that she has, as when she gets abdominal cramps at 35 weeks, the app connected to her device reassures her that she is not going into labour, saving her unnecessary anxiety and trips to the hospital.

Will there be a change in what is considered to be 'responsible' pregnant behaviour?

Will the influx of data generated ultimately be time saving?
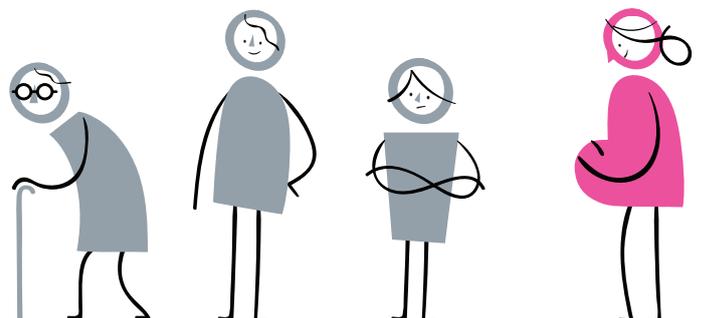
My Healthy Future

My healthy future: neonatal

As well as earlier diagnoses of genetic conditions, technology could have an increasing role in alerting parents to behavioural signals for developmental delay. We can also expect to see an increased focus on the mother's mental wellbeing. Will the technologisation of early parenting affect bonding? And will it help or hinder equal sharing of parental roles?

Emerging developments in neonatal care

Whole genome sequencing

Whole genome sequencing of newborns for existing and potential disorders is already technologically possible. If WGS was employed as a screening tool for all newborns, more babies at risk of serious genetic disorders could be identified earlier, allowing treatment for diseases hinged on early detection. There may also be potential to identify those at risk, or with increased susceptibility to adult onset disease.
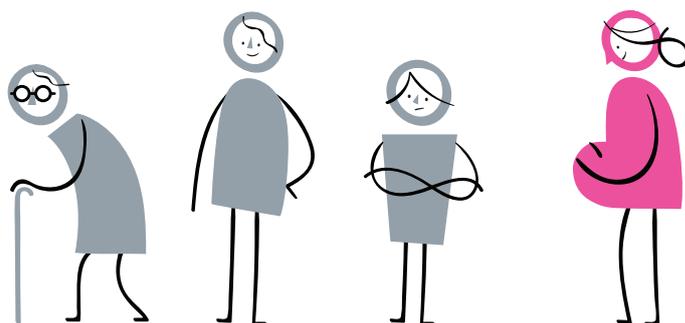
Will technology help or hinder equal sharing of parental roles?

Mental health of the mother

Postnatal maternal health needs include both physical and psychological wellbeing, which already can be monitored through apps.

IBM predict that within five to ten years, what we say and write will be used as indicators of mental health and physical wellbeing. Patterns in our speech and writing analysed by new cognitive systems will provide tell-tale signs of early-stage developmental disorders, mental illness and degenerative neurological diseases that can help doctors and patients better predict, monitor and track these conditions.

Could cognitive assistants in smart devices be developed to 'listen' out for signs of wellbeing?

My Healthy Future

Child development

Smart technologies that monitor childhood development in the baby's first years are already available or in development:

- Onni - this smart baby monitor provides video streaming, baby events log, records the child's growth and development, and compares the baby's measurements with WHO stats. It can be connected to Beddit, a wireless sensor between the mattress and sheet that rates quality of sleep and senses heart rate, breathing, and movement

- Smart Diaper - a panel on the front comes equipped with a smartphone-scannable QR code which analyses waste makeup and tracks health information such as hydration levels, infections, and vitamin deficiencies

- Sensory baby vest - fully-integrated sensors measure electrocardiography (ECG), respiration, temperature and humidity (to detect excessive sweating) to allow early detection of potential life-threatening events

- Wrist and Ankle Movement Sensor (WAMS) - wearable sensor systems may help parents understand their infants needs through measurements of their body's vital signs or analysis of behaviors such as different types of crying, hand flapping and eye movement

- Integrative Personal 'Omics Profile – home monitoring of the proteins, metabolites and transcripts in the baby's blood

Can we ensure equal access to these devices for all parents who want to use them?

What do these technologies mean for parent/child communication?

Discussion - Chloe

Could technology lead to an increase child supervision referrals?

Chloe has given birth to a baby boy, Ben. Whole genome sequencing has been adopted as a primary screening tool for newborns, and within 24 hours of birth a blood sample is drawn. This gives her reassurance that should Ben become unwell, his sequence could be analysed quickly to check for relevant mutations, enabling a precise, early diagnosis.
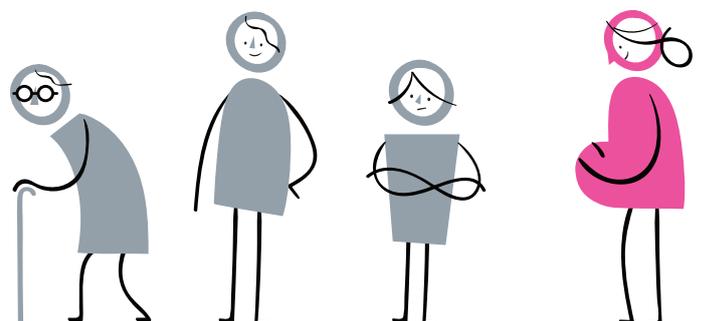
Chloe buys an Onni baby monitor. Approved smart devices can connect to the monitor (and have access to its data) so Chloe's parents, who live in New Zealand, can log in and view Ben through the smart camera whenever they choose, using two way communication between the baby unit and their tablet to talk to him. It also connects to a babylog app where Chloe can record and track Ben's growth and development, and compare his progress to WHO stats.

Wearable sensors are given to all new mothers to monitor signs of intimacy/bonding between mother and baby. After two months Chloe receives a call from her clinician expressing concern about limited eye contact and close body contact between them, and asking her to come in for a consultation to assess her mental state and how it may be affecting Ben.

How much genetic information should parents be given about their newborns?

Next, Ben does not meet the milestones of holding his head up and sitting up on his own at the expected ages and at 15 months, Ben still isn't walking – below average according to the app. This causes Chloe to become concerned about Ben's development to the point that she is not sleeping, because she wakes frequently during the night to monitor his sleep.

What if these devices effect life choices and are wrong - who bears responsibility?

Will these devices be time-saving or time-consuming?

Who will data from these devices be shared with?

How will technology change the role of men in reproduction?

How will data from these devices be combined with health records?

Could these devices increase or ameliorate health inequalities?

Will these devices have an affect on the mental health of the user?

Who will pay for these devices?

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