What's new in genetics for the pre-pregnancy consultation?

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THE UNIVERSITY OF MELBOURNE

murdoch children's research institute

mercy perinatal
kickstart for life

“Do you have any idea how fast you were evolving?”

CATEGORY: BEST PRACTICE STATEMENT

Pre-pregnancy Counselling

4.3 Genetic/Family history

Pre-pregnancy screening for inheritable genetic conditions is preferable to antenatal screening as this provides more options for carrier couples.

https://ranzcog.edu.au/wp-content/uploads/2022/05/Pre-pregnancy-Counselling.pdf

Genetics for the pre-pregnancy consultation

1. Family history
2. Reproductive carrier screening
3. New option: Mitochondrial donation

Family history on the run…

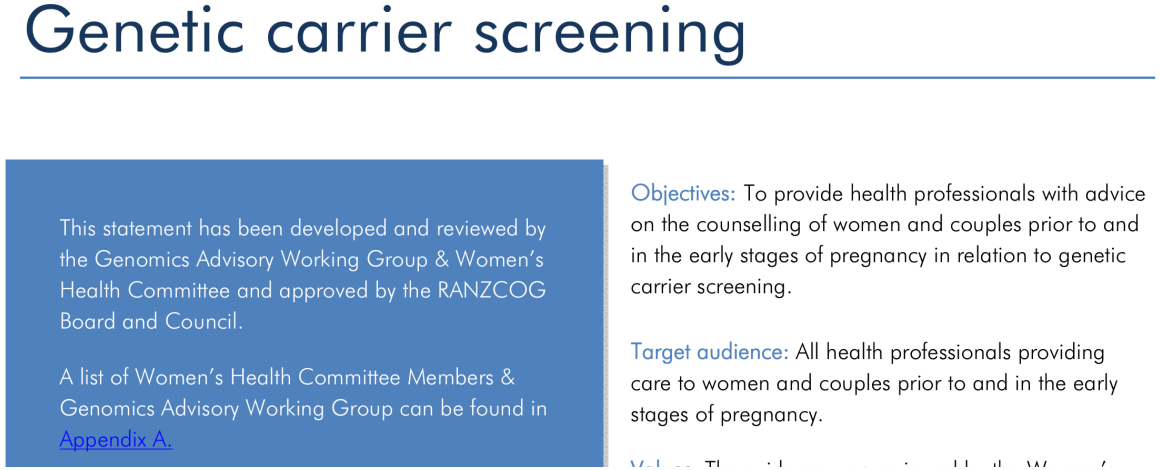
1. Health status of parents, siblings
2. Congenital anomalies and intellectual disability
3. Racial/ethnic background, consanguinity

Are there any health conditions that run in your side of the family?
Are your parents alive and well? Do you have any siblings? Are they in good health? Do any of your siblings have children?

Can I ask you about your family background? In which countries were your parents born? What is your genetic ancestry/ethnic/racial background?
Do you and your partner (biological father of the baby) share any blood relatives?

Have any children in your family been born with a health problem?
Do any members of your family have an intellectual disability or learning problems?

Who should be offered genetic carrier screening?



Genetic carrier screening

This statement has been developed and reviewed by the Genomics Advisory Working Group & Women's Health Committee and approved by the RANZCOG Board and Council.

A list of Women's Health Committee Members & Genomics Advisory Working Group can be found in Appendix A.

Objectives: To provide health professionals with advice on the counselling of women and couples prior to and in the early stages of pregnancy in relation to genetic carrier screening.

Target audience: All health professionals providing care to women and couples prior to and in the early stages of pregnancy.

The Royal Australian and New Zealand College of Obstetricians and Gynaecologists

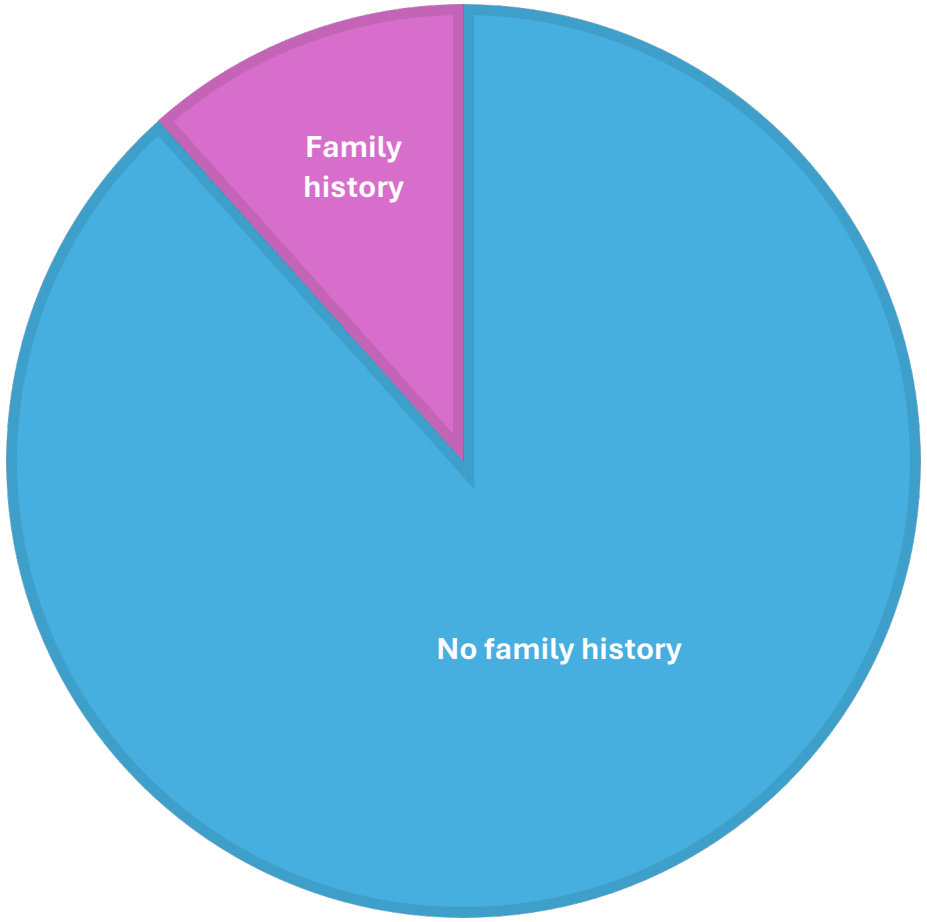
Excellence in Women's Health

Information on carrier screening should be offered to all women planning a pregnancy or in the first trimester of pregnancy

- The benefits and limitations, and any associated costs, should be discussed

RANZCOG C-Obs 63 https://ranzcog.edu.au

"But our family doesn't have a history of any problems"



Most carriers have ***no*** **family history***

**Archibald, Smith et. al (2017) https://doi.org/10.1038/gim.2017.134*

How do we offer genetic carrier screening?

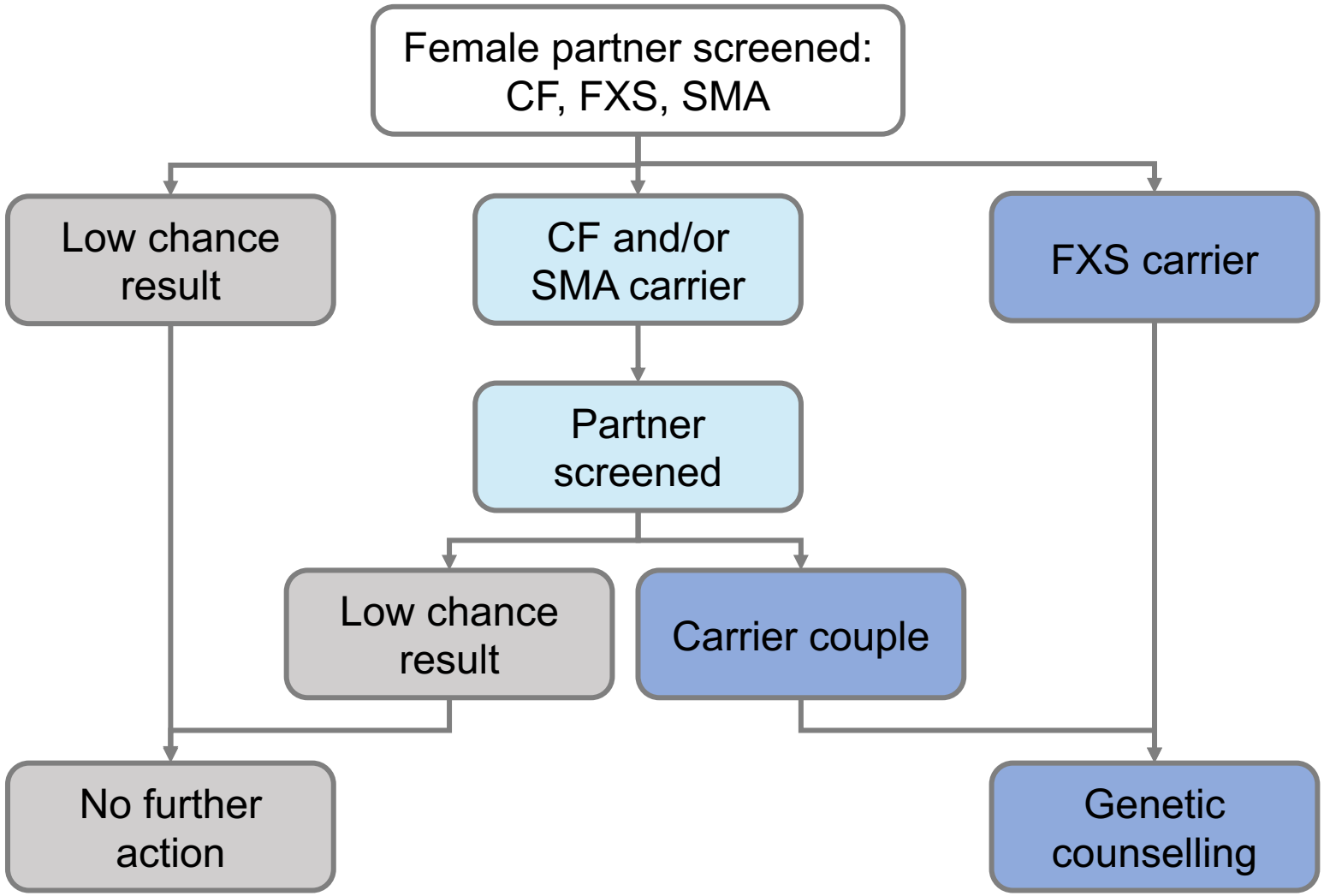
- Provides couples with information about their chance of having children with an inherited genetic condition – **voluntary, informed consent**
- Relevant to **all** prospective parents regardless of family history or ethnicity
- While individually rare, collectively 1-2% of couples are carriers for a particular condition

Conditions screened	
Screening approach	

Most common conditions in Australian population

Condition	Carrier	Affected	Main clinical features
Thalassemia	1 in 30	1 in 3600	Anaemia, mild to transfusion-dependent

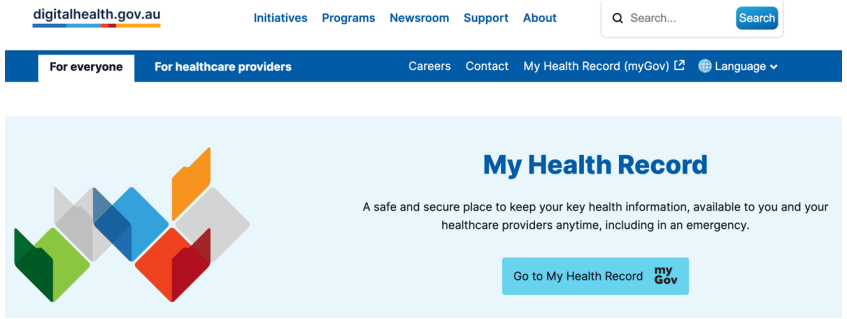
How do we offer genetic carrier screening?



Slide courtesy of Alison Archibald

Medicare funding for genetic screening

- MBS 73541 for 3-gene panel
  - Non-eligible patients : ~$400
- Ashkenazi Jewish descent: 9 recessive conditions (MBS 73453, 73454, 73455)
- Sequential screening
  - male partner of a carrier female MBS 73452
- Only claimable once in a lifetime
  - *“Have you ever had genetic carrier screening?”*



Should you be the one ordering the carrier screening?

- Public hospital patients must be an outpatient in an **MBS clinic** to be eligible for the Medicare rebate, and the referral must be made by a **doctor with a provider number attached to that MBS clinic.**
- Women in non-MBS clinics should be referred to GP for further discussion
  - Ensures records are held with a practitioner with continuity of care

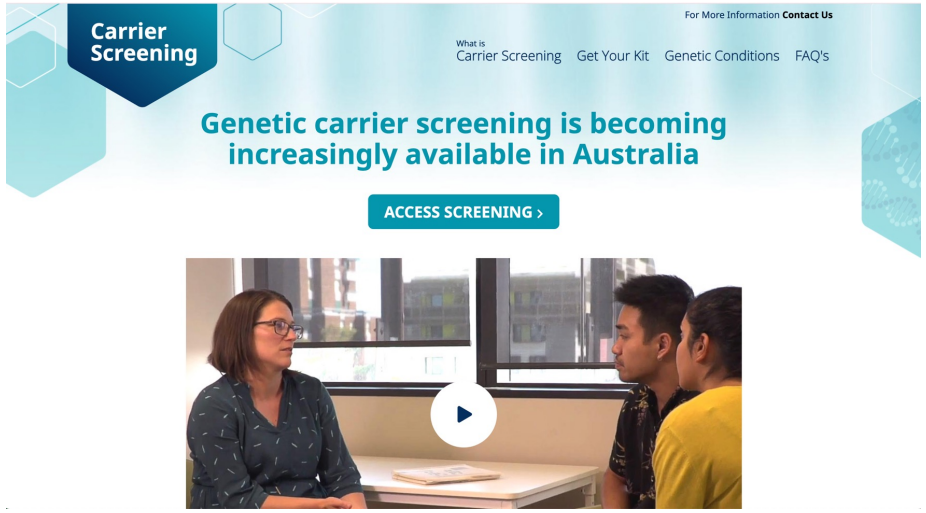
Resources for patients

Factsheet on RCS from the Centre for Genetics Education, NSW Health, Nov 2023

RANZCOG patient information on RCS 2009

The Fertility Society patient information on RCS 2021

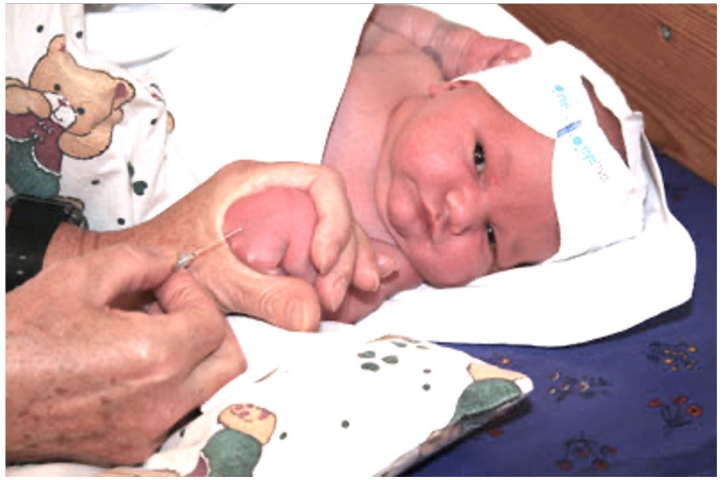
- Mercy Health patient information
  - *Genetic testing for people planning to have children*
  - *Understanding reproductive carrier screening*

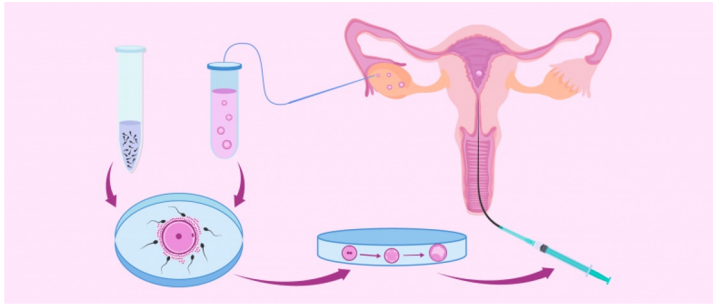


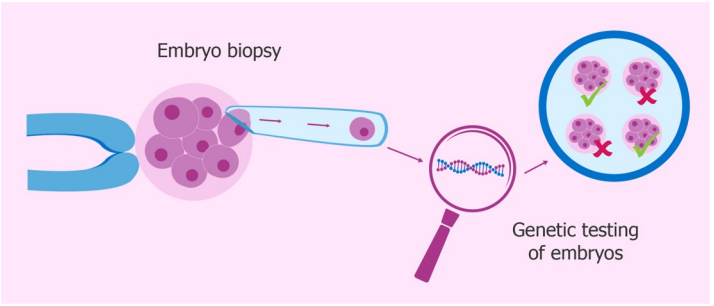
https://carrierscreening.org.au/#whatsSMA

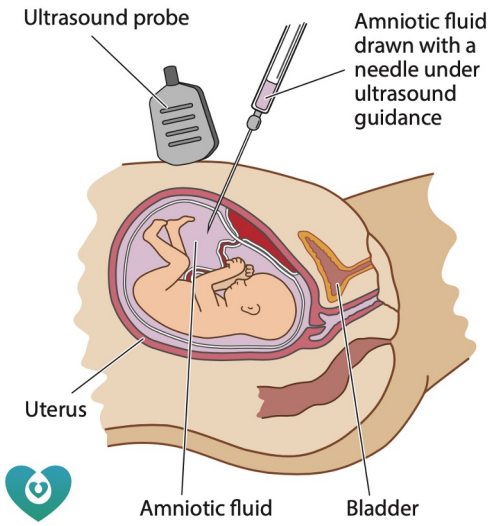
"Do you, Ashley, take Nesbitt and his genome to be your husband?"

Options for couples at increased risk









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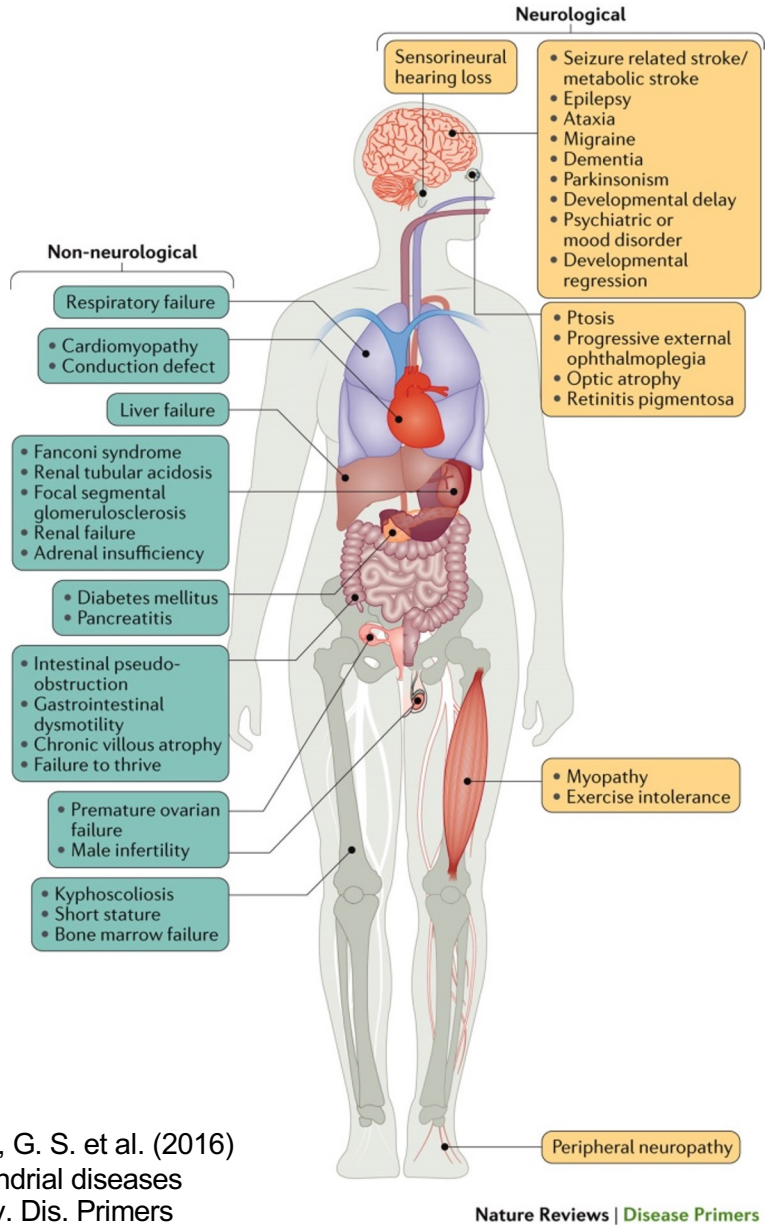
Introducing Mitochondrial Donation into Australia: The mitoHOPE (Healthy Outcomes Pilot and Evaluation) Program

murdoch children's research institute



Gorman, G. S. et al. (2016)
Mitochondrial diseases
Nat. Rev. Dis. Primers
doi:10.1038/nrdp.2016.80

Mitochondrial diseases

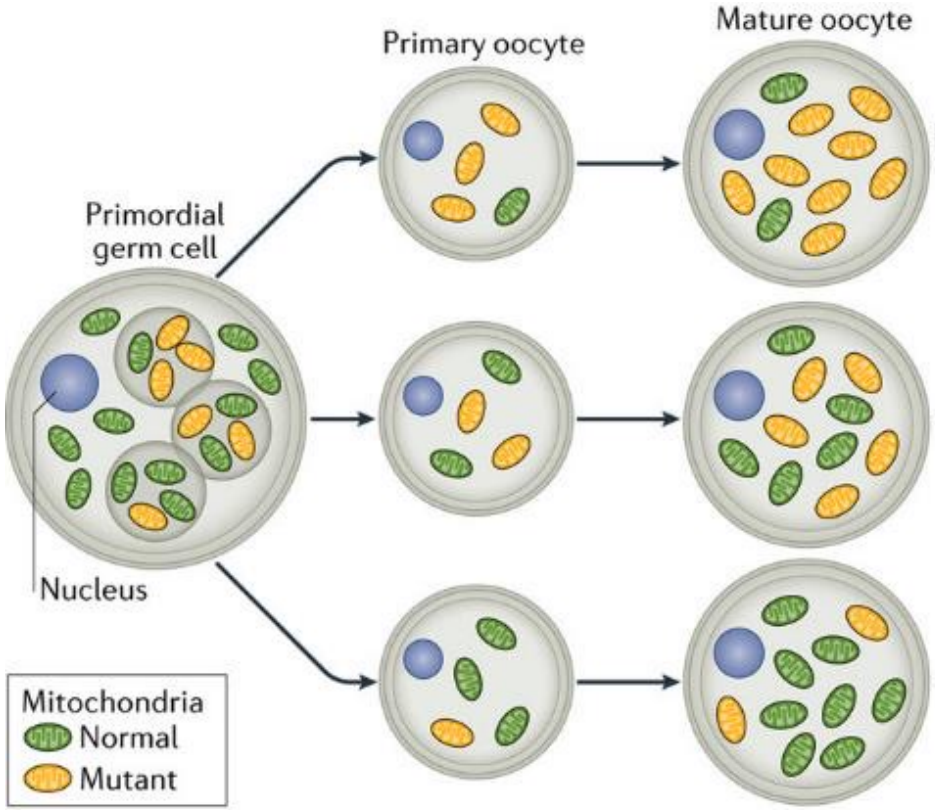
"Any symptom, any organ, any age, any inheritance!"*

- Usually multi-system disease, typically affecting organs highly dependent on aerobic metabolism
- Affect ~1:5000 children and adults
- Caused by mutations in **mitochondrial DNA** or **nuclear DNA** genes encoding mitochondrial proteins
- e.g MELAS syndrome: *mitochondrial encephalopathy, lactic acidosis, stroke-like episodes*

**** Munnich and Rustin, Am J Med Genet 2001: 106; 4 - 17***

Mitochondrial DNA Genetics

Maternal Inheritance, Multiple Copies, Heteroplasmy, Bottleneck & Threshold Effects



<u>Mitochondrial Donation</u> could potentially allow any couple at risk for transmitting mtDNA disease to have a healthy child who is genetically related to both parents

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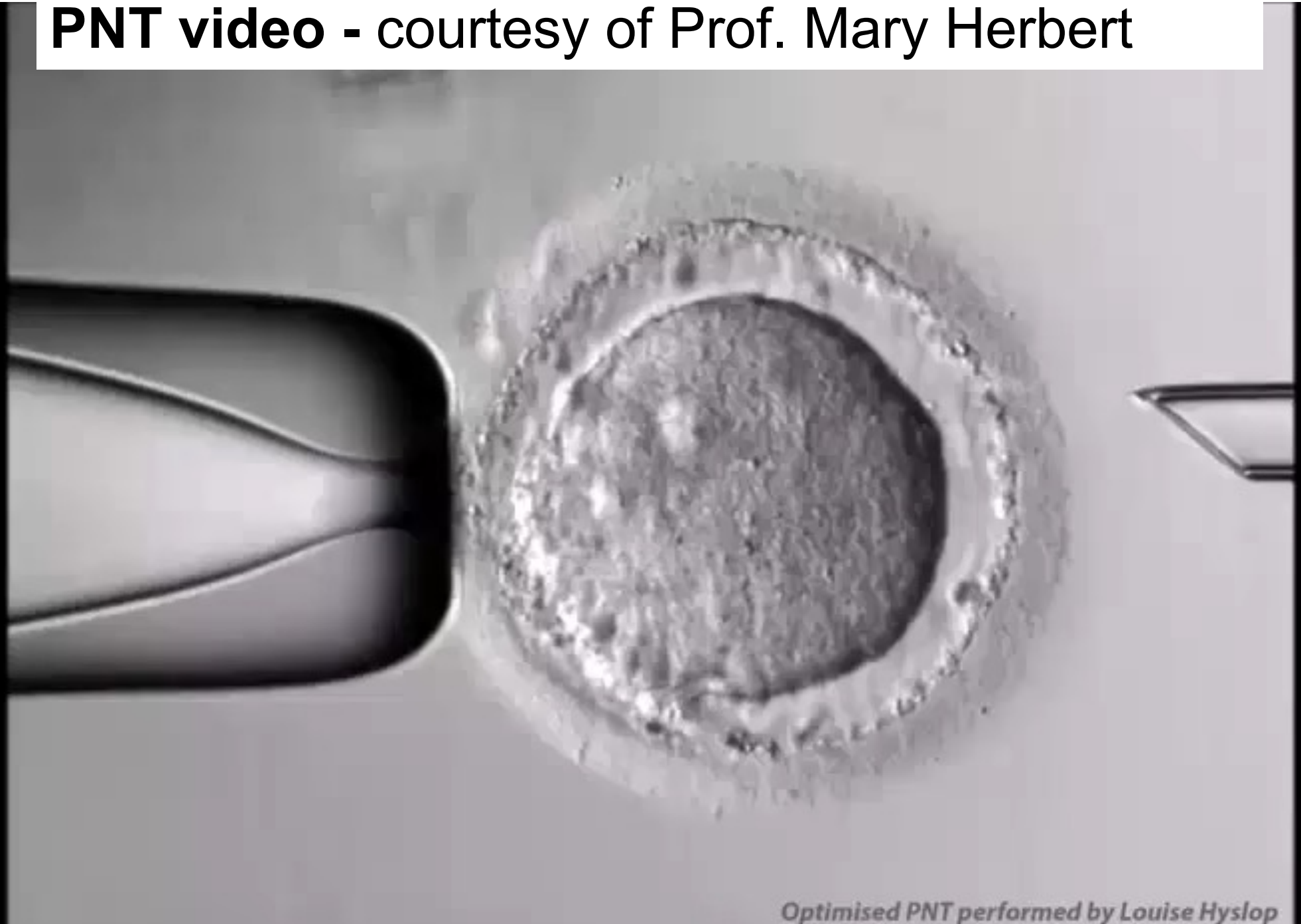
Mitochondrial Donation (MST)

PNT video - courtesy of Prof. Mary Herbert



Status of Mitochondrial Donation in Australia

The *Prohibition of Human Cloning for Reproduction Act 2002* and the *Research Involving Human Embryos Act 2002* prohibit research involving human embryos containing genetic material (including mtDNA) from more than two persons

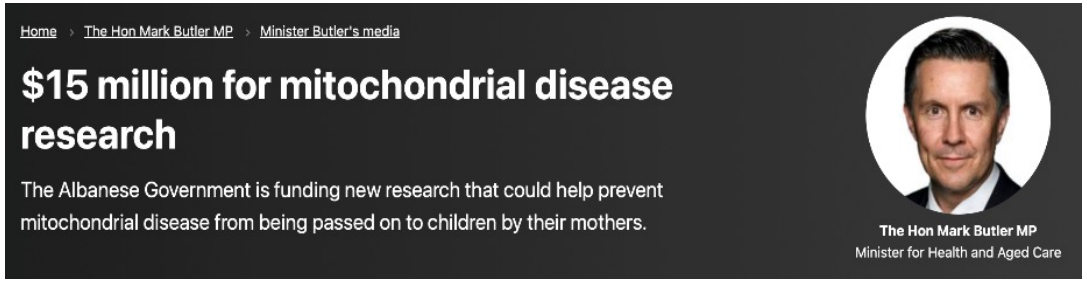
Legislation reviewed in 2010/11 – no change

Mito Foundation began lobbying

- Senate Inquiry
- NHMRC Review & Public Consultation
- Draft Legislation tabled

- Conscience vote House of Representatives Dec 2021: 92 to 29
- Conscience vote Senate Mar 22: 37 to 17

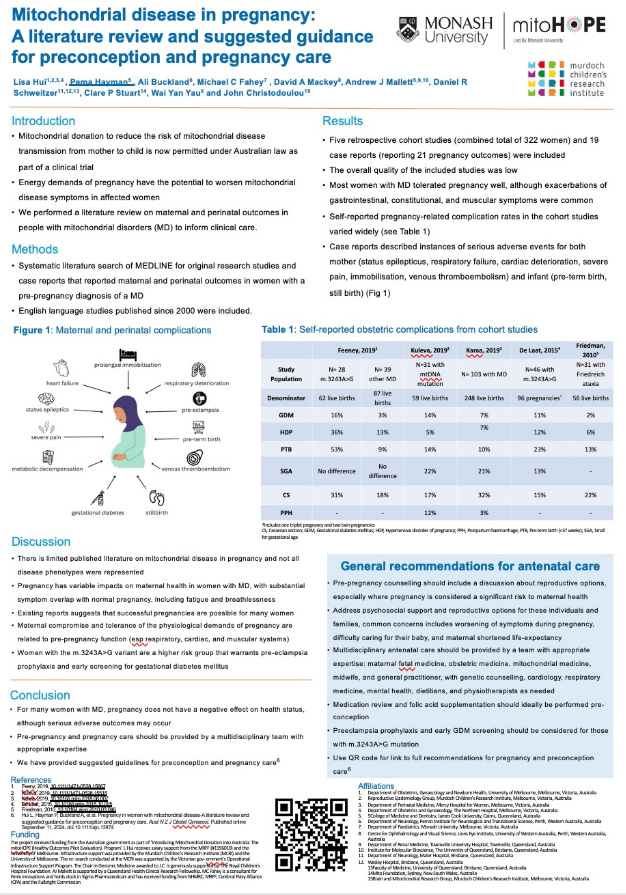
Maeve's Law passed!



Effect of pregnancy on maternal disease

Effects of maternal disease on pregnancy

Poster S29



Mitochondrial disease in pregnancy: A literature review and suggested guidance for preconception and pregnancy care

Lisa Hui[1,2,3,4], Pema Hayman[5], Ali Buckland[6], Michael C Fahey[7], David A Mackey[8], Andrew J Mallett[5,9,10], Daniel R Schweitzer[11,12,13], Clare P Stuart[14], Wai Yan Yau[6] and John Christodoulou[15]

Introduction

- Mitochondrial donation to reduce the risk of mitochondrial disease transmission from mother to child is now permitted under Australian law as part of a clinical trial
- Energy demands of pregnancy have the potential to worsen mitochondrial disease symptoms in affected women
- We performed a literature review on maternal and perinatal outcomes in people with mitochondrial disorders (MD) to inform clinical care.

Methods

- Systematic literature search of MEDLINE for original research studies and case reports that reported maternal and perinatal outcomes in women with a pre-pregnancy diagnosis of a MD
- English language studies published since 2000 were included.

Results

- Five retrospective cohort studies (combined total of 322 women) and 19 case reports (reporting 21 pregnancy outcomes) were included
- The overall quality of the included studies was low
- Most women with MD tolerated pregnancy well, although exacerbations of gastrointestinal, constitutional, and muscular symptoms were common
- Self-reported pregnancy-related complication rates in the cohort studies varied widely (see Table 1)
- Case reports described instances of serious adverse events for both mother (status epilepticus, respiratory failure, cardiac deterioration, severe pain, immobilisation, venous thromboembolism) and infant (pre-term birth, still birth) (Fig 1)

Figure 1: Maternal and perinatal complications

Table 1: Self-reported obstetric complications from cohort studies

	Feeney, 2019[1]		Kuleva, 2019[2]	Karaa, 2019[3]	De Laat, 2015[4]	Friedman, 2010[5]
Study Population	N= 28 m.3243A>G	N= 39 other MD	N=31 with mtDNA mutation	N= 103 with MD	N=46 with m.3243A>G	N=31 with Friedreich ataxia
Denominator	62 live births	87 live births	59 live births	248 live births	96 pregnancies†	56 live births
GDM	16%	3%	14%	7%	11%	2%
HDP	36%	13%	5%	7%	12%	6%
PTB	53%	9%	14%	10%	23%	13%
SGA	No difference	No difference	22%	21%	13%	-
CS	31%	18%	17%	32%	15%	22%
PPH	-	-	12%	3%	-	-

†Includes one triplet pregnancy and two twin pregnancies
CS, Cesarean section; GDM, Gestational diabetes mellitus; HDP, Hypertensive disorder of pregnancy; PPH, Postpartum haemorrhage; PTB, Pre-term birth (<37 weeks); SGA, Small for gestational age

Discussion

- There is limited published literature on mitochondrial disease in pregnancy and not all disease phenotypes were represented
- Pregnancy has variable impacts on maternal health in women with MD, with substantial symptom overlap with normal pregnancy, including fatigue and breathlessness
- Existing reports suggests that successful pregnancies are possible for many women
- Maternal compromise and tolerance of the physiological demands of pregnancy are related to pre-pregnancy function (esp respiratory, cardiac, and muscular systems)
- Women with the m.3243A>G variant are a higher risk group that warrants pre-eclampsia prophylaxis and early screening for gestational diabetes mellitus

General recommendations for antenatal care

- Pre-pregnancy counselling should include a discussion about reproductive options, especially where pregnancy is considered a significant risk to maternal health
- Address psychosocial support and reproductive options for these individuals and families, common concerns includes worsening of symptoms during pregnancy, difficulty caring for their baby, and maternal shortened life-expectancy
- Multidisciplinary antenatal care should be provided by a team with appropriate expertise: maternal fetal medicine, obstetric medicine, mitochondrial medicine, midwife, and general practitioner, with genetic counselling, cardiology, respiratory medicine, mental health, dietitians, and physiotherapists as needed
- Medication review and folic acid supplementation should ideally be performed pre-conception
- Preeclampsia prophylaxis and early GDM screening should be considered for those with m.3243A>G mutation
- Use QR code for link to full recommendations for pregnancy and preconception care[6]

Conclusion

- For many women with MD, pregnancy does not have a negative effect on health status, although serious adverse outcomes may occur
- Pre-pregnancy and pregnancy care should be provided by a multidisciplinary team with appropriate expertise
- We have provided suggested guidelines for preconception and pregnancy care[6]

References

1. Feeny, 2019, 10.1111/1471-0528.15667
2. Kuleva, 2019, 10.1111/1471-0528.15515
3. Karaa, 2019, 10.1016/j.mito.2018.06.007
4. De Laat, 2015, 10.1016/j.mito.2015.10.005
5. Friedman, 2010, 10.1016/j.ajog.2010.03.046
6. Hui L, Hayman P, Buckland A, et al. Pregnancy in women with mitochondrial disease-A literature review and suggested guidance for preconception and pregnancy care. *Aust N Z J Obstet Gynaecol*. Published online September 11, 2024. doi:10.1111/ajo.13874

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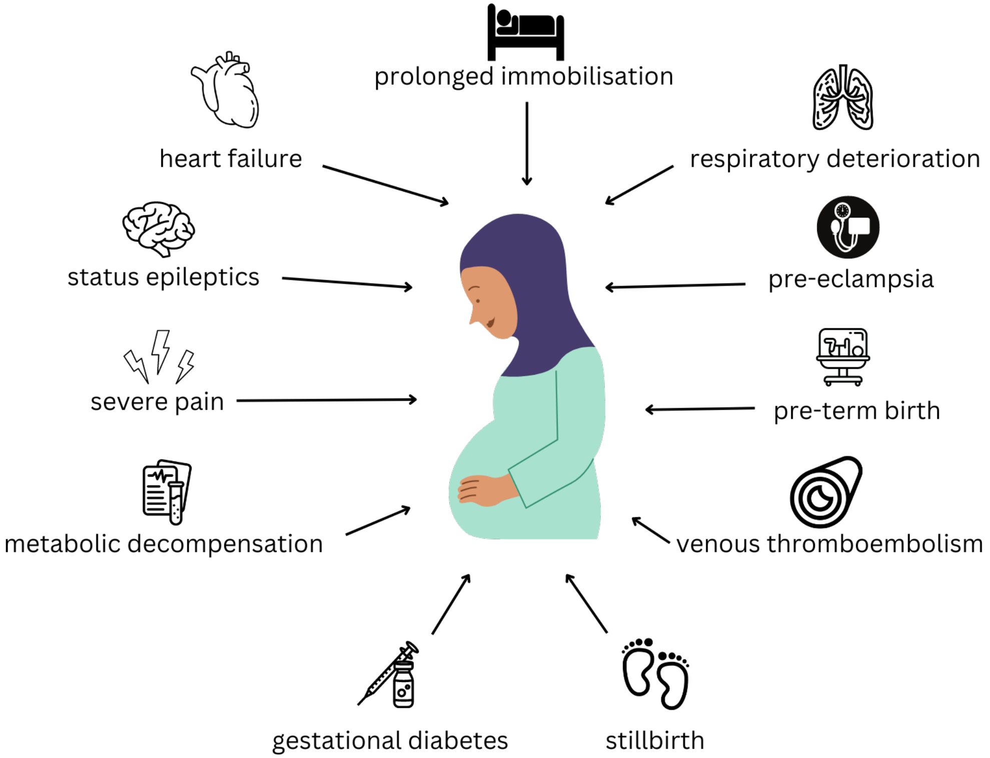

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Register Interest in Mitochondrial Donation

2

Counselling by Local Clinical Team

Consent to be Screened for Eligibility

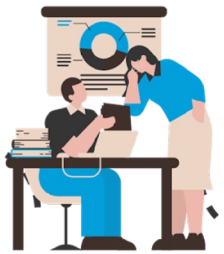
Baseline Medical Evaluation

Individualised Tests

Genetic Counselling (IVF, MD, Obstetric Outcomes)

Individualised Counselling (Risks/benefits of IVF and Pregnancy)

Review at Multidisciplinary Team Meeting



License Application Review by Embryo Research Licensing Committee

Entry into mitoHOPE Clinical Trial

Clinical Trial Consent

Counselling 1+ Weeks Later (Trial Participation, Fertility Treatment, Antenatal Care)

2. Prepregnancy counselling

- Discuss the full range of options for having children:
  - Spontaneous conception +/- prenatal diagnosis +/- termination of affected pregnancies
  - IVF with egg donation
  - Adoption
  - Mitochondrial donation trial participation
- Provide best practice in routine pre-pregnancy care:
  - Obstetric, medical, family history, medication review, optimization of MD
  - Reproductive carrier screening
  - Weight and lifestyle optimization
  - Periconceptional vitamin supplementation
  - Vaccination, hygiene education (CMV)
- Discuss care model/location for future pregnancy
  - multidisciplinary expertise

Guidance for pregnancy with mito

General advice when preparing for pregnancy

There are steps all women can take to ensure they start their pregnancies in the best possible health.

- Nutritional supplements +
- Healthy lifestyle +
- Genetic testing +
- Preventing infections +

*More information on planning for pregnancy from the Royal Australian and New Zealand College of Obstetricians and Gynaecologists can be found **here.***

> **I think it is so important that new parents with mito use their 'village' as much as possible. The societal pressure, late nights and breastfeeding were very demanding on my body. You can only be a good parent if you look after yourself.**
>
> - Alice, adult with mito - 2024

Summary

- Having mitochondrial disease (mito) may increase your risk of health problems during pregnancy. One reason for this is that your body needs to produce more energy during this time.
- For many women with mito, pregnancy and childbirth don't seriously affect their health.
- For others, mito symptoms can worsen during pregnancy, and some pregnancy complications may be more likely in women with mito. Most of these women make a full recovery after giving birth.
- While most women with mito have a smooth pregnancy and have a healthy baby. It's important to get specialised care and advice before, during, and after pregnancy.

Pregnancy guidelines for mito

This summary is to help you understand the recommended pregnancy care for women with mito. You can use this summary and the full publication to start a conversation with your health care team.

The recommendations are:

- A multi-disciplinary care approach +
- Understanding how mito affects you +
- Recommended care before, during and after pregnancy +
- Possible risk of complications in pregnancy +

https://www.mito.org.au/resource/fact-sheet-page/guidance-for-pregnancy-with-mito/

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4. Baseline medical assessment

Local care team

1. **Obstetric, medical and family history**
2. **Medication review**
3. **Psychosocial assessment**
4. **Baseline fertility investigations**
    - AMH, semen analysis, karyotype
5. **Baseline assessment of mitochondrial disease severity**
    1. NMDAS and QoL baseline score

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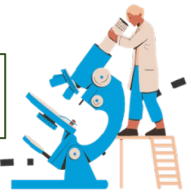

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Individualized medical investigations

Aust N Z J Obstet Gynaecol 2024; 1–7

ANZJOG

DOI: 10.1111/ajo.13874

BRIEF REVIEW

Pregnancy in women with mitochondrial disease—A literature review and suggested guidance for preconception and pregnancy care

System	Investigations
Cardiac	· Standard 12-lead electrocardiogram (ECG) · Echocardiogram (with measurement of left ventricular mass and systolic/ diastolic function) Pulmonary artery pressure (PAP) · 24-hour ECG (Holter monitoring) in patients with palpitations, paroxysmal events, or in high-risk patients including patients with cardiomyopathy · Stress test
Respiratory	· Baseline evaluation of respiratory status to assess for muscle weakness and other cardiopulmonary comorbidities. · Pulse oximetry with vital signs · Formal respiratory function testing in both the supine and upright positions · Targeted screening for additional comorbidities including obstructive sleep apnoea, bulbar weakness, risks for aspiration, gastroesophageal reflux, asthma, and chronic obstructive lung disease.
Endocrine	· Haemoglobin A1c, 75g oral glucose tolerance test · Thyroid-stimulating hormone, free thyroxine level, vitamin D · Hypoparathyroidism: serum calcium magnesium, phosphate, parathyroid hormone, vitamin D (25-OHD and 1,25-OHD); urine creatinine, calcium, and phosphate
Renal	· Blood urea, creatinine, eGFR sodium, potassium, calcium, magnesium, phosphate · Urinary albumin/creatinine ratios, protein/creatinine ratio · renal US, other imaging
Neurological	· Baseline function, mobility and exercise tolerance · Headache history · Seizure history · Document baseline neurological exam · Consider neuroimaging · Consider EEG for those with recurrent stereotypical spells, episodes of behaviour arrest or alterations of state from baseline · Assessment for movement disorder and tone · Baseline muscle enzymes (CK, LDH) · Pre-pregnancy trough for patients on anti-epileptic medication (where relevant)
Psychiatric	Consider baseline neuropsychological testing for those with CNS disease at risk of neurological regression.
Immune function	Patients experiencing recurrent or severe infections should have: · quantitative immunoglobulin levels · vaccine-specific IgG titres · lymphocyte subset levels (T cell, B cell, switched memory B-cell compartment, natural killer cells).
Ophthalmology	Visual acuity, colour vision, ocular motility, ptosis and fundoscopy Consider baseline visual fields and OCT.
Orthopaedics	Examination for orthopaedic complications including scoliosis, contractures, dislocations, and limb deformities, especially if underlying abnormalities in tone, muscle strength, or neurologic functioning.
Other	· Standard markers of nutritional status, vitamin levels, and trace elements · Body mass index · Iron studies, B12, folate · Liver function tests, lactate

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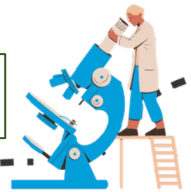

Individualised Tests

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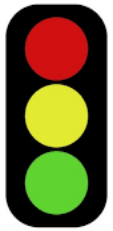

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Counselling 1+ Weeks Later (Trial Participation, Fertility Treatment, Antenatal Care)

Clinical Trial Consent

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Consent for mitochondrial donation

National Health and Medical Research Council Ethical Framework

Mitochondrial donation supplementary section: guiding principles

- ART activities must minimize harm and maximize benefit for individuals involved, including any children born as a result.
- The clinical team must provide participants with "*an appreciation of the risk of mortality, permanent disability or other serious morbidities that may result from ART procedures, and from medical complications in any resulting pregnancy, including those specific to mitochondrial disease.*"

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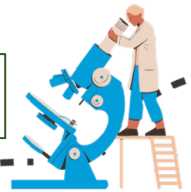
Genetic Counselling (IVF, MD, Obstetric Outcomes)

6



Individualised Tests

Review at Multidisciplinary Team Meeting

Individualised Counselling (Risks/benefits of IVF and Pregnancy)

9

Counselling 1+ Weeks Later (Trial Participation, Fertility Treatment, Antenatal Care)

Clinical Trial Consent

10

License Application Review by Embryo Research Licensing Committee

11

12

Entry into mitoHOPE Clinical Trial

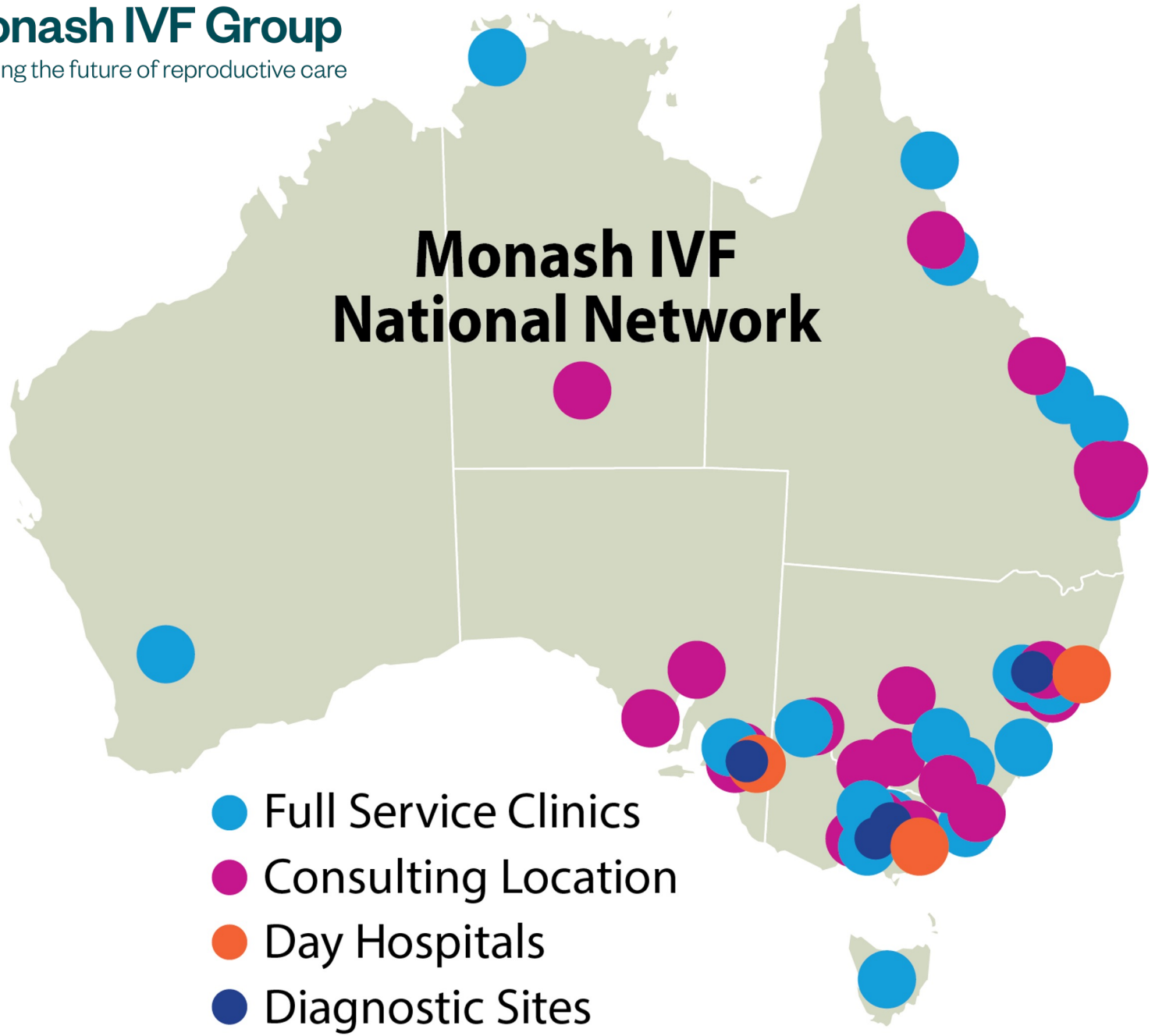
mitoHOPE

Monash IVF Group
Leading the future of reproductive care

Mito patient oocyte cryopreservation and storage at Monash IVF clinics nationally.

Mitochondrial Donation at Monash IVF Cremorne.

mitoHOPE Clinical Coordinator to assist trial participants with travel and logistics.



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BRIEF REVIEW

Pregnancy in women with mitochondrial disease—A literature review and suggested guidance for preconception and pregnancy care

TABLE 4 General principles of antenatal care of women with mitochondrial disease

	Recommended care
Pre-conception counselling	Review with specialists in mitochondrial disease and obstetric medicine for baseline medical, obstetric and psychosocial assessment (see Table S1 and Sue et al.[1]) Discuss the full range of options for having children: spontaneous conception +/− prenatal diagnosis +/− termination of affected pregnancies, gamete donation, and adoption Provide best practice in routine pre-pregnancy care, including reproductive carrier screening, weight and lifestyle optimisation, periconceptional vitamin supplementation, reducing risks of perinatal and vaccine-preventable infections[34]
Medication review	Discuss risks and benefits of current medication (esp. anti-epileptic medications,[35] antihypertensives). ACE inhibitors and angiotensin II inhibitors are contraindicated in pregnancy[36]
Folic acid	Recommend preconception and pregnancy high-dose folic acid supplementation for patients with diabetes[37] or on anti-epileptic medications[38]; other patients should have routine supplementation
Multidisciplinary antenatal care	Maternal fetal medicine, obstetric medicine, mitochondrial medicine, midwife, and general practitioner, with genetic counselling, cardiology, respiratory medicine, mental health, dietitians, and physiotherapists as needed
Management of nausea and vomiting of pregnancy (NVP)	All women should be asked about NVP at each visit and if present, severity should be assessed by PUQE-24 score, measurement of weight and hydration status. Due to the symptom overlap between mitochondrial disease and NVP, clinical assessment and care of women with severe NVP (PUQE-24 score ≥13) should involve the multidisciplinary team[39]
Gestational diabetes mellitus (GDM) screening	Perform early oral glucose tolerance testing at 20 weeks for women with mtDNA variants associated with diabetes (M.3243A > G, 14709 T > C); screen all women at 26–28 weeks as per usual care. Avoid metformin for treating GDM due to the risk of lactic acidosis[37]
Pre-eclampsia prophylaxis	150 mg aspirin nightly from 12 weeks for those with m.3243A > G or other risk factors[36]
Venous thromboembolism (VTE) prophylaxis	If prolonged immobility or other risk factors for VTE occur during pregnancy or in the postpartum period, consider physical +/− pharmacological thromboprophylaxis[40, 41]
Magnesium sulphate	If magnesium sulphate infusion is clinically indicated during pregnancy (eg for eclampsia or extreme preterm birth), vigilance for magnesium toxicity is advised[24,30]
Fetal growth surveillance	Growth scan at 28–30 and 32–34 weeks
Mode of birth	Mitochondrial disease is not a contraindication to vaginal delivery, and this should be considered the first option for delivery, monitoring maternal fatigue and hydration Caesarean section should be reserved for obstetric indications or when maternal complications of mitochondrial disease are severe
Anaesthesia	Caesarean should be performed using regional anaesthesia where possible. An anaesthetic plan should be discussed antenatally and clearly documented in the medical notes[42]
Breastfeeding	Breastfeeding should be supported in accordance with best practice with close monitoring for fatigue

Adapted from the Ref. [8].

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mitoHOPE team

If you would like to register your interest in participating in the mitoHOPE Clinical Trial, you can do so via the mitoHOPE website at:
www.monash.edu/medicine/mitohope

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MONASH University

murdoch children's research institute

THE UNIVERSITY of ADELAIDE

Newcastle University

mito FOUNDATION
Hope for mitochondrial disease

MONASH University | mitoHOPE
Led By Monash University

Thank you

"What will we ever think about now the genome project is complete?"