Published in final edited form as:
N Engl J Med. 2015 February 26; 372(9): 885–887. doi:10.1056/NEJMc1500960.

Mitochondrial Donation — How Many Women Could Benefit?

Gráinne S. Gorman, M.D.[#], **John P. Grady, Ph.D.**[#], and **Doug M. Turnbull, Ph.D.**
Newcastle University Newcastle upon Tyne, United Kingdom doug.turnbull@newcastle.ac.uk

[#] These authors contributed equally to this work.

TO THE EDITOR

Inherited mutations in mitochondrial DNA (mtDNA) are an important cause of genetic diseases for which there is no effective treatment. New techniques that are based on in vitro fertilization (IVF), including pronuclear and metaphase II spindle transfer,[1,2] have the potential to prevent the transmission of serious mtDNA diseases. However, before these techniques are permitted in the United Kingdom, Parliament must agree to new regulations regarding enforcement of the Human Fertilisation and Embryology Act (1990). Central to the debate about the use of these IVF techniques is estimating how many women could potentially benefit from these procedures. This calculation depends on the prevalence of clinically relevant pathogenic mtDNA mutations in the population and the fertility of women with pathogenic mtDNA mutations.

Using fertility data regarding live births per 1000 person-years among women 15 years of age or older obtained from the Medical Research Council (MRC) Mitochondrial Disease Cohort U.K., we assessed whether fertility is affected in carriers of pathogenic mtDNA mutations, as compared with the general population (with data obtained from the U.K. Office for National Statistics).[3] In addition, we estimated the national prevalence of women with potentially inheritable mtDNA mutations between the ages of 15 and 44 years and used these data together with the most recent national total fertility rates to estimate the number of affected live births per year in both the United Kingdom and the United States (with fertility rates of 1.85 in 2013[4] and 1.88 in 2012,[5] respectively).

We identified 154 women with inherited mtDNA mutations in the MRC Mitochondrial Disease U.K. Cohort (Table S1 in the Supplementary Appendix, available with the full text of this letter at NEJM.org) and found that pathogenic mtDNA mutations had no significant effect on the female fertility rate (Table 1). Carriers of mtDNA mutations had a rate of 63.2 live births per 1000 person-years, as compared with 67.2 live births per 1000 women in the general population ($P = 0.36$). In addition, there was no significant difference in fertility rates between the most severely affected carriers (those with the top decile of scores on the Newcastle Mitochondrial Disease Adult Scale below the age of 30 years) and a comparable weighted group of the general population, with a rate of 50.6 live births (95% confidence

A complete list of authors is available with the full text of this letter at NEJM.org.
Disclosure forms provided by the authors are available with the full text of this letter at NEJM.org.

Europe PMC Funders Author Manuscripts

Europe PMC Funders Author Manuscripts

interval [CI], 21.9 to 99.8) per 1000 person-years and 52.6 live births per 1000 women, respectively (P = 1.00).

In 2011 in the United Kingdom, 4.08% of women between the ages of 15 and 44 years were living in North East England (506,100 of 12,391,000 women), resulting in an extrapolation factor of 24.48 for the entire United Kingdom. In North East England, we identified 101 women of childbearing age who are symptomatic carriers or are at risk for transmitting mtDNA disease (for details, see the Supplementary Appendix). On the basis of the extrapolation factor, we estimated that 2473 women (95% CI, 2019 to 3246) are at risk for transmitting mtDNA disease nationally. In the United States, using midyear 2012 data for women in the same age group (totaling 62,246,000) and the same extrapolation methodology, we estimated that 12,423 women (95% CI, 10,146 to 15,064) are at risk for transmitting mtDNA disease nationally.

Using national fertility rates for the United Kingdom and the United States, we estimated that these women will give birth 4574 and 23,354 times, respectively, over a 30-year period. Thus, the average number of births per year among women at risk for transmitting mtDNA disease is 152 (95% CI, 125 to 200) in the United Kingdom and 778 (95% CI, 636 to 944) in the United States.

There are several implicit assumptions in these calculations; in particular, we have not considered possible effects of differing age profiles or ethnic diversity of women in the fertile period in comparing North East England with the national and international profile. These factors almost certainly affect the accuracy of the extrapolated estimates. However, our findings have considerable implications for all countries that are considering the use of IVF techniques to prevent the transmission of serious mtDNA diseases, although we accept that access to these techniques will vary widely. In the United Kingdom, the Human Fertilisation and Embryology (Mitochondrial Donation) Regulations 2015, if passed by Parliament, would enable the licensing of clinics to perform these IVF procedures to the potential benefit of about 150 births per year if all women opted for the procedure.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Supported by grants from the Wellcome Trust Centre for Mitochondrial Research, www.newcastle-mitochondria.com (G906919), Newcastle University Centre for Ageing and Vitality (supported by the Biotechnology and Biological Sciences Research Council and the MRC [G016354/1]), MRC Centre for Neuromuscular Disease (G000608-1), MRC Centre for Translational Research in Neuromuscular Disease Mitochondrial Disease Patient Cohort (U.K.) (G0800674), the Wellcome Trust Senior Fellow in Clinical Science (084980/Z/08/Z), Lily Foundation, the U.K. National Institute for Health Research Biomedical Research Centre in Age and Age Related Diseases award (to the Newcastle upon Tyne Hospitals NHS Foundation Trust), and U.K. NHS Specialist Commissioners Rare Mitochondrial Disorders of Adults and Children Service.

References

1. Craven L, Tuppen HA, Greggains GD, et al. Pronuclear transfer in human embryos to prevent transmission of mitochondrial DNA disease. Nature. 2010; 465:82–5. [PubMed: 20393463]

2. Tachibana M, Sparman M, Sritanaudomchai H, et al. Mitochondrial gene replacement in primate offspring and embryonic stem cells. Nature. 2009; 461:367–72. [PubMed: 19710649]
3. Cohort fertility, England and Wales, 2012. Office for National Statistics; London: 2012. http://www.ons.gov.uk/ons/rel/fertility-analysis/cohort-fertility--england-and-wales/2012/cohort-fertility-2012.html
4. Births in England and Wales, 2013. Office for National Statistics; London: 2014. http://www.ons.gov.uk/ons/rel/vsob1/birth-summary-tables--england-and-wales/2013/stb-births-in-england-and-wales-2013.html
5. Monte, LM.; Ellis, RR. Fertility of women in the United States: 2012. Jul. 2014 http://www.census.gov/content/dam/Census/library/publications/2014/demo/p20-575.pdf

Europe PMC Funders Author Manuscripts

Europe PMC Funders Author Manuscripts

Table 1

Fertility Rates in Women with Inherited Pathogenic Mitochondrial DNA Mutations, as Compared with Rates in the General Population.*

Age Range	Women with Mitochondrial DNA Mutations			General Population	P Value
	No. of Live Births	No. of Person-Years	Live Birth Rate (95% CI)	Live Birth Rate	
			no./1000 person-yr		
15–19 yr	17	761	22.3 (13.0–35.8)	32.2	0.14
20–24 yr	69	713	96.8 (75.3–122.5)	100.4	0.82
25–29 yr	91	651	139.8 (112.5–171.6)	117.6	0.12
30–34 yr	41	588	69.7 (50.0–94.6)	86.9	0.17
35–39 yr	12	516	23.3 (12.0–40.6)	38.5	0.08
40–44 yr	2	446	4.5 (0.54–16.2)	8.0	0.62
15–44 yr	232	3674	63.1 (55.2–71.8)	67.2	0.36

*Values for women with inherited pathogenic mitochondrial DNA mutations are compared with the equivalent age- and era-weighted fertility rates (live births per 1000 women) and for the general population obtained from the U.K. Office for National Statistics.