CORRESPONDENCE

Mitochondrial Donation — Which Women Could Benefit?

TO THE EDITOR: Mitochondrial donation is a new in vitro fertilization–based technique that has recently been regulated and licensed by the Human Fertilisation and Embryology Authority (HFEA) for clinical use in the United Kingdom. Mitochondrial donation allows the replacement of mutated mitochondrial DNA (mtDNA) in human oocytes or zygotes, offering at-risk couples the chance of having their own healthy child. HFEA licensing requirements for mitochondrial donation specify that its use should be permitted for patients who are at substantial risk for transmitting serious mtDNA disease in situations in which preimplantation genetic diagnosis is deemed inappropriate or likely to be unsuccessful. Predicting the risk of serious mtDNA disease in children and the likely success of preimplantation genetic diagnosis is complicated by singular aspects of mitochondrial genetics, including mtDNA heteroplasmy (i.e., the mix of mutated [pathogenic] and wild-type [normal] mtDNA within a cell), threshold effect (i.e., the level of mtDNA mutation load below which no disease symptoms emerge), and mitochondrial genetic bottleneck (i.e., the process that can lead to offspring being born with a range of different mutation loads).[1]

Preimplantation genetic diagnosis is suitable only for women who are expected to produce some eggs with low levels of mutated mtDNA and are therefore at lower risk for having a child with serious mtDNA disease. To evaluate the risk of disease transmission, we focused on the *MT-TL1* mutation m.3243A→G (because inheritance patterns are mutation-specific), the most common heteroplasmic mtDNA pathogenic variant associated with severe mtDNA disease (carried by approximately one third of adults in our mitochondrial clinics). We identified 183 mother–child pairs from 113 mothers (Table S1 in the Supplementary Appendix, available with the full text of this letter at NEJM.org).[2,3] Using Bayesian methods (see the Supplementary Appendix), we forecasted the proportion of children with heteroplasmy levels that were expected to be no higher than 18%, a level associated with a 95% or greater chance of being clinically unaffected (although this chance might be lower for m.3243A→G) and a cutoff value aligning with current preimplantation genetic diagnosis embryo-transfer practice guidelines.[4,5] We found marked variability in the children's levels of m.3243A→G heteroplasmy (Fig. S1 in the Supplementary Appendix). We have used these data to predict likely pregnancy outcomes. Only one quarter of children born to mothers harboring a 50% load of m.3243A→G

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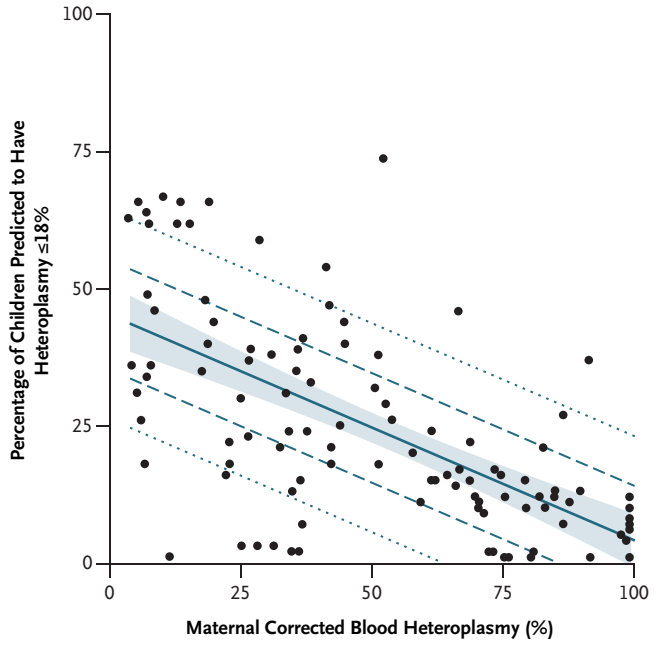

Figure 1. Percentage of Children Predicted to Have 18% or Lower Heteroplasmy for a Given Maternal Heteroplasmy.

Each point represents the percentage of children predicted to have 18% or lower age-corrected m.3243A→G heteroplasmy for each of 113 individual mothers, plotted against maternal heteroplasmy. The solid line represents the linear fit of these forecasts against maternal heteroplasmy ($R^2=0.44$, $P<0.001$), and the shaded area indicates the 95% confidence interval of this regression line. The upper and lower prediction interval boundaries are indicated by the dashed (50%) and dotted (80%) lines. To achieve these forecasts, the mean child heteroplasmy for each mother was predicted with a Bayesian mixed-effect regression model, with maternal heteroplasmy as a predictor and mother's identity as a random effect. Forecasts were obtained from the probability distribution for each mother, with the probability closest to 18% heteroplasmy reported as the percentage of children predicted to have heteroplasmy less than or equal to 18%. In addition to the data showing that a large number of oocytes would need to be screened for women with high mtDNA heteroplasmy, there is great variability around the line of best fit, suggesting that there will be many women for whom an oocyte with acceptable heteroplasmy cannot be found, despite the prediction.

are predicted to have heteroplasmy levels of 18% or lower (Fig. 1). For mothers with heteroplasmy levels of 90% or higher, the percentage of children with 18% or lower heteroplasmy is only 8%. The substantive variability in biologic transmission, indicated by the many points outside the prediction intervals, is also a finding of relevance in the counseling of affected women and the deliberations of regulators.

Our data show that the risk of having a clinically affected child can be predicted on the basis of maternal m.3243A→G heteroplasmy. For some women, the number of oocytes required to produce an embryo with sufficiently low mutation load (≤18%), and hence the chance of a healthy child, may be prohibitively high for "successful" preimplantation genetic diagnosis — one that results in the birth of a healthy child who is at minimal risk for mtDNA disease.

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