Measuring what trials miss: decision modelling for value-based reproductive health

Randomised controlled trials are foundational in reproductive medicine, yet they often do not address the outcomes that matter most to patients, clinicians, and health systems. Follow-ups tend to be short and endpoints proximate, such as live birth per cycle, while many consequences of reproductive decisions, including ovarian ageing, cardiometabolic risk, treatment burden, and quality-adjusted survival, unfold over years or decades. Reproductive health is thus a long-horizon discipline still guided largely by short-horizon evidence.

Decision-analytic modelling and cost-effectiveness analysis offer a means to bridge this gap. These approaches do not replace trials but extend their relevance by integrating data with observational evidence, utilities, and costs over clinically meaningful time horizons (panel).[1] Their value is greatest when outcomes are delayed, uncommon, or span multiple domains of health.

Frozen embryo transfer illustrates the problem clearly. Comparative studies typically conclude where the fertility clinic's dashboard ends: implantation, pregnancy, and live birth. Yet, recent randomised controlled trials comparing natural-cycle and programmed frozen embryo transfer report similar singleton healthy delivery rates but lower rates of pre-eclampsia with natural cycles.[2] This distinction becomes more meaningful when viewed beyond delivery. Pre-eclampsia is an established independent risk factor for future cardiovascular disease and is recognised by the American Heart Association and American College of Cardiology as an atherosclerotic cardiovascular disease risk enhancer.[3] A modelling framework that links short-term reproductive and perinatal outcomes to later maternal cardiovascular consequences could therefore provide a more meaningful assessment of comparative value than live birth alone.

The same logic applies to fertility preservation strategies. Oocyte and embryo cryopreservation might appear more practical or cost-effective when evaluated solely on pregnancy outcomes. However, unlike these approaches, ovarian tissue cryopreservation can restore endocrine function after transplantation, potentially delaying treatment-induced premature menopause.[4] This distinction might influence bone and cardiovascular health, quality of life, and the timing of family completion. A narrow focus on pregnancy outcomes therefore risks missing outcomes that could matter the most to patients. As with frozen embryo transfer, this decision problem is well suited to a decision tree linked to a Markov model that bridges short-term reproductive outcomes and long-term health trajectories.

A similar limitation arises in the management of endometrioma-associated infertility. Surgery might alleviate pain, particularly when deep endometriosis is present, and reduce the risk of malignant transformation, but at the cost of surgical morbidity and diminished ovarian reserve; an in-vitro fertilisation-first approach preserves ovarian reserve while leaving the endometrioma and its associated risks in situ.[5] Focusing only on reproductive outcomes therefore

Panel: **Decision-model structures and potential applications in reproductive medicine**

Decision tree

- Short-term, discrete outcomes without time dependence
- Becomes impractical for recurrence, time-dependent risk, or evolving patient history
- Application: clinical pregnancy, miscarriage, or live birth after in-vitro fertilisation or frozen embryo transfer

Markov cohort model (cohort state-transition model)

- Long-term transitions between defined health states over recurring cycles
- Transition probabilities depend only on the current state, not on previous history (memoryless or Markov property)
- Application: pregnancy progression, obstetric complications, and later maternal cardiovascular health

Dynamic compartmental model

- Outcomes shaped by population-level feedback, in which the state of one group influences risk in another, and typically governed by ordinary differential equations
- Typically represents populations at an aggregate level and cannot track patient-level histories or heterogeneity in detail
- Application: sexually transmitted infections, congenital infection risk, or vaccination strategies in pregnancy

Individual-based microsimulation

- Heterogeneous, path-dependent life-course trajectories shaped by individual characteristics and treatment history
- Requires richer data inputs and substantially more computation but can capture individual histories, baseline heterogeneity, and path dependence that cannot be achieved by simpler models
- Application: ovarian reserve decline, endometrioma recurrence, repeated assisted reproductive technology attempts, treatment crossover, timing of family completion, and malignant transformation risk

misses trade-offs that unfold over the life course, including pain, recurrence, malignant transformation, premature ovarian insufficiency, and quality of life. Because recurrence and previous treatment history dynamically shape subsequent risks and management options, this decision problem is better evaluated using individual-based microsimulation rather than simple cohort Markov models.

If reproductive medicine is to align with value-based care, decision modelling should become a routine complement to clinical trials. The field must move beyond asking which intervention improves live birth to determining which strategy best improves a patient's life course.

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Murat Erden, Atalay Demiray, Rosanne M Kho, Kutluk H Oktay
haldunmurat.erden@yale.edu

Department of Obstetrics, Gynecology, and Reproductive Sciences, Yale University School of Medicine, New Haven, CT 06510, USA (ME, KHO); Obstetrics and Gynecology Residency Program, Creighton University East Valley Arizona, Gilbert, AZ, USA (ME); Department of Health Policy and Management, Yale School of Public Health, New Haven, CT, USA (AD); Department of Obstetrics and Gynecology, University of Arizona College of Medicine – Phoenix/Banner – University Medical Center Phoenix, Phoenix, AZ, USA (RMK); Innovation Institute for Fertility Preservation New York, NY, USA (KHO)

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