

Perivable birth: A review of ethical considerations

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Abstract

Background: Advances in perinatology and medical technology have pushed the limits of viability to unprecedented extremes, leading to a growing population of NICU “graduates” with a wide range of health issues. Although survival rates from 22 weeks of gestation onwards have improved over the last 30 years, the incidence of disabilities remains the same. Providing intensive care to a high-risk population with significant mortality and morbidity raises the fundamental conflict between sanctity and quality of life. Potential severe handicap and need for frequent tertiary care inevitably impact the whole family unit and may outweigh the benefit of survival. The aim of this study is to explore and summarize the ethical considerations in neonatal care concerning perivable birth.

Methods: Eligible studies published on PubMed were included after a systematic search using the PICO methodology.

Results: Forty-eight studies were systematically reviewed regarding guidelines, withholding or withdrawing treatment, parental involvement, and principles applied in marginal viability. As perivable birth raises an array of complex ethical and legal concerns, strict guidelines are challenging to implement.

Conclusions: Active life-sustaining interventions in neonatology should be balanced against the risk of putting infants through painful and futile procedures and survival with severe sequelae. More evidence is needed on better prediction of long-term outcomes in situations of imminent preterm delivery, while good collaboration between the therapeutic team and the parents for life-and-death decision-making is of utmost importance. HIPPOKRATIA 2021, 25 (1):1-7.

Keywords: Extreme prematurity, perivability, limit of viability, guidelines, withholding treatment, withdrawing treatment, ethics

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Introduction

Perivability is defined as the stage of fetal maturity with a marginal chance of extrauterine survival. Most neonates born at or above 26 weeks of gestation have, with active intervention, a high likelihood of survival, while below 22 weeks are virtually nonviable. This time window between 22 and 26 weeks of gestational age is considered as the period of perivability¹, and it is a “gray zone” for clinical and ethical decision-making. Terms used for these neonates are “extremely preterms”, “micro-preemies”, and “at the threshold of viability”². There is a widespread consensus that 22 weeks of gestation is the lowest threshold of human viability^{3,4}, limited by the physiologic development of the lungs. Consequently, the limit of viability is not expected to decrease any further, at least not with the current knowledge and technologic

resources⁵. Perivable neonates are susceptible to significant morbidities (periventricular leukomalacia, severe intraventricular hemorrhage, bronchopulmonary dysplasia, necrotizing enterocolitis, severe retinopathy of prematurity), with a high risk for permanent sequelae and neurodevelopmental impairment (NDI)⁶. This risk is inversely proportional to gestational age (GA)⁷ and determines these children’s physical, emotional, intellectual, and social well-being in the ensuing years (long-term outcome). As the boundaries between utility and futility in decision-making are unclear, management of extremely preterm infants (EPIs) may present a variety of complex medical, social, and economic issues requiring significant ethical decisions. Ethical dilemmas derive primarily from the prospect of severe neurological sequelae; therefore, the contribution of neuroimaging to more accurate prediction

of long-term NDI is crucial⁸. Nevertheless, extremely preterm survivors do not associate the self-reported quality of life (QoL) with their degree of disability in neither later childhood nor adulthood³.

According to the EXPRESS study, the 1-year mortality rate of neonates born between 22 and 24 weeks of gestation was 35 % in the high-activity regions and 59 % in the low-activity regions⁹. In neonates of 22-26 weeks, intensive perinatal care was associated with a reduction in the 1-year mortality rate and survival with NDI at 2.5 years corrected age (CA)⁹. Increased survival was not correlated to increased neonatal morbidity or NDI rate. At the 6-year follow-up, 44 % of children born at <23 weeks had no or mild functional disability, 35 % had moderate disability, and 22 % had severe functional impairment, while 66.4 % of EPIs born at <27 weeks had no or mild disability at 6.5 years of age, 20.2 % had moderate disability, and 13.4 % had severe functional impairment. The risk of death or survival with severe sequelae decreased, at 6.5 years of age, from 92 % at 22 weeks to 25 % at 26 weeks¹⁰. In the EPIPAGE and EPICure studies, Intelligence Quotient differences of EPIs compared to controls were estimated at 24 points¹¹ and 18 points, respectively¹². Long-term impairments affect the overall outcome of former EPIs and significantly impact the quality of life of the whole family unit^{13,14}.

The present study aims to evaluate ethical aspects of guidelines and clinical decision-making for neonates born at the margins of viability. Many State legislatures, including the Greek, have not enacted legislation to regulate ethical and legal questions concerning the care of the neonates at the limits of viability. Consequently, varying existing approaches across Neonatal Intensive Care Units (NICUs) in all medical, ethical, and socioeconomic issues may seriously impact the quality of care of these infants and add emotional burden to the families and health care professionals involved.

Material and Methods

Search strategy

This study was performed in strict accordance with guidelines for systematic reviews and meta-analyses, and specifically the PRISMA methodology¹⁵. Relevant studies published on PubMed between 2000 and 2020 were selected as being potentially eligible to be included in the study. PubMed was selected as the primary search database as it is prevalent in the medical community worldwide; it focuses only on medicine, is accessible, and includes about 30 million publications¹⁶. To compensate for publications not available in PubMed or missed due to query issues or inappropriate reported MeSH terms, the authors performed additional searches (for example, in Google Scholar) and added any papers relevant to the study.

Search question formation

The search query was formulated according to the PICO framework^{17,18}. PICO is used in evidence-based medicine to set up in a systematic way clinical or health-

related questions and strategies for literature research and is compatible with the PRISMA methodology¹⁸. PICO is an acronym that stands as follows: P: for the patient, population, or problem, I: for intervention, C: for comparison or control, and O: for outcomes. Besides PICO, there are many other methodologies to formulate research questions, such as PICOS (S stands for Study type) and SPIDER¹⁹ (Sample Phenomenon of Interest Design Evaluation Research Type), and simpler methods such as PICO (Population or Problem Interest Context)^{20,21}. No method was perfectly suitable for the research question of this study, as the C part was used for terms such as guidelines. It may seem that the Context component of the PICO method is suitable; however, PICO is missing the outcome component. Therefore, PICO was considered the most suitable approach. According to this strategy, the formation of individual query parts and the final query issued in PubMed is depicted in Table 1. MeSH terms were the most compliant with the standard practice.

The query was issued to the PubMed database using the advanced search builder, which allows manual editing of the query terms. Each part of the query was applied for specific searches: The P part, which can provide 596,774 or more results in return, was used to search for newborns or extremely premature or extremely low birth weight infants. The I part was used for terminal or hospice or palliative care or treatment withholding; this component can provide 99,457 results. The C part was used to search for practice or health-planning guidelines, or for the standard of care, or evidence-based emergency medicine or practice; this query can return 234,340 or more results from PubMed. The final component (O part) was applied to include ethics, and it can return 181,466 results. The above components' combination utilizing the AND operator resulted in the final query (Table 1), which returned 109 potentially eligible research papers.

Selection of publications

During the screening process, two independent researchers reviewed all search results based on titles and abstracts, and relevant studies were included for the subsequent full-text review stage. In case of disagreements, a third researcher's opinion was requested. Other researchers participated in data extraction stages. This work represents a qualitative synthesis of the selected data based on a systematic literature review. Figure 1 outlines the data collection and selection process.

Guidelines on providing resuscitation and intensive care to EPIs at birth

Neonatal resuscitation guidelines are based on GA as follows^{22,23}:

GA <22 weeks of gestation

No resuscitation should be offered due to zero or near-zero chance of survival. Compassionate care is indicated. Resuscitation attempts of an infant should only take place in the context of a clinical research study (ap-

Table 1: Structured query according to the PICO framework. The final query according to the synthesis of the individual components appears in the last table row.

PICO component	Query
P(atients)	“Infant, Newborn”[Mesh]OR “Infant, Extremely Premature”[Mesh]OR “Infant, Extremely Low Birth Weight”[Mesh]→ 596,774 results
I(ntervention)	“Terminal Care”[Mesh]OR “Hospice Care”[Mesh]OR “Withholding Treatment”[Mesh]OR “Palliative Care”[Mesh]→ 99,457 results
C(omparison)	“Guidelines as Topic”[Mesh]OR “Guideline”[Publication Type]OR “Practice Guidelines as Topic”[Mesh]OR “Health Planning Guidelines”[Mesh] OR “Standard of Care”[Mesh]OR “Evidence-Based Emergency Medicine”[Mesh]OR “Evidence-Based Practice”[Mesh]→ 2643,40 results
O(utcome)	“Ethics”[Mesh] OR “ethics”[Subheading]→ 181,466
Complete query (individual parts combined with AND operators)	(“Infant, Newborn”[Mesh] OR “Infant, Extremely Premature”[Mesh] OR “Infant, Extremely Low Birth Weight”[Mesh]) AND (“Terminal Care”[Mesh] OR “Hospice Care”[Mesh] OR “Withholding Treatment”[Mesh] OR “Palliative Care”[Mesh]) AND (“Guidelines as Topic”[Mesh] OR “Guideline”[Publication Type] OR “Practice Guidelines as Topic”[Mesh] OR “Health Planning Guidelines”[Mesh] OR “Standard of Care”[Mesh] OR “Evidence-Based Emergency Medicine”[Mesh] OR “Evidence-Based Practice”[Mesh]) AND (“Ethics”[Mesh] OR “ethics” [Subheading])→ 109 results

proved by an Ethics Committee and following informed parental consent)²⁴.

GA 22^{0/7} - 24^{6/7} weeks of gestation

According to mainstream bioethics, the initial approach for neonates of this gestational age is not to provide resuscitation unless parents request so and doctors

agree²⁵. Experienced neonatologists should attend births from 22+0/7 weeks, while resuscitation should be considered from 22+0/7 weeks and recommended from 23+0/7 weeks^{26,27}. Current guidelines propose individualized management; in general, resuscitation and intensive care are provided and subsequently escalated or withheld depending on the initial response of the infant and parental choices.

GA 25 weeks and above

Resuscitation and intensive care are provided. Exceptions can be made in case of aggravating factors (e.g., anencephaly, lethal genetic disorders or congenital malformations, severe growth restriction)^{26,27}.

For all three categories, it is generally acceptable to initiate and withdraw resuscitation later after reevaluation, in case that efforts are disproportionate to any prospect of improvement. In such circumstances, parental permission to discontinue resuscitation is not legally required²⁸. Withdrawing efforts after 10 minutes without improvement is an overall acceptable time frame, as the outcome beyond this time is uniformly poor^{29,30}. Delayed, graded, or partial support should be avoided because if the infant survives, the outcome will be grave³⁰.

Pregnant women at a gestational age of 22+0/7 weeks or more with imminent preterm delivery should be transported to a specialized perinatal center. Antenatal steroids are recommended from 23+0/7 weeks and indicated from 25+0/7 weeks; cesarean delivery is recommended from 24+0/7 weeks and indicated from 25+0/7 weeks as well.

The initial appearance at birth⁹ and Apgar scores at 1 and 5 minutes are not predictors for survival⁶. Moreover, *GA per se* is neither a sensitive nor a specific indicator for

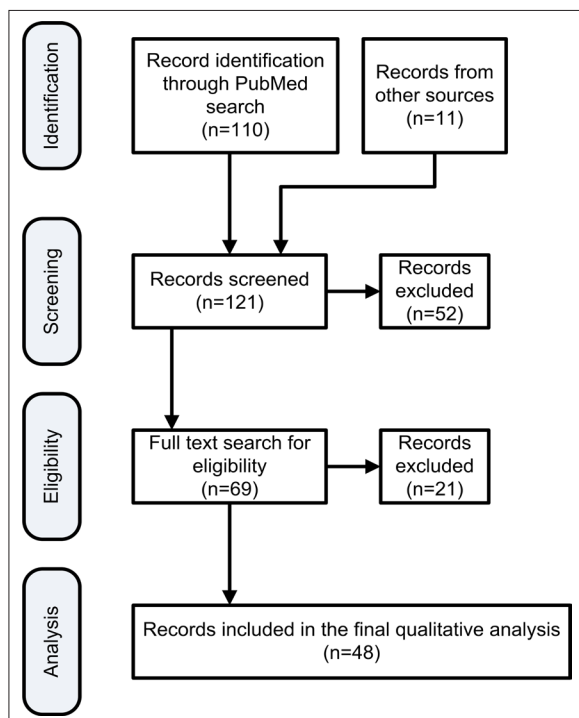


Figure 1: Flowchart of the search strategy for data collection and selection process.

survival and disability³¹⁻³³; fetal ultrasonography at the first-trimester provides an estimate of GA with an accuracy of +/- 7-10 days, while at the second-trimester it could be discrepant by almost 2 weeks^{34,35}. Additional factors like singleton birth, female gender, higher birth weight (BW) for GA, and exposure to antenatal steroids are associated with increased survival rates^{6,34}. The likelihood of death between 22 and 25 weeks of GA falls by almost 3% per day³⁶. Socioeconomic parameters, proactive intervention, willingness to intervene³², and birth in a tertiary center also impact the outcome of EPIs^{37,38}. Therefore, the risk of death or profound impairment for infants born between 24 and 25 weeks GA may vary by 2.5-fold³⁴. Consequently, life-and-death decisions based only on GA guidelines with rigid boundaries (Gestational ageism)^{30,35} are scientifically and ethically wrong^{34,36}. If the clinical age and the estimated GA differ, medical management should be based on the more advanced one³³. A realistic assessment of an infant's clinical condition can be provided by PAGE (the acronym stands for Prognosis for Average Gestation Equivalent infant), a multiparameter prognosis-based framework for crucial decisions concerning periviable neonates (Table 2)³⁸.

Withholding and withdrawing life-sustaining treatment

As the limits of viability shifted towards lower gestational ages, dilemmas concerning selective nontreatment of disabled neonates have become much more complex than previously thought. Withholding applies to omitting active life-sustaining treatments (LSTs) considered as non-beneficial (i.e., primary nonintervention), while withdrawal refers to discontinuing LSTs proved to be futile (i.e., redirection of care). Futility is defined as quantitative (an intervention “does not work”), or qualitative (the intervention is “not worth it”)³⁶. Withdrawal of treatment is permissible in a narrow time window (called “window of opportunity”) right after birth if serious complications arise and in case of severe aggravation later. The window closes when the infant has been stabilized; withdrawing life support in a stable situation is not considered permissible^{35,39,40}. While withholding treatment is merely regarded as an omission to intervene, withdrawal is considered an active intervention. However, the Equivalence thesis (ET), in accordance with *Utilitarianism-or*

consequence ethics, does not support any ethical difference between withholding and withdrawing of treatment⁴¹⁻⁴² as long as the consequences are the same^{24,43,44}. In this concept, most legal jurisdictions consider both withdrawal and withholding of treatment as omissions (withdrawal seen as “postponed withholding”), and permit doctors to withdraw treatment⁴³.

The goal of demonstrating the moral equivalence of withholding and withdrawal of treatment is to overcome *withdrawal aversion* (preference for withholding over withdrawal)⁴⁵, a form of cognitive bias with potential serious ethical consequences (i.e., ineffective treatments being prolonged or beneficial treatments unjustly withheld)⁴³. Resuscitation at birth can also provide the advantage of the time required to make a more accurate prognosis and, therefore, more well-founded decisions³³. Nevertheless, perceived psychological and social non-equivalence still exists between withholding and withdrawal of treatment (prognostic and conditional non-equivalence)^{43,44}. In order to ease the burden of decision-making in critical illness, the “No Escalation of Treatment” (NoET) thesis proposes to continue LSTs at their current intensity but to withhold new or higher-intensity treatments, meaning that care will not escalate⁴⁵. Another strategy is to enforce limits on the provided treatment (for example, by accepting a maximum respiratory or cardiovascular support)³⁶. Clinically assisted nutrition and hydration are regarded as LSTs, and there is no legal obligation to provide them in an antemortem stage⁴¹. Certain pain or symptom relief medication could potentially shorten life when administered in higher doses; however, this is morally and legally acceptable when it provides comfort to a dying infant - the Principle of Double Effect (PDE)⁴¹. The Double Effect Theory (the “tolerable risk” theory in criminal law - “Erlaubtes Risiko”), otherwise called indirect active euthanasia, refers to the administration of a treatment in order to improve the situation of a patient, with the possible parallel consequence of accelerating death⁴⁶. Its legal interpretation is not robust, though, due to lack of adequate research under criminal evidence legislature^{41,47}. PDE requires a moral distinction between intending an outcome and foreseeing it and does not sanction acts in which both positive and negative outcomes are intended⁴¹.

Table 2: A prognosis-based framework for decisions on resuscitation and intensive care for extremely premature neonates.

Estimated chance of poor outcome if intensive care is provided (%)†	PAGE	Treatment category	Obstetric management
≤50	≥25 weeks gestation	Usual (active management directed towards survival)	Maternal/fetus-focused
50–90	23–24 weeks gestation	Optional (life sustaining treatment should be guided by parents' wishes)	Depends on parents' wishes
≥90	20–22 weeks gestation	Palliative care (comfort focused)	Maternal-focused

†: Poor outcome refers to the probability of either death or profound disability (severe, non-ambulant cerebral palsy or severe cognitive disability), PAGE: Prognosis for Average Gestation Equivalent infant.

Parental involvement in end-of-life decision-making

Ongoing evaluation and discussion between the health care team and parents should guide decisions regarding continuation or withdrawal of support²⁶. Parents should be informed in detail about their infant's status and institutional policies on managing extreme prematurity so that varying practices regarding end-of-life decisions (EoLDs) would not result in parental confusion, misgiving, and lack of trust in medical management. This variability in neonatal end-of-life care among NICUs on both national and international levels, which also reflects physicians' cultural background and personalities, accounts for 75 % of differences in survival and survival without disability^{9,35,37}. Senior staff should perform parental counseling, preferably prior to delivery, and must include discussion on the potential need for palliative care. Appropriate support for the grieving process and post-death arrangements should also be provided⁴⁸. The emotional distress of health care professionals should not be underestimated, and psychological support should be available for them as well⁴⁹.

If the primary goal cannot be reached and the burden of interventions appears unjustified, redirection to palliative care is indicated^{7,50}. Palliative care is deemed an active and holistic approach to providing care with physical, emotional, social, and spiritual elements that enhance the infant's quality of life and offer support for the family. It includes relief of distressing symptoms, providing compassionate care for infants and families, and support through death and bereavement⁴¹. However, a decision to forego intensive care that no longer corresponds to the actual condition of the infant must be distinguished from euthanasia^{30,40}.

The development of uniform clinical guidelines on EoLDs would alleviate some subjectivity and enforce clarity, consistency, and transparency, enhancing parental trust⁴⁸. Physicians' and parents' shared decision-making^{51,52} should be based on direct and open communication sensitive to their culture and appropriate for their level of understanding complex issues regarding medical condition, prognosis, and treatment options^{1,37,53}. Clinical staff should be supported with continuing professional education and training in communication skills, ethics, and issues raised by EoLDs⁴¹.

Collaborative decision-making is the most reliable and robust model, which incorporates and balances the observation, knowledge, and insights of both the family and the treating team¹³. This model can adapt to most circumstances; it protects against extremes in decision-making and provides conclusions' validation for the key decision-makers⁴⁸. Parents should be informed of institutional policies regarding the management of extremely preterm neonates, ideally prior to birth; an individual NICU's culture and message framing (i.e., positive frame: focus on survival without disability; negative frame: focus on mortality and neurologic impairment), significantly affects shared decision-making¹. Parents are charged as decision-makers on their infants' behalf⁶, after being fully informed ("substitute consent")²⁹.

The term "best interest" in a marginally viable newborn is framed according to the following criteria: i) intensive care is contraindicated when early death is highly possible and survival carries a significant risk of unacceptably severe morbidity, ii) intensive care is indicated when survival is likely and the risk of unacceptably severe morbidity is low, while iii) in the "gray area" -where the "best interest" of the infant is unclear and proposed treatment is either investigational or optional, parental authority is of utmost importance^{52,53}. Outside this gray zone, when treatment is mandatory (the benefit outweighs the burden) or unreasonable (the burden outweighs the benefit), parental authority is limited¹.

There are specific circumstances when limiting intensive treatment that should be considered, as they oppose the child's "best interest":

i) When life expectancy is limited, it may not be in the child's "best interest" to provide treatment that it would be unlikely to prolong life significantly. These include a. Brain stem death determined by agreed professional criteria; b. Imminent death, where deterioration occurs regardless of the treatment; c. Inevitable death (not immediately imminent) where prolonged life by LST confers no overall benefit.

ii) When life's quality is limited: Treatment may prolong life significantly without relieving the burden associated with illness or the treatment itself. These comprise a. Burden of treatment that produces sufficient pain and suffering outweighing any actual or potential benefits; b. Burden due to the infant's underlying condition that causes such distress and pain as to overwhelm any actual or potential benefit in sustaining life; c. Lack of ability to benefit; the infant's condition severity is such that it is impossible to benefit from life prolongation⁴¹.

Parents can withhold or withdraw consent for the treatment of their infant; however, the parental will is respected only as long as it causes no harm to the child (The Zone of Parental Discretion)³⁸. Otherwise, decisions are assessed *via* the Best Interests' Principle on the child's benefit and the Harm Principle, which calls for the involvement of the Institutional Bioethics Committee⁴¹.

Principles of bioethics applied in marginally viable infants

As treatment can be justified only by a proportionate patient's benefit, treatment decisions for extremely premature neonates are divided into four categories: mandatory, optional, investigational, and unreasonable^{54,55 55}. The two extremes, the "vitalistic" approach (preserving life at any cost) and the "easy" alternative of euthanasia, should be avoided to maintain the holistic view of the human person. Treatments that offer the parents a reasonable hope of benefit and are not too burdensome for the infant are considered as "proportionate means", while "disproportionate means" are those not offering a reasonable hope of benefit or involve an unreasonable burden for the infant or the family³⁰. Therefore, the sanctity of life does not take precedence in all circumstances²². "Baby Doe" legislation rejected vitalism from clinical judgment, stating that not

every reduction in mortality is worth the resulting morbidity among the survivors¹³. There is no legal obligation to provide treatment that is not medically indicated or is futile^{13,48}. Forgoing intensive care is rendered following a rigorous evidence-based process and a primary assessment (burden acceptable). It is determined by the Best Interest Standard¹³: in case of adverse prognostic factors, intensive care would be conditionally recommended after a secondary assessment (burden likely to be acceptable), and a shared decision would direct either to palliative care or to provisional intensive care^{7,32}. Cost-effectiveness-based thresholds in intensive care raise a moral debate, based on the argument that ineffective treatments would harm others through the unfair consumption of scarce resources in the public health system⁵⁶. Indeed, in low-income areas, prioritization of available resources condemns certain infants who could survive in more resource-intensive areas³⁴. United Nations Convention on the children's rights recognizes the right to life from the moment of birth irrespective of gestational age^{8,22-24}; therefore, periviable neonates are equally worthy to full-term ones^{2,57}. Decisions regarding the continuation or interruption of LSTs are based on four ethical principles: autonomy, beneficence, justice, and non-maleficence (the treatment dilemma). As prognosis at the limits of viability remains uncertain, the same live-saving medical technology may unintentionally lead to severe residual comorbidities, extremely long hospitalizations, and a technologically-dependent survival, or increase the average age of death (Benevolent Injustice)^{57,58}.

The concept of health-related Quality of Life (QoL) refers to an individual's subjective perception of the consequences of their health state on their physical, emotional, and social development⁵⁹. Limitation of intensive care based on future QoL is controversial; the EURONIC project demonstrated that such decisions are culturally and sociologically related phenomena⁶⁰. Quality-adjusted life-year (QALY) calculations quantify health outcomes' value of by considering both the quality and the quantity of life lived. Subjective QoL is similar in very low BW survivors when compared to normal BW peers, and extremely low-BW infants have health-related QoL as young adults similar to those born at normal weight⁶¹.

Summary

At present, marginally viable neonates are routinely rescued, posing troubling questions concerning the long-term consequences (biological and social) of the immediate technological triumphs. The high morbidity rate necessarily imposes an iatrogenic burden on the survivors and a financial one on their families and society. EoLDs should be made by the therapeutic team in collaboration with the parents, based on shared knowledge and mutual respect. The primary criterion in decisions to limit intensive care should be the child's "best interests". Professional responsibilities should not discontinue when a child succumbs, and the provision of bereavement support services for the families and emotional support for the involved staff are recognized as necessary parts of the

grieving process for all concerned.

Conclusions

Periviability is one of the greatest challenges of bioethics and modern hi-tech neonatology. Developing an international database on these practices and outcomes is necessary to evaluate variabilities between countries in survival and the QoL of former micro-preemies and their families. A distinct corpus of legislation concerning decision-making in critical neonatal care would help institutions establish common parental counseling and involvement policies. New guidelines and innovative developing projects (artificial uterus) will expectedly improve early interventions for quality improvement to better long-term health outcomes for these "new survivors".

Conflict of interest

Authors declare no conflict of interest.

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