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Economic evaluation of Medically Assisted Reproduction: An educational overview of methods and applications for healthcare professionals

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A B S T R A C T

Economic evaluations of the value-for-money of Medically Assisted Reproduction (MAR) interventions are increasingly important due to growing pressure on healthcare budgets. Although such evaluations are commonplace in the published literature, the number/methodological complexity of different evaluations available, and the challenges specific to MAR interventions, can complicate the interpretation of such analyses for fertility treatments. This article aims to serve as an educational resource and provide context on the design/interpretation of economic analyses for MAR interventions. Several areas are relevant for first-line providers and decision makers: scope of analysis, comparator used, perspective/time horizon considered, outcomes used to measure success, and how results from cost-effectiveness studies can be summarised and used in clinical practice. We aim to help clinicians better understand the strengths/weaknesses of economic analyses, to enable the best use of the evidence in practice, so resources available for MAR interventions can provide maximum value to patients and society.

Introduction

Increasingly, publicly and privately funded fertility clinics are under threat due to constrained resources, increasing demand, costs of increasing technical improvements and reprioritisation in healthcare budgets. Under these conditions, there has never been a more important time for using economic evaluations to optimise outcomes for patients and society with limited resources available. The current environment underpins the need for clinicians to better understand how to apply a cost-effectiveness rationale in clinical practice and resist the temptation to focus only on costs without considering the effectiveness and the overall value-for-money of Medically Assisted Reproduction (MAR) interventions.

Clinicians, as first-line providers and often as decision makers, are in a unique position to improve MAR delivery. Each choice that they make can have cost and outcome implications. As such, to help clinicians translate economic evaluations into practice, the aim of this paper is to provide recommendations for designing economic evaluations and to help clinicians better understand their application. This paper focuses on several key questions on economic evaluation that MAR practitioners and policy makers are likely to encounter in daily practice and about which a better understanding is essential.

The key themes of this paper were agreed at a panel meeting of experts, including all co-authors, who have experience in conducting and/or contributing to economic evaluations of MAR, which was convened in Frankfurt in November 2019.

Does the analysis produce broad or narrow cost-effectiveness estimates?

An economic evaluation always compares two or more interventions in terms of their costs and outcomes. The goal is to provide information on how efficient an investment of resources in one intervention is compared with its alternatives. There can be several possible conclusions: the costs and outcomes can be equivalent, the intervention can be either more or less costly than its comparator, and more or less effective in generating a desired outcome. From an economic perspective, costlier/less-effective interventions should never be implemented, whereas less costly/more -effective interventions should always be selected. More difficult questions, where judgements of cost-effectiveness need to be made, occur when an intervention is costlier but also more effective, or when it is less costly but also less effective.

Depending on the scope of interventions being compared, a different type of economic evaluation will have to be used. The first and broadest scope considers the allocation of resources across many healthcare settings and beyond. These analyses consider how increased spending on one particular area of healthcare might compare in terms of value for money with the investments made in health services in other areas or even in other sectors of the economy beyond healthcare. Here, a health-economic approach of societal value is about understanding those services and outcomes that are important to citizens and allocating budget to those programmes deemed most important to society, with the aim of maximising societal welfare [1,2]. Cost-utility analyses (CUAs) and societal cost-benefit analyses (CBAs) assess the benefits of a programme in the broad and generic terms of quality-adjusted life years (QALYs) or monetary units, respectively, so that they allow broad comparisons (e.g. across disease categories [see Table 1]). These analyses inform policy makers about allocative efficiency: the 'optimal' resource allocation within the constraints of the budget. It is this resource allocation that needs to be addressed during discussions regarding whether MAR should be publicly funded at all and, if so, how big its budget should be relative to other healthcare domains (e.g. oncology/mental health) or other ways of spending public money (e.g. infrastructure). This type of economic study is rarely executed in MAR.

The second scope, which is most commonly reported in the published literature of MAR and in clinical practice, is narrower and only compares interventions by their ability to achieve a well-defined set of outcomes. It investigates, within the narrow boundaries of a condition-specific outcome measure (in this case, a live birth), which intervention delivers this outcome at the lowest cost or what additional costs are needed to generate one additional unit of that outcome (i.e. live birth rate). This type of information is provided by a cost-effectiveness analysis (CEA). By the nature of its specific outcome metric, it allows a much narrower scope of comparisons and, in its traditional use, is most suited to informing the maximisation of a desired unit of outcome in the context of an earmarked budget for MAR.

However, it is common to see the results of cost-effectiveness studies of MAR technology reported as an incremental analysis, whereby an 'incremental cost-effectiveness ratio (ICER)' is calculated by measuring the incremental cost of a new therapeutic approach and dividing it by the incremental effects (e.g. additional live births). In situations where this infers an increase in MAR spending for an increase in live births, this takes us into the realms of allocative efficiency: depending on the cost of the new therapeutic approach, its adoption may require further allocation of scarce resources [3].

In short, in the context of MAR, CUAs and societal CBAs address the degree to which healthcare systems should treat the condition of infertility or increase spending on MAR treatments compared with other healthcare domains. CEAs help to identify those MAR programs that optimise live birth rates [4], although an incremental analysis can also be informative in terms of allocative efficiency when it is understood how valuable one birth is to society (see also the section How are economic evaluation results summarised?).

What is the comparator intervention used in the analysis?

One of the first considerations in conducting or evaluating an economic evaluation is establishing the comparator: the intervention or standard of care to be replaced following the introduction of a new medical technology. Alternatively, a new MAR intervention can be compared to many products when multiple treatment options exist. By choosing the wrong comparator, or omitting a relevant comparator, an intervention can easily be made to look more or less cost-effective than it really is. When assessing the applicability of cost-effectiveness studies to clinical practice, one must scrutinise whether the comparator is appropriate for their patient population and local setting (see also the section How can evidence be used in practice?). For example, when comparing two stimulation protocols, it is

Table 1
Types of economic evaluation.

Type of evaluation	Cost measure	Outcome measure		MAR example
Cost-effectiveness analysis (CEA)	Volume of physical resource times unit cost	**Physical, natural units**	• Pregnancy • Delivery • Live birth • Cumulative live birth	• Sequential single embryo transfers, when clinically appropriate, can reduce total ART treatment and pregnancy/infant-associated medical costs by reducing multiple births without lowering live birth rates [9]. • Single embryo transfer followed by an additional frozen-thawed single embryo transfer (if available) was dominant: less costly and more effective than double embryo transfer in women under 32 years [33]
Cost-utility analysis (CUA)		'**Utilities**' that take into account public preferences for different health states	• Quality-adjusted life year (QALY) • Disability-adjusted life year (DALY) • Healthy years equivalent (HYE)	• In the short term (1 year), single embryo transfer is more cost-effective than double embryo transfers; however, in the intermediate (5 years) and long terms (18 years), double embryo transfer becomes the most cost-effective strategy, with a ceiling ratio of €20,000 per QALY [6]. • The 2:1 combination of recombinant human follicle stimulating hormone and recombinant human luteinising hormone was a cost-effective option for ovarian stimulation (ICER per QALY was below the €20,000 willingness to pay threshold) compared with urinary gonadotrophins in the Italian National Health System [34].
Cost-benefit analysis (CBA)		**Monetary equivalents**	• Monetary willingness to pay (WTP) • Monetary value of a statistical life (VSL)	• A CBA based on the WTP approach for intra-uterine insemination and assisted reproductive technology highlighted the substantial role of financial constraints on the valuation of advanced fertility treatments in communities in Iran [35].
Cost-consequence analysis (CCA)		**Multiple outcomes used**: most appropriate unit for every outcome (information in disaggregated format)	• Pregnancies achieved • Live births • QALY • Monetary return on investment (ROI)	• A modelling study compared single and double embryo transfer strategies in terms of costs to the health service, live birth rate, singleton live birth rate, twin pregnancy rate, incidence of disability among infants born, and QALYs accruing to women. The cost-effectiveness of double embryo transfer improves with age, and may be considered cost-effective in some groups of older women. The decision may best be considered on a case-by-case basis for women aged 37–39 years [36].

necessary to assess whether the dosing in each arm reflects current standard of care according to international professional guidelines/recommendations and existing ART treatment practices in a real-world context. If doses or practices vary dramatically versus a benchmark/recommended practice, this may substantially limit the interpretation of the findings when implemented under different settings.

When there are many possible interventions to compare, a full incremental analysis should be performed, whereby all alternatives are compared incrementally in order of increasing costs and effects. The rules of 'dominance' and 'extended dominance', whereby interventions with higher costs and lower benefits than one alternative or a combination of alternatives are eliminated, indicate which of the interventions are the relevant ones to compare using ICERs [5]. For example, when comparing five alternative in vitro fertilisation (IVF) embryo transfer strategies, van Heesch et al. found that four and five cycles of elective single-embryo transfer were extendedly dominated by a combination of three cycles of elective single-embryo transfer and then three cycles according to standard-embryo transfer policy; therefore, the two dominated strategies were not considered in the incremental analysis [6].

What is the perspective adopted in the analysis?

Depending on the target audience, different costs and outcomes are relevant. The narrowest perspective would be for the patients themselves, followed by the clinic, private health insurance provider, public healthcare payer and societal perspectives. Any analysis will consequently present a comparison of costs and outcomes from the chosen perspective (i.e. relative to who pays the costs and who receives the outcome) and excluding costs and effects that fall on other parties. An intervention can be cost-effective from one perspective but not from another perspective (e.g. because the former party only carries part of the costs incurred). For example, influenza or depression cost most in terms of their impact on work absenteeism (productivity costs) and cost less in terms of actual medical treatment [7,8]. Therefore, prevention of these diseases is much more cost-effective from a societal than from a healthcare payer perspective, because most of the associated cost savings are societal ones that fall outside the budgets of healthcare payers. The cost of multiple pregnancies as a result of MAR are paid for by the public health system (society/taxpayers) in most countries, and are often not paid directly by the patient [9]. As such, individuals paying out of pocket may prefer to transfer two or more embryos, in an effort to increase the probability of live birth per embryo transfer, without fully realising the medical maternal and perinatal risks associated with multiple pregnancy and, as such, impose higher costs related to multiple pregnancies/births.

For many, the societal perspective is considered the most relevant, as this broad perspective captures all benefits and costs for society [10]. Alternatively, for others, narrower perspectives can be applied to evaluate costs that fall on individuals or organisations being asked to pay for a new product or technology. For example, many national health technology assessment (HTA) agencies apply a narrow health service perspective that only considers those costs that are paid by the public health system, excluding costs like productivity losses or out-of-pocket payments for patients. There are limitations to applying a narrow perspective that can lead to inefficient allocation of resources and inefficient treatment choices, as this fails to consider the implications of certain choices for involved third parties that were not considered in the analysis.

Costs associated with MAR are often shared among public systems, private insurers and patients. Whilst all fractions can be important cost components, the perspective defines those costs to be included in the analysis. In the strictest sense, once the perspective has been determined, only those costs relevant to the perspective applied in the analysis should be considered. Similarly, if costs are shared for a particular item of service delivery, for example, prescription medicines and patient co-payments, these contributions should be deducted from the overall costs of the medicine to ensure only those aligned with the perspective are considered. For MAR this can again be complicated, as there is usually a mix of public and private funding for different MAR treatment components. Unlike other areas of healthcare, there are varied public reimbursement programmes for MAR, but a large proportion of cycles are delivered in private clinics that incur patient fees [11]. The reliance on patients paying out-of-pocket for care can cause many issues that disrupt the efficient and timely delivery of care. Financial barriers can often limit access to treatment for couples, influence treatment practices and can impact pregnancy outcomes [12–14]. The variance in who funds the treatment influences how we must think about the cost-effectiveness of treatments. In some instances, couples may pay for MAR treatment, with the national health system funding the consequences of adverse outcomes, such as multiple pregnancies, all of which should be considered in decision-making.

What is the time horizon adopted in the analysis?

Costs and effects can be measured for different time horizons. Usually, in the context of MAR, a short time perspective is adopted, limiting the analysis to the period of treatment until delivery of a live birth, often less than one year of follow-up. In some cases, limiting the analysis to the point of delivery can be short-sighted, as many costs can occur further downstream. Furthermore, choosing an appropriate analytic time horizon is a particularly important construct for MAR because a newborn generates a lifetime of benefits (and costs) for parents and society. Similarly, childlessness, and the physical or mental consequences of childlessness that can occur, persist over the remaining lifetime. Furthermore, this is also true for multiple pregnancies, which can give rise to more complications at delivery and perhaps persistent complications that require ongoing medical care. When a study compares options that confer different risks of multiple birth or other complications per live birth that affect the health of the offspring, the chosen time horizon can be influential.

In practice, many published cost-effectiveness studies fail to report the timeline of the analysis, which can limit their usefulness. A previous review of cost-effectiveness studies observed that 58% of included studies did not clearly define a time horizon, and only 13% considered a time horizon of more than one year [15]. The general recommendation is that the time horizon should be long enough to capture any relevant differences in costs and outcomes between the different approaches being compared, and this should also consider the use of subsequent treatments in the context of the clinical care pathways that couples have access to throughout their MAR journey [16]. However, the question over when to stop counting costs associated with the outcome of MAR is more ambiguous, and the reality is that most cost-effectiveness studies based on randomised studies only consider costs to the point of a live birth.

Where to draw the line and from which point onwards costs and benefits should not be counted is arbitrary as, in principle, newborns could be followed for a lifetime. The practice of stopping cost counting from the delivery onwards may be justified on the grounds that the live birth is the primary desired outcome of MAR treatment, and future costs and health outcomes for infants may be considered irrelevant in this context. However, successful MAR leads to future perinatal and delivery costs, and including these costs in association with a successful outcome treats live births as an adverse event, which could negatively influence the cost per live birth comparison. In this context it might be of interest to exclude costs associated with live births, as interventions increasing live birth rates will be associated with higher costs but may still be cost-effective if the cost per live birth is considered. Similar arguments may be made in relation to pregnancy costs, in that the provision of antenatal care is considered a cost-effective use of healthcare resources for pregnant women, regardless of how the pregnancy was conceived. However, this becomes less justifiable when comparing MAR treatments that confer different risks of complications that affect the cost of pregnancy and/or costs and outcomes for offspring. In the case of multiple births, the excess costs could be considered an adverse event worth including in the analysis, and a much longer time horizon may be required to fully capture the impact of this; potentially, the lifetime of the infant. Similarly, if one MAR treatment led to increases in early pregnancy loss, pre-term births or congenital abnormalities compared with an alternative MAR treatment, it is important to capture the excess costs attributable to these. Safety as well as success matters.

Which outcomes are measured to assess effectiveness?

For narrow cost-effectiveness analyses, first live birth (following a fresh or frozen embryo transfer following ART treatment) or cumulative live birth (all live births following successive ART treatments) are logical outcome measures, more than pregnancies or deliveries. Furthermore, (cumulative) live births also integrate the occurrence of early pregnancy loss related to ectopic pregnancies and miscarriages. For broader analyses (CUAs and CBAs), however, it becomes more difficult to establish appropriate outcome measures.

What are the likely benefits achieved from treating infertility? For couples, the medical diagnosis is labelled as infertility, which is 'a disease of the male or female reproductive system, defined by the failure to achieve pregnancy after 12 months or more of regular unprotected sexual intercourse' [17]. Although infertility is often caused by conditions presenting with specific symptoms, such as pelvic/menstrual pain (endometriosis, uterine fibroids, chronic pelvic inflammatory disease, postoperative pelvic adhesions, etc.) or menstrual cycle abnormalities (anovulation caused by polycystic ovarian syndrome, hyperprolactinemia, etc.), it can also be largely asymptomatic. The main goal of infertility treatment is to produce a child, thereby satisfying the desire to have children, whereas obviously also managing, to whatever extent possible, the causes of infertility. To inform the allocation of constrained healthcare budgets, the reference case for economic evaluation tends to focus attention on the individual medical condition and health benefits acquired by individuals undergoing treatment, although more attention is paid to spill-over effects in more recent analyses. This approach treats the resulting live birth as an 'externality'; in other words, it is external to the individuals experiencing infertility.

Such thinking underpins the cost-effectiveness modelling conducted to inform recent NICE guidelines on the provision of ART and treatment for endometriosis causing infertility [18,19], where the value of treatment was captured through its impact on satisfying the desire of infertile couples for a child, using QALYs as the unit of outcome. Although it was recognised, in the interpretation of results, that decision makers may value live births beyond their impact on the QALYs of couples seeking treatment. However, the QALYs of the future child are not considered in the evaluation. Whether or not to count QALYs of future children is a complex ethical matter in itself, with both exclusion and inclusion leading to counterintuitive results. QALYs were developed as a generic measure of health benefit to capture improvements in health among patients. As such, it has been argued that they are not appropriate for capturing the value of live births achieved through MAR treatment [20]. Nevertheless, focussing only on the QALYs of couples seeking treatment ignores the fact that the child represents future value for society and the government, and potentially undervalues MAR treatment. Whilst it is possible to enumerate the QALYs accruing to children born as result of MAR, it would, in this situation, be incorrect to apply the same rules of interpretation that are applied to incremental cost per QALY estimates for other health conditions. How to fully capture the value of live births to society in the context of economic evaluation remains an area requiring further research and debate [21]. Monetary valuation in the context of return on investment or CBA offer an alternative approach in this respect (discussed further below).

How are economic evaluation results summarised?

The two main cost-effectiveness measures reported in the literature are the average cost-effectiveness ratio (ACER) and the ICER, both often expressed as a cost per live birth. In practice, the ACER is a simpler construct to understand, as it is reported as a ratio of average costs over the average benefits for each alternative intervention considered in the analysis. The ACER therefore reflects the sum of all costs incurred by an intervention, divided by the likelihood of achieving a live birth (Equation (1)), which can then be compared across all of the competing MAR interventions to select the most technically efficient option. However, when comparing interventions with each other, it is customary to report the ICER per live birth (i.e. the increase in costs to achieve one additional live birth with one intervention compared with another (Equation (2)). To interpret this outcome, the ICER per live birth measure does pose a problem, as no willingness-to-pay threshold has been established for how much society is willing to pay for an additional child. Many cost-effectiveness studies report incremental results, but there are no rules that govern whether $30,000 or $100,000 per additional live birth is considered acceptable. Incremental results would be more applicable if there were better understanding of societies' willingness to pay for an additional child in the context of MAR provision, where it is often competing for scarce resources with other healthcare interventions. This is an area that would benefit from further research to assess the preference of society and the willingness to trade-off health benefits for other groups of patients against live births delivered through the provision of MAR. In this regard, when making resource allocation decisions in relation to MAR treatments, cost-effectiveness analyses might currently be more suited to evaluating the average cost per live birth for each product individually, where the one with the lowest cost per live birth is likely to be the more technically efficient option.

$$Average\ cost\ per\ live\ birth\ of\ program\ A = \frac{\Sigma costs\ of\ program\ A}{\Sigma live\ births\ A} \tag{1}$$

$$Incremental\ cost\ per\ live\ birth\ of\ program\ A\ vs.B = \frac{(\Sigma costsA - \Sigma costsB)}{(\Sigma Live\ Births\ A - \Sigma Live\ Births\ B)} \tag{2}$$

To inform allocative efficiency on the broadest level, CBA is used, whereby all outcomes are reported in monetary units (see Table 1), in a return-on-investment metric or net-benefit estimate. This involves converting live births and other MAR outcomes into monetary values. In the strictest sense, MAR is used to treat infertility, which is a medical disease experienced by couples, the consequence of which is fewer children are born. As already discussed, because the benefits attributed to unborn children are not considered part of the medical problem of infertility, successful treatment (i.e. live births) represent an externality to the initial medical problem of infertility. However, the resulting child does have value when considered from the perspective of parents, families, society and governments. Examples of this were observed in Korea [22] and Japan [23], where the respective governments increased funding for MAR treatment, not because of the burden on couples caused by infertility, but as a policy measure to aid falling birth rates [24]. By valuing the externality of children and future economic contributions of the child, these governments elected to fund MAR for infertile couples as a way to secure future economic benefits provided by their children.

The government perspective cost-benefit framework has been applied in several previous studies, to inform allocative efficiency by capturing the lifetime net tax contributions attributed to MAR-conceived children [25,26]. The aim of these previous studies was to show the future value of MAR-conceived children in relation to treatment costs. Because funding for MAR competes with all other healthcare programmes for funding within tax-financed public systems, to inform on allocative efficiency suggests that we know the relative value of these other programmes, although this is seldom the case. Considering that MAR is the only intervention that creates human life, when the externalities are valued few medical technologies are likely to show greater economic value in the future, especially in societies where the birth rate is below replacement level. The analyses show that, from the perspective of government, MAR investment costs yield a significant future fiscal gain over the lifetimes of these children.

Stated preference techniques offer an alternative approach to placing monetary value on the provision of MAR and its associated outcomes, by assessing what individuals, patients or members of the general population are hypothetically willing to pay for it. For example, using such an approach Botha et al. estimated that individuals in a representative sample of the Australian population were willing to pay an additional $27.43 in annual tax contributions for a preferred configuration of fertility treatment provision [27]. Furthermore, Spiegel, et al. estimated that the willingness to pay for an IVF cycle in Israel among patients ($5482) and the general public ($4398) was more than the actual average cost of IVF treatment ($3257), highlighting the perceived net benefits of IVF for both patients and society [28]. Such values provide a means for allowing direct comparison with the costs of providing fertility in a CBA.

How can evidence be used in practice?

The extent to which economic evaluation studies inform choices for privately paying patients is not well understood. Patients as customers, who are already paying out-of-pocket for treatment, are clearly governed by different principles, where securing a live birth and time to pregnancy have heightened importance. As privately paying patients may not fully understand the potential risks, in particular for multiple pregnancies, there is potential for adverse treatment selection. In these cases, privately paying couples may expose themselves to the risks of multiple pregnancies, without the consequences of having to pay for many of the additional health service costs associated with multiple deliveries and complications.

The results from economic evaluations can be applied at several levels within a healthcare system to improve efficiency. For instance, national level bodies are often responsible for evaluating the cost-effectiveness of products as part of the national reimbursement process and are sometimes involved in negotiating prices [29]. Nationally, this mostly occurs when new products enter the market or when developing clinical guidelines, which is performed by agencies such as NICE in the UK. In addition, local hospital formulary committees also consider economic data when making local funding decisions [30]. Many important attributes are not captured in cost-effectiveness ratios that may need to be considered. For instance, live births and even QALYs, do not address equity, dignity, autonomy, and patient choice — all factors that have value to individuals and society, but are not captured within CEAs.

The cost-effective delivery of MAR, the area where economic evaluation studies are likely to have the greatest impact, is at the level of the clinic and hospital, where clinical groups are often charged with procuring products and making decisions regarding products and services to improve treatment outcomes — often with fixed budgets. There are a few important points that clinicians and other decision-makers can take into consideration when adopting economic evaluation research into their practice. Firstly, the most important consideration is the clinical evidence on which the model is based. Therefore, evaluating whether the evidence meets established standards and whether the evidence is based on randomised studies or real-world practices can influence the results. Secondly, it is necessary to consider whether the treatment practices (e.g. diagnostics, clinic visits, oocyte extraction) and associated costs, as reported in the evidence, reflect those applied within the practice. Thirdly, many economic evaluation studies simulate different treatment practices based on sequences of fresh and frozen ART cycles. Often, these are based on data from RCTs, and only rarely include a long-term, real-world perspective, which takes into account that many patients are treated during multiple fresh (up to three and sometimes more) ovarian stimulation cycles for ART and related fresh and frozen ART cycles. Typically, these models mostly reflect a cohort of people treated in a fairly homogenous manner. Therefore, it is important to consider whether the cohort reported in economic evaluation studies reflects those of the local practice, and additionally how one integrates frozen cycles into treatment practice. The more the practice may vary from the standard treatment approach reported in the study, the more likely it is that these study findings have limited applicability.

Another important consideration when looking to apply economic evaluation results is the transferability of findings across geographic boundaries. By design, cost-effectiveness models use country-specific cost data. As there is considerable variation in treatment practices and costs, the results from economic evaluation studies are not always transferable to different markets [31]. This limitation suggests the need to localise economic models to each market to address cost-effectiveness questions. When applying studies in clinical practice, it is important to consider whether the costs are relevant to the practice. The same could be said about clinical data used in models and whether it is applicable in other settings. Current practice is often to use the results from international randomised studies for the basis of outcomes data; however, RCTs are often limited by selected study populations, usually patients with a good prognosis and excluding patients at risk for poor or exaggerated response to ovarian stimulation, representing only a minority of the wider real-world population treated with ART [32]. Local real-world data sources may, in this case, provide more accurate estimates of treatment effects and resource consumption.

Summary

In this educational article, we have bundled a set of key questions that need to be answered, in order to better understand the value of an economic evaluation in the context of MAR. These questions, their answers, and also an appropriate understanding of the remaining issues, can help clinicians understand the strengths and weaknesses of studies and enable them to make best use of the evidence in practice, so that the resources available for MAR treatment can be used to create maximum value to patients and society. It is important to recognise that achieving efficiency in budget allocation for MAR treatment is not the same thing as providing fewer services or lowering costs. In many cases, doing more or spending more is necessary to achieve increased live birth rates. The question to consider is whether increased expenditure is justifiable in relation to the additional outcomes achieved (i.e. whether extra investment is 'worth it', either to patients, clinics, insurance companies, healthcare systems or societies as a whole). Economic evaluations aim to assist decision makers in making these judgements. However, they can often appear callous, as they focus on a single measure of effect and the costs of achieving such measures, often evaluated over a short time period. Moreover, in the context of MAR there are many methodological issues that obstruct a clear interpretation of cost-effectiveness analyses.

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Authors' contributions

All authors contributed to the conception and design of the analysis, as well as interpretation of data and critical review of this manuscript. All authors approved the manuscript for submission to the journal.

Data availability

Any requests for data by qualified scientific and medical researchers for legitimate research purposes will be subject to Merck KGaA's Data Sharing Policy. All requests should be submitted in writing to Merck KGaA's data sharing portal https://www.merckgroup.com/en/research/our-approach-to-research-and-development/healthcare/clinical-trials/commitment-responsible-data-sharing.html. When Merck KGaA has a co-research, co-development, or co-marketing or co-promotion agreement, or when the product has been out-licensed, the responsibility for disclosure might be dependent on the agreement between parties. Under these circumstances, Merck KGaA will endeavour to gain agreement to share data in response to requests.

Practice points

- Cost-effectiveness analyses help to identify those MAR programmes that optimise live birth rates
- Cost-utility analyses and societal cost-benefit analyses address the degree to which healthcare systems should treat the condition of infertility or increase spending on MAR treatments compared with other healthcare domains
- The comparator used must be appropriate for the patient population and setting
- The time horizon should be reported, and should be long enough to capture any relevant differences in costs/outcomes between different approaches being compared
- For narrow health economic analyses of interventions by their ability to achieve a well-defined set of outcomes, first live birth or cumulative live birth are logical outcome measures.
- Broader health economic analyses that look at the allocation of resources across many healthcare domains and beyond must consider which outcomes will be most appropriate
- To summarise the results, the average cost-effectiveness ratio and the incremental cost effectiveness ratio may be used

Research agenda

- The preference of society and the willingness to trade-off health benefits for other groups of patients against live births delivered through the provision of MAR
- The extent to which economic evaluation studies inform choices for privately paying patients and for public or private MAR teams
- The concept of willingness-to-pay needs to be further explored from both a societal and a patient perspective, taking into account existing benchmarks where possible.

Declaration of competing interest

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