Human Reproduction, Vol.35, No.9, pp. 2037–2046, 2020
doi:10.1093/humrep/deaa158

human reproduction

ORIGINAL ARTICLE *Infertility*

Cost-effectiveness of medically assisted reproduction or expectant management for unexplained subfertility: when to start treatment?

R. van Eekelen[1,*], M. J. Eijkemans[2], M. Mochtar[1], F. Mol[1], B. W. Mol[3], H. Groen[4], and M. van Wely[1]

[1]Centre for Reproductive Medicine, Amsterdam UMC, location Academic Medical Centre, 1105 AZ Amsterdam, the Netherlands [2]Department of Biostatistics and Research Support, Julius Centre, University Medical Centre Utrecht, 3584 CX Utrecht, the Netherlands [3]Department of Obstetrics and Gynaecology, Monash Medical Centre, VIC 3800 Clayton, Australia [4]Department of Epidemiology, University of Groningen, University Medical Centre Groningen, 9713 GZ Groningen, the Netherlands

*Correspondence address. Centre for Reproductive Medicine, Academic Medical Centre, Meibergdreef 9 1105 AZ Amsterdam, the Netherlands. E-mail: r.vaneekelen@amsterdamumc.nl

Submitted on November 28, 2019; resubmitted on June 4, 2020; editorial decision on June 7, 2020

STUDY QUESTION: Over a time period of 3 years, which order of expectant management (EM), IUI with ovarian stimulation (IUI-OS) and IVF is the most cost-effective for couples with unexplained subfertility with the female age below 38 years?

SUMMARY ANSWER: If a live birth is considered worth €32 000 or less, 2 years of EM followed by IVF was the most cost-effective, whereas above €32 000 this was 1 year of EM, 1 year of IUI-OS and then 1 year of IVF.

WHAT IS KNOWN ALREADY: IUI-OS and IVF are commonly used fertility treatments for unexplained subfertility although many couples can conceive naturally, as no identifiable barrier to conception could be found by definition. Few countries have guidelines on when to proceed with medically assisted reproduction (MAR), mostly based on the expected probability of live birth after treatment, but there is a lack of evidence to support the strategies proposed by these guidelines. The increased uptake of IUI-OS and IVF over the past decades and costs related to reimbursement of these treatments are pressing concerns to health service providers. For MAR to remain affordable, sustainable and a responsible use of public funds, guidance is needed on the cost-effectiveness of treatment strategies for unexplained subfertility, including EM.

STUDY DESIGN, SIZE, DURATION: We developed a decision analytic Markov model that follows couples with unexplained subfertility of which the woman is under 38 years of age for a time period of 3 years from completion of the fertility workup onwards. We divided the time axis of 3 years into three separate periods, each comprising 1 year. The model was based on contemporary evidence, most notably the dynamic prediction model for natural conception, which was combined with MAR treatment effects from a network meta-analysis on randomized controlled trials. We changed the order of options for managing unexplained subfertility for the 1 year periods to yield five different treatment policies in total: IVF-EM-EM (immediate IVF), EM-IVF-EM (delayed IVF), EM-EM-IVF (postponed IVF), IUIOS-IVF-EM (immediate IUI-OS) and EM-IUIOS-IVF (delayed IUI-OS).

PARTICIPANTS/MATERIALS, SETTING, METHODS: The main outcomes per policy over the 3-year period were the probability of live birth, the average treatment and delivery costs, the probability of multiple pregnancy, the incremental cost-effectiveness ratio (ICER) and finally, which policy yields the highest net benefit in which costs for a policy were deducted from the health effects, i.e. live births gained. We chose the Dutch societal perspective, but the model can be easily modified for other locations or other perspectives. The probability of live birth after EM was taken from the dynamic prediction model for natural conception and updated for Years 2 and 3. The relative effects of IUI-OS and IVF in terms of odds ratios, taken from the network meta-analysis, were applied to the probability of live birth after EM. We applied standard discounting procedures for economic analyses for Years 2 and 3. The uncertainty around effectiveness, costs and other parameters was assessed by probabilistic sensitivity analysis in which we drew values from distributions and repeated this procedure 20 000 times. In addition, we changed model assumptions to assess their influence on our results.

© The Author(s) 2020. Published by Oxford University Press on behalf of European Society of Human Reproduction and Embryology.
This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (http://creativecommons.org/licenses/by-nc/4.0/), which permits non-commercial re-use, distribution, and reproduction in any medium, provided the original work is properly cited. For commercial re-use, please contact journals.permissions@oup.com

MAIN RESULTS AND THE ROLE OF CHANCE: From IVF-EM-EM to EM-IUIOS-IVF, the probability of live birth varied from approximately 54–64% and the average costs from approximately €4000 to €9000. The policies IVF-EM-EM and EM-IVF-EM were dominated by EM-EM-IVF as the latter yielded a higher cumulative probability of live birth at a lower cost. The policy IUIOS-IVF-EM was dominated by EM-IUIOS-IVF as the latter yielded a higher cumulative probability of live birth at a lower cost. After removal of policies that were dominated, the ICER for EM-IUIOS-IVF was approximately €31 000 compared to EM-EM-IVF. The range of ICER values between the lowest 25% and highest 75% of simulation replications was broad. The net benefit curve showed that when we assume a live birth to be worth approximately €20 000 or less, the policy EM-EM-IVF had the highest probability to achieve the highest net benefit. Between €20 000 and €50 000 monetary value per live birth, it was uncertain whether EM-EM-IVF was better than EM-IUIOS-IVF, with the turning point of €32 000. When we assume a monetary value per live birth over €50 000, the policy with the highest probability to achieve the highest net benefit was EM-IUIOS-IVF. Results for subgroups with different baseline prognoses showed the same policies dominated and the same two policies that were the most likely to achieve the highest net benefit but at different threshold values for the assumed monetary value per live birth.

LIMITATIONS, REASONS FOR CAUTION: Our model focused on population level and was thus based on average costs for the average number of cycles conducted. We also based the model on a number of key assumptions. We changed model assumptions to assess the influence of these assumptions on our results. The change in relative effectiveness of IVF over time was found to be highly influential on results and their interpretation.

WIDER IMPLICATIONS OF THE FINDINGS: EM-EM-IVF and EM-IUIOS-IVF followed by IVF were the most cost-effective policies. The choice depends on the monetary value assigned to a live birth. The results of our study can be used in discussions between clinicians, couples and policy makers to decide on a sustainable treatment protocol based on the probability of live birth, the costs and the limitations of MAR treatment.

STUDY FUNDING/COMPETING INTEREST(S): This work was supported by the ZonMw Doelmatigheidsonderzoek (80-85200-98-91072). The funder had no role in the design, conduct or reporting of this work. B.W.M. is supported by a NHMRC Practitioner Fellowship (GNT1082548). B.W.M. reports consultancy for ObsEva, Merck KGaA and Guerbet and travel and research support from ObsEva, Merck and Guerbet.

TRIAL REGISTRATION NUMBER: N/A.

Key words: medically assisted reproduction / unexplained subfertility / IVF / IUI / expectant management / cost-effectiveness / decision analytic model / Markov model / decision tree

Introduction

Medically assisted reproduction (MAR), i.e. IUI with ovarian stimulation (IUI-OS) and IVF, is commonly used to treat couples with unexplained subfertility (Calhaz-Jorge *et al.*, 2017). Only a few countries have a national guideline for clinical management of couples with unexplained subfertility. For example, in the UK National Health Service (NHS), couples with unexplained subfertility of which the woman is under 40 years of age are eligible for up to a maximum of three reimbursed IVF cycles after 2 years of trying to conceive (NICE, 2013). In the Netherlands, unexplained subfertile couples comprising women below 38 years of age who have a predicted probability to conceive naturally of <30% over the following year, as estimated by the Hunault model, are eligible for up to six reimbursed cycles of IUI-OS and, if unsuccessful, three reimbursed IVF cycles thereafter (Hunault *et al.*, 2004; van der Steeg *et al.*, 2007; NVOG, 2010).

Both of these approaches are meant to avoid overtreatment with MAR, as many of these couples may still conceive naturally and do not necessarily require any treatment (Kersten *et al.*, 2015). Not only are IUI-OS and IVF expensive treatments, but IUI-OS leads to a considerably higher probability of multiple pregnancy, and IVF with single embryo transfer is still an invasive and stressful procedure (van den Boogaard *et al.*, 2011). Postponing treatment saves the patient an invasive procedure and avoids unnecessary costs for couples who might have conceived naturally.

Because couples with better prognoses conceive before couples with poorer prognoses, this leads to a selection over time in which eventually a subgroup with a particularly low prognosis remains (van Eekelen *et al.*, 2017a). This low prognosis group might benefit from MAR treatment (van Eekelen *et al.*, 2017b). In times when health care costs are increasing and becoming a larger relative expenditure for governments with health service providers, this is a crucial concept for evidence-based decision-making (OECD, 2013). When it comes to unexplained subfertility, the question is thus not who to treat, but when to treat with IUI-OS and when to treat with IVF.

The current body of evidence on this is inconclusive: we previously found that the prognosis of natural conception determines the relative and absolute benefit of IUI-OS, which suggests that expectant management (EM) is the best option until so much selection has occurred that the prognosis crosses below a certain threshold (van Eekelen *et al.*, 2019a). In contrast, it is also known that the probability of live birth after IVF declines rapidly above a female age of 35 years, providing an important argument to limit the period of EM that is advised (McLernon *et al.*, 2016; van Eekelen *et al.*, 2017b; van Eekelen *et al.*, 2019a,b).

If we consider costs and patient harm, it is better to delay treatment, especially if this does not substantially change the probability of live birth over a fixed time period. A cost-effectiveness study compared IVF-EM-EM (immediate IVF) to EM-IVF-EM (delayed IVF) and found that the probabilities of live birth over a 2-year period were similar, but the authors used observational data and did not consider IUI-

OS as an intermediate option as unexplained subfertility was not the main focus of the study (Eijkemans *et al.*, 2017). More evidence is necessary on this topic to decide on sustainable, evidence-based treatment protocols for unexplained subfertility that best utilize public funds.

The aim of the present study is to assess the cost-effectiveness of policies regarding different ordering of EM, IUI-OS and IVF for couples with unexplained subfertility using the most up-to-date body of evidence.

Materials and methods

Study design

To answer the research question we did not use patient data, but instead combined evidence from contemporary sources to develop a statistical model commonly referred to as a decision analytic model (Briggs *et al.*, 2006). We chose a population-level (average) model based on probabilities known as a Markov model. Since our model does not contain many 'intermediate' states, we show this as a decision tree. The R programming code used to run the model is available online (Supplementary Data 1 and 2) as well as Supplementary Data 3, which includes all model parameters such that other researchers can readily implement the model in their own country or setting in which parameters such as costs might differ.

Our health outcome of interest is the cumulative probability of live birth as this is the outcome that matters most to patients and quality-adjusted life years are poorly defined for this population (Barnhart, 2014; Eijkemans *et al.*, 2017).

The three options for treatment of couples with unexplained subfertility are EM, IUI-OS and IVF. EM is defined as no intervention other than the advice to continue trying. IUI-OS using clomiphene citrate, as clomiphene citrate was shown to lead to similar ongoing pregnancy rates as gonadotrophins, whilst clomiphene citrate is less expensive and less invasive for patients to use (Danhof *et al.*, 2018).

We chose a time window of 3 years as a treatment decision generally has to (first) be made within 3 years after the diagnosis and, in addition, to allow sufficient time for couples to undergo both IUI-OS and IVF, even after postponing treatment for 1 year. We chose (calendar) time instead of cycles since this aligns with the measures of relative effectiveness in the network meta-analysis and since one cycle of EM does not take the same amount of time as one cycle of IVF, which hampers comparisons. We divided these 3 years into three separate periods, each comprising 1 year. We then reordered the three options to be offered over 1-year periods to constitute five policies that are shown in Table I. For instance, couples might start with IVF straight away (immediate IVF, order IVF-EM-EM), or opt for the Dutch standard for couples with a good prognosis of natural conception by delaying IUI-OS by 1 year (delayed IUI-OS, order EM-IUIOS-IVF). After 3 years, we assumed that treatment is finished for the vast majority of couples and that the years of EM thereafter are similar for all policies. We assumed most couples would finish IUI-OS and/or IVF within 1 year, which might differ between countries based on reimbursement or availability. Options with multiple years of treatment (e.g. IVF-IVF-EM) were considered unrealistic as policies reflect population-level guidelines and very few couples receive more than two cycles of IVF or more than four cycles of IUI-OS, which are most often done within the same year (Custers *et al.*, 2007; McLernon *et al.*, 2016; Eijkemans *et al.*, 2017; van Eekelen *et al.*, 2019a,b). The option without treatment, i.e. EM-EM-EM was considered unethical and unfeasible given the current guidelines (NVOG, 2010).

Population

As the question concerns couples who are in a position to postpone treatment, we chose the population of interest to be couples with unexplained subfertility who present at a fertility clinic and where the woman is 38 years old or younger. We defined subfertility as not conceiving within 1 year of trying. Unexplained subfertility was defined as couples with no major causes explaining the fertility problem, regular menstrual cycles of length between 23 and 35 days, at least one patent fallopian tube and semen analyses with a total motile sperm count of $>1 \times 10^6$ (van Eekelen *et al.*, 2017a). We chose 38 years as the age limit for women as for couples in which the woman over 38 years of age, the treatment choice is complicated by the rapid decline in the probability of live birth after IVF and after EM as female age increases, such that IVF-EM-EM might be preferred (McLernon *et al.*, 2016; van Eekelen *et al.*, 2019b).

Perspective

We chose the health economic perspective of society as reimbursement in the Netherlands is based on public funds, i.e. taxpayer money. Work absenteeism was considered a loss of productivity to society. The model can be easily modified for other perspectives or other locations.

Primary data sources

Probability of live birth after EM.

As the baseline probability of live birth after EM in the model, we chose to use our dynamic prediction model for natural conception (van Eekelen *et al.*, 2017a). This prediction model has been externally validated in Scottish data and can be used to not only predict the probability of natural conception after completion of the fertility workup that leads to ongoing pregnancy, but also to update predictions when couples return to the clinic later after a period of EM (van Eekelen *et al.*, 2018). This is a crucial property of the decision analytic model, as it covers 3 years in total and two moments at which the situation is re-evaluated. The outcome of the dynamic prediction model was natural conception leading to ongoing pregnancy, but the outcome of interest is live birth. To estimate the probability of live birth after natural conception, we multiplied the probability of ongoing pregnancy from the dynamic prediction model with a probability of continuing to a live birth (Arce *et al.*, 2005; Braakhekke *et al.*, 2014). We refer to that as live birth from now on. The average probability of live birth after natural conception plugged into the economic model was approximately 26% over the first year and was derived from the cohort used in that same study for couples in which the woman was below 38 years of age (van Eekelen *et al.*, 2017a). The average female age in this cohort was 31.7 years. The probability of live birth of 26% in the first year decreased to 15% in Year 2 and to 10% in Year 3. Over the

Table I The five possible treatment policies for unexplained infertility based on the ordering of EM, IUI-OS and IVF.

Policy	Explanation	Year 1	Year 2	Year 3
IVF-EM-EM	Immediately start with IVF and skip IUI-OS	IVF	EM	EM
EM-IVF-EM	Delay IVF for 1 year and skip IUI-OS	EM	IVF	EM
EM-EM-IVF	Postpone IVF for 2 years and skip IUI-OS	EM	EM	IVF
IUIOS-IVF-EM	Immediately start IUI-OS, then continue with IVF if unsuccessful	IUI-OS	IVF	EM
EM-IUIOS-IVF	Delay IUI-OS for 1 year, then continue with IVF if unsuccessful	EM	IUI-OS	IVF

EM, expectant management; EM-EM-IVF, postponed IVF; EM-IUIOS-IVF, delayed IUI-OS; EM-IVF-EM, delayed IVF; IUI-OS, IUI-ovarian stimulation; IUIOS-IVF-EM, immediate IUI-OS; IVF-EM-EM, immediate IVF; OS, ovarian stimulation.

period of 3 years, the cumulative probability of live birth after natural conception was 43%.

Probability of live birth after IUI-OS and IVF.

For the probability of live birth after treatment, we applied relative effects in terms of odds ratios from a recent network meta-analysis on unexplained subfertile couples to the aforementioned probability of live birth after EM (Wang *et al.*, 2019). The study found an odds ratio after IUI-OS of 1.61 (95% CI 0.88–2.94) and after IVF of 1.88 (95% CI 0.81–4.38, only indirect evidence), both compared to EM. IVF refers to a weighted average of IVF and ICSI as the authors of the network meta-analysis did not distinguish between IVF and ICSI since there is no indication for ICSI in unexplained subfertility (Wang *et al.*, 2019).

In previous research, we found that the odds ratio of both IUI-OS and IVF increased over time, because the probability of live birth after EM decreases more rapidly than the probability of live birth after IUI-OS or IVF. The increase in odds ratio was estimated as 1 point per year for both IUI-OS (Supplementary Data 4). We incorporated this increase of the odds ratio in our model.

Probability of multiple pregnancy.

We expected a probability of multiple pregnancy after EM of 1% (Eijkemans *et al.*, 2017; van Eekelen *et al.*, 2017a), after IUI-OS of 6% (Custers *et al.*, 2007) and after IVF of 3.3% (NVOG, 2018).

Costs

Considered costs were from a health care perspective (procedures regarding treatment, medication, delivery of multiple pregnancy) and societal (work absenteeism). Costs from the health care perspective were obtained from an expert panel on cost-effectiveness from the Dutch consortium for Research in Women's Health consisting of gynaecologists, an economist and a methodologist. This group collected the total medical costs per resource unit from two university hospitals and one general hospital. These costs were averaged and then used to determine the average costs of one full year of IUI-OS and the average costs of one full year of IVF. Details are reported in Supplementary Data 3.

Direct medical costs of one cycle of IUI-OS were estimated at €321 (including ovarian stimulation, sonography, semen sample processing, etc.) and for one cycle of IVF were estimated at €1365 (including ovarian stimulation, sonography, oocyte collection, possible complications during oocyte collection, embryo culture, embryo transfer, etc.). The costs of a freeze/thaw attempt were estimated at €350 (including sonography and embryo transfer).

Indirect costs, i.e. unrelated to medical procedures were due to absence from work, estimated at €263 for one full day for a woman and €316 for one full day for a man (Hakkaart-van Roijen *et al.*, 2016). Total costs due to absence from work were estimated at €726 per IUI-OS cycle and €2294 per IVF cycle, the difference mostly being due to oocyte collection and subsequent rest in IVF.

Most cost data were from 2013 or 2014, so we applied the inflation factor reported by the Dutch government to update costs to 2018 (CBS, 2020).

The number of cycles conducted in clinical practice is crucial to inform the expected average costs. The average number of IUI-OS cycles received within 1 year, including cancellations and couples that successfully conceived leading to live birth, was estimated at 4 (Custers *et al.*, 2007; van Eekelen *et al.*, 2019a). The average number of IVF cycles received was estimated at 1.5 and every cycle was estimated to include one freeze/thaw attempt (Eijkemans *et al.*, 2017; van Eekelen *et al.*, 2019b).

The incremental cost of delivery in case of a multiple pregnancy was estimated at €13 312 and was defined as the costs of a multiple pregnancy delivery minus the cost of a singleton delivery, as the latter applies to all deliveries (Lukassen *et al.*, 2004). Other costs related to pregnancy and delivery were not considered in the model as they were assumed to be a result of a 'successful' treatment rather than relevant to the treatment decision.

Combining direct medical costs, indirect costs and the inflation factor, the total average costs of 1 year of IUI-OS comprising four cycles were estimated at €4528. Four IUI-OS cycles were chosen because when the protocol is to have up to six cycles, the number of cycles conducted will be lower due to pregnancies and drop-out (Custers *et al.*, 2007). Total average costs of 1 year of IVF comprising 1.5 cycles and subsequent freeze/thaw attempts were estimated at €6595: 1.5 IVF cycles were chosen because when the protocol is to have up to three cycles, the number of cycles conducted will be lower due to pregnancies and drop-out (van Eekelen *et al.*, 2019b).

Cost-effectiveness analyses

Model structure.

The decision analytic model is shown as a decision tree in Fig. 1. Following clinical practice, the couples enter the model after at least 1 year of trying to conceive naturally and diagnosis at a fertility clinic.

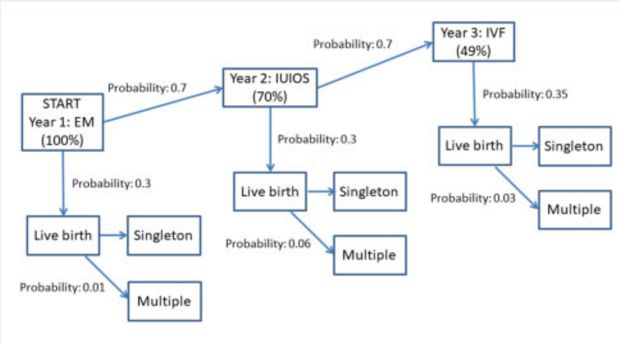

Figure 1. The decision analytic model, shown as a decision tree, in this example for the policy EM-IUI-OS-IVF. The policy of delayed IUI-ovarian stimulation with expectant management (EM-IUI-OS-IVF) is shown. Only couples with unexplained subfertility that do not achieve live birth in Year 1 continue to Year 2 and incur costs and the same goes for couples in Years 2 and 3. In addition, couples who have a multiple pregnancy incur costs. No health outcomes other than live birth were considered. Shown probabilities are only examples. Other policies were similar except for the treatment offered per year.

Depending on the policy, the couples have a probability of achieving a live birth in each year, which can be singleton or multiple. Couples who achieve a live birth are not considered further. For instance, in Fig. 1 we show the policy EM-IUI-IVF, which means that couples who achieved live birth in year 1 after EM did not incur any treatment costs. No other health consequences are considered apart from the probability of having a live birth. Results of the model are cumulative over the full-time window of 3 years.

An example calculation and its explanation are provided in the Supplementary Data 4.

All parameters used, their distribution and the sources of evidence are reported in Table II and are reported in more detail in Supplementary Data 3.

Discounting and uncertainty.

The main outputs from the model were the cumulative probability of live birth, the average costs and the cumulative probability of multiple pregnancy.

We applied standard discounting procedures for economic analyses for Years 2 and 3, a mechanism which reflects that it is desirable that costs are made later but undesirable that health outcomes, i.e. live birth are gained later (Briggs *et al.*, 2006). The Dutch government advises discounting rates of 4% per year for costs and 1.5% per year for health outcomes, i.e. live birth (Zorginstituut Nederland, 2016). The uncertainty around effectiveness, costs and other parameters was assessed by probabilistic sensitivity analysis in which we drew values from distributions and repeated this procedure 20 000 times.

Reporting results for cost-effectiveness

The main cost-effectiveness results were the incremental cost-effectiveness ratios (ICERs) and the probability that a certain policy was most likely to yield the highest net benefit.

The ICER is the increase in average cost divided by the increase in the probability of live birth for a more effective but also more expensive policy (Briggs *et al.*, 2006). We opted for a step-wise approach to compare ICERs for increasingly more effective but also more expensive policies (Briggs *et al.*, 2006).

For net benefit, we expressed how much monetary gain there is to be had for each policy by expressing the health outcome of live birth in terms of a monetary value. We achieved this by multiplying the cumulative probability of live birth by a monetary value between €1 and €100 000 and deducting the costs of that policy (Briggs *et al.*, 2006). The result is the monetary benefit of that policy in terms of health gained minus the costs. For each simulation replication, we determined which of the five policies yielded the highest net benefit for the range of possible monetary values, then calculated the proportion of simulation replications in which each policy was the best. The results are thus interpretable as the probability that a policy yields the highest net benefit, given that we assume live birth to be worth a certain monetary value. This curve is more informative than just the ICER as it takes into account all possible monetary values per live birth that vary from perspective or setting, the uncertainty around all parameters and it includes all policies simultaneously without the need for arbitrarily choosing a reference policy.

Sensitivity analyses

In addition to the primary analysis, we changed model assumptions to assess their influence on our results. First, to see the difference with the population average, we looked at the cost-effectiveness within subpopulations with a probability of live birth of 10%, 20%, 30% or 40% over the first year after the fertility workup. These subpopulations can be seen as couples in which the female age varies (increased age 10% vs younger age 40%).

Second, we changed the time window from 3 years to 1.5 years, with each period comprising 6 months, to show what would occur if the treatment decision were made earlier.

Third, we removed indirect costs due to absence of work from the model, yielding a model with only direct medical costs which can be viewed as a health service provider perspective or insurer perspective.

Fourth, we fixed the odds ratio of IVF over time, instead of increasing the odds ratio by 1 point per year, to assess the influence of this assumption.

Fifth, we used probability distributions for the probability of multiple pregnancy instead of assuming fixed values of 1% for EM, 6% for IUI-OS and 3.3% for IVF to see if this changed results.

Results

The main results are displayed in Table III. From the policy with the lowest probability of live birth IVF-EM-EM to the highest EM-IUIOS-IVF, the probability of live birth varied from approximately 54–64%, the average costs from approximately €4000 to €9000 and the probability of multiple pregnancy from 1.4% to 3.4%. The policies IVF-EM-EM and EM-IVF-EM were dominated by EM-EM-IVF (postponed IVF) as the latter yielded a higher cumulative probability of live birth at a lower cost. The policy IUIOS-IVF-EM (immediate IUI-OS) was dominated by EM-IUIOS-IVF as the latter yielded a higher cumulative

Table II Parameters, their distribution, assumptions, evaluations of assumptions and data source as used in the decision analytic model.

Parameter	Distribution	2.5th and 97.5th percentile	Underlying assumptions	Assumptions checked by	Source (see also Supplementary Data 3)
Costs for IUI-OS	Normal (4528,380)	3783–5273	Costs for 4 IUI-OS cycles including work absence	Inputs vary in probabilistic sensitivity analysis	Dutch medical centre cost data
Costs for IVF	Normal (6595,600)	5419–7771	Costs for 1.5 IVF cycles including work absence	Inputs vary in probabilistic sensitivity analysis	Dutch medical centre cost data
Costs for multiple delivery	Normal (13312,250)	12 821–13 802	Costs known	Inputs vary in probabilistic sensitivity analysis	Dutch medical centre cost data
Odds ratio of IUI-OS versus expectant management	Lognormal (ln (1.61) 0.3072)	0.88–2.94	Known relative effect that relies on the baseline rate	Inputs vary in probabilistic sensitivity analysis	Network meta-analysis (Wang *et al.*, 2019)
Odds ratio of IVF versus expectant management	Lognormal (ln (1.88) 0.4315)	0.81–4.38	Known relative effect that relies on the baseline rate	Inputs vary in probabilistic sensitivity analysis	Network meta-analysis (Wang *et al.*, 2019)
Increase in IUI-OS and IVF odds ratio per year	Fixed: 1		Relative effect of IUI-OS and IVF increases over time due to selection of couples who benefit more	Assessed in supplementary analysis	van Eekelen *et al.* (2019a,b)
Probability of multiple pregnancy after EM	Fixed: 1%		Fixed value because this parameter is negligible	Assessed in supplementary analysis	van Eekelen *et al.* (2017a)
Probability of multiple pregnancy after IUI-OS	Fixed: 6%		Fixed value because this parameter is negligible	Assessed in supplementary analysis	Custers *et al.* (2007)
Probability of multiple pregnancy after IVF	Fixed: 3.3%		Fixed value because this parameter is negligible	Assessed in supplementary analysis	Dutch annual IVF reports
Probability of ongoing pregnancy that leads to live birth	Beta (68.5)	0.86–0.98	This probability is independent from ongoing pregnancy rate	Inputs vary in probabilistic sensitivity analysis	Arce *et al.* (2005) and Braakhekke *et al.* (2014)
Population mean probability of ongoing pregnancy in the first cycle	Normal (0.03735,0.0003)	0.0373–0.0374	Dutch population from previous research is representative of today's population	Inputs vary in probabilistic sensitivity analysis	van Eekelen *et al.* (2017a)
Discount rates	Fixed: 4% (costs) Fixed: 1.5% (live birth)		Costs made later are less important than health outcomes gained later	NA, values were determined by Dutch government	Dutch government

Table III Main outcomes from the cost-effectiveness analysis (all scenarios).

Policy	Cumulative probability of live birth (%)	Probability of live birth (Year 1)* (%)	Probability of live birth (Year 2)* (%)	Probability of live birth (Year 3)* (%)	Average costs (€)	Average costs (€) (Year 1)	Average costs (€) (Year 2)	Average costs (€) (Year 3)	Probability of multiple pregnancy (%)	Incremental cost-effectiveness ratio (€)
IVF-EM-EM	53.9	40.1	14.7	10.3	6798	6779	12	7	1.6	Dominated by EM-EM-IVF
EM-IVF-EM	55.5	25.9	33.8	10.3	4851	36	4808	7	1.5	Dominated by EM-EM-IVF
EM-EM-IVF	56.0	25.9	14.7	31.4	3999	36	15	3948	1.4	0 (reference)
IUIOS-IVF-EM	61.8	36.4	33.8	10.3	8967	4832	4130	6	3.4	Dominated by EM-IUIOS-IVF
EM-IUIOS-IVF	64.4	25.9	31.4	31.4	6637	36	3412	3189	3.2	31 141 (25–75%: 78 672 to 64 684)

All costs in € EUR.
*Note that the cumulative probabilities on population level are a. Discounted and b. Calculated as: Year 1 + (1 − Year 1) * Year 2 + (1 − (1 − Year 1) * Year 2) * Year 3.

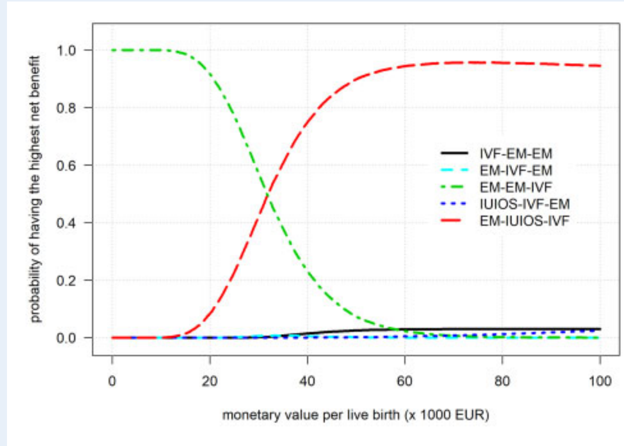

Figure 2. Net benefit curves for all five policies. EM-EM-IVF, postponed IVF; EM-IUIOS-IVF, delayed IUI-OS; EM-IVF-EM, delayed IVF; IUIOS-IVF-EM, immediate IUI-OS; IVF-EM-EM, immediate IVF.

probability of live birth at a lower cost. After removal of policies that were dominated, the comparison was made between the two remaining policies: the ICER for EM-IUIOS-IVF was approximately €31 000 compared to EM-EM-IVF. The range of ICER values between the lowest 25% and highest 75% of simulation replications was broad.

The net benefit curves for a range of monetary value per live birth are shown in Fig. 2.

The curve showed that when we assume a live birth to be worth approximately €20 000 or less, the policy EM-EM-IVF had a probability over 90% to achieve the highest net benefit. Between €20 000 and €50 000 monetary value per live birth, it was uncertain whether EM-EM-IVF was better than EM-IUIOS-IVF (delayed IUI), with the turning point at €32 000. When we assume a monetary value per live birth over €50 000, the policy EM-IUIOS-IVF had a probability over 90% to achieve the highest net benefit.

Sensitivity analyses

ICERs from the sensitivity analyses choosing a prognosis subgroup ranging from a probability of live birth ranging 10–40% over the year after the fertility workup are shown in Supplementary Tables SI, SII, SIII and SIV. The cumulative probability of live birth over 3 years ranged from 25% (IVF-EM-EM in the 10% prognosis group) to 81% (EM-IUIOS-IVF in the 40% prognosis group). All four analyses showed the same dominance pattern as the primary analysis, with EM-EM-IVF and EM-IUIOS-IVF being the remaining policies to compare. The ICERs for EM-IUIOS-IVF compared to EM-EM-IVF for the four prognoses groups were €59 000, €36 000, €30 000 and €28 000, respectively.

The net benefit curves for the prognosis subgroups ranging from 10% to 40% are shown in Supplementary Figs S1, S2, S3 and S4. Similar to the primary analysis on the overall population, EM-EM-IVF was the most likely to yield the highest benefit up to €60 000 (10% prognosis) decreasing to €29 000 (40% prognosis), after which EM-IUIOS-IVF was the most likely to yield the highest net benefit.

The results of the analysis with a time window of 18 months comprising of three 6-month periods are reported in Supplementary Table SV and Fig. S5. The same dominance pattern as in the primary analysis was found and the ICER of EM-IUIOS-IVF compared to EM-EM-IVF was €18 000.

The results of the analysis in which we removed indirect costs, i.e. absence of work are reported in Supplementary Table SVI and Fig. S6. Average costs were considerably lower compared to the primary analysis and ICERs were lower. The same dominance pattern as in the primary analysis was found and the ICER of EM-IUIOS-IVF compared to EM-EM-IVF was €9400.

The results of the analysis in which we assumed the relative treatment effects remained stable over time are reported in Supplementary Table SVII and Fig. S7. The policies in which treatment was started earlier now showed an increased cumulative probability of live birth compared to policies in which treatment was postponed. The policy EM-IUIOS-IVF was now dominated by IVF-EM-EM, yielding a higher cumulative probability of live birth at a lower cost. The net benefit curve was not straightforward for this policy with multiple policies competing. Up to a value of €44 000 per live birth, EM-EM-IVF was the most likely to yield the highest net benefit, after which none of the other policies reached a probability over 50% to yield the highest net benefit and thus results remained inconclusive.

Applying a distribution for the chance of multiple pregnancy had a negligible influence on the results (data not shown).

Discussion

We found that if stakeholders or society as a whole consider a live birth to be worth a relatively low monetary value (€20 000 or less), the least expensive but most cost-effective policy in terms of net benefit was 2 years of EM followed by IVF. If a live birth is considered to be worth more than €50 000, the most cost-effective policy in terms of net benefit was 1 year of EM followed by 1 year of IUI-OS and then 1 year of IVF. Between these values, with a turning point at €32 000, it was uncertain which policy yielded the highest net benefit.

If indirect costs are ignored, this threshold monetary value was much lower at €9500. If the relative effect of IUI-OS and IVF would not change over time, policies in which treatment is started earlier yield a higher cumulative probability of live birth over 3 years.

Strengths of this study include the combination of evidence from contemporary sources, presentation of model results in several ways to showcase different perspectives and the honest reflection of uncertainty by using distributions in a probabilistic sensitivity analysis in which the model simulation was repeated 20 000 times.

The quality of the present study is nonetheless limited by the current evidence regarding the effectiveness of MAR for unexplained subfertility, most notably the MAR treatment effects in terms of odds ratios compared to EM, the uncertainty around these odds ratios and whether these can be expected to be similar at later treatment start (Wang *et al.*, 2019). The effect of IVF compared to EM as estimated in the network meta-analysis was based on indirect comparisons only. Previous work suggested that as the prognosis of natural conception decreases over time due to selection, but the absolute chance after MAR decreases much slower, the relative effect expressed as hazard ratios or odds ratios tends to increase over time (van Eekelen *et al.*, 2019b). Please see the Supplementary Data 4 for more details. We incorporated this in our analysis, and removed this mechanism in a sensitivity analysis, which was highly influential on results and their interpretation on the influence of postponing treatment on the cumulative probability of live birth, i.e. how many livebirths would be 'lost'. As there is no clear evidence on this matter, we were unable to address this further. The same can be said on finding subgroups for which MAR is more, or less, effective than the average odds ratio from the network meta-analysis, which could lead to different results in the sensitivity analyses on prognosis groups. Another call of evidence of MAR treatment effects for unexplained subfertility seems warranted to improve precision of the decision analytic model, improve our knowledge on cost-effectiveness and ultimately help make a treatment decision for couples with unexplained subfertility.

Our model, although based on contemporary evidence, was not free of assumptions and was based on calendar time to align with the network meta-analysis and to make a fair comparison for an average number of cycles conducted within the 1-year periods. We acknowledge that this was an important choice but wish to emphasize that other options, such as cycle-based models, come with even more crucial assumptions. We incorporated uncertainty around important parameters, such as relative treatment effects and costs, by drawing from distributions rather than choosing one fixed value.

Our results reaffirm the logic behind guidelines for subfertility from the UK and the Netherlands in which IVF is reimbursed using public funds but not immediately offered after completion of the fertility workup. Despite some couples receiving both IUI-OS and IVF, and thus stacking costs, the EM-IUIOS-IVF policy was comparable to IVF-EM-EM in terms of average costs, i.e. the policy in which all couples start with IVF, but in the EM-IUIOS-IVF policy not all couples will receive the most invasive procedure IVF and the cumulative probability of live birth was higher. For couples under 38 years of age who can still pursue EM for longer, it might be worthwhile to wait another year or two before starting IVF to avoid unnecessary invasive and expensive treatment. After 2 years of waiting, the subgroup that remains is expected to benefit considerably from IVF treatment.

EM may be perceived as 'pointless' by unexplained subfertile couples, which can also decrease their quality of life (van den Boogaard *et al.*, 2011). However, counselling by a clinician and providing realistic treatment success probabilities can help couples have realistic expectations and improve their satisfaction with the decision-making process.

The results of our study can be used in discussions between clinicians, couples and policy makers to decide on a sustainable treatment protocol based on the probability of live birth, the costs and the limitations of MAR treatment. Our model used contemporary evidence and all necessary programming code is provided such that it is easy to apply in other countries where, for instance, costs might differ.

Conclusion

EM-EM-IVF and EM-IUIOS-IVF followed by IVF were the most cost-effective policies. The choice depends on how much a live birth is considered to be worth in terms of monetary value.

Supplementary data

Supplementary data are available at *Human Reproduction* online.

Acknowledgements

The authors would like to thank Prof. Patrick Bossuyt for his insightful commentary on the study design and fertility doctors N. Danhof and T. Zaat for their insights on IVF treatment protocols.

Authors' roles

M.v.W., M.M., F.M., H.G. and B.W.M. conceived the study. R.v.E., M.v.W. and M.J.E. designed the statistical analysis plan. R.v.E. programmed the model, ran simulations and analysed the results. R.v.E. and M.v.W. drafted the manuscript. All authors contributed critical revision to the paper and approved the final manuscript.

Funding

This work was supported by a grant from ZonMw, call Doelmatigheidsonderzoek (cost-effectiveness), number 80-85200-98-91072. The funder had no role in the design, conduct or reporting of this work. B.W.M. is supported by a NHMRC Practitioner Fellowship (GNT1082548).

Conflict of interest

B.W.M. reports consultancy for ObsEva, Merck KGaA and Guerbet and travel and research support from ObsEva, Merck and Guerbet.

References

Arce JC, Nyboe Andersen A, Collins J. Resolving methodological and clinical issues in the design of efficacy trials in assisted reproductive technologies: a mini-review. *Hum Reprod* 2005;**20**:1757–1771.

Barnhart KT. Live birth is the correct outcome for clinical trials evaluating therapy for the infertile couple. *Fertil Steril* 2014;**101**:1205–1208.

Braakhekke M, Kamphuis EI, Dancet EA, Mol F, van der Veen F, Mol BW. Ongoing pregnancy qualifies best as the primary outcome measure of choice in trials in reproductive medicine: an opinion paper. *Fertil Steril* 2014;**101**:1203–1204.

Briggs A, Claxton K, Sculpher M (2006). *Decision Modelling for Health Economic Evaluation*. Oxford: Oxford University Press.

Calhaz-Jorge C, De Geyter C, Kupka MS, de Mouzon J, Erb K, Mocanu E, Motrenko T, Scaravelli G, Wyns C, Goossens V. Assisted reproductive technology in Europe, 2013: results generated from European registers by ESHRE. *Hum Reprod* 2017;**32**:1957–1973.

CBS, Dutch Central Bureau for Statistics. *Annual Mutation of Price Index; From 1963*. https://opendata.cbs.nl/statline/#/CBS/nl/dataset/70936ned/table?ts=1580740889682 (20 February 2020, date last accessed).

Custers IM, Steures P, van der Steeg JW, van Dessel TJ, Bernardus RE, Bourdrez P, Koks CA, Riedijk WJ, Burggraaff JM, van der Veen F *et al.* External validation of a prediction model for an ongoing pregnancy after intrauterine insemination. *Fertil Steril* 2007;**88**:425–431.

Danhof NA, van Wely M, Repping S, Koks C, Verhoeve HR, de Bruin JP, Verberg MFG, van Hooff MHA, Cohlen BJ, van Heteren CF *et al.* Follicle stimulating hormone versus clomiphene citrate in intrauterine insemination for unexplained subfertility: a randomized controlled trial. *Hum Reprod* 2018;**33**:1866–1874.

Eijkemans MJC, Kersten FAM, Lintsen AME, Hunault CC, Bouwmans CAM, Roijen LH, Habbema JDF, Braat DDM. Cost-effectiveness of 'immediate IVF' versus 'delayed IVF': a prospective study. *Hum Reprod* 2017;**32**:999–1008.

Hakkaart-van Roijen L, van der Linden N, Bouwmans C, Kanters T, Tan SS, Nederland Z.. Kostenhandleiding: Methodologie van kostenonderzoek en referentieprijzen voor economische evaluaties in de gezondheidszorg. Diemen, Zorginstuut Nederland report, 2016.

Hunault CC, Habbema JD, Eijkemans MJ, Collins JA, Evers JL, te Velde ER. Two new prediction rules for spontaneous pregnancy leading to live birth among subfertile couples, based on the synthesis of three previous models. *Hum Reprod* 2004;**19**:2019–2026.

Kersten FA, Hermens RP, Braat DD, Hoek A, Mol BW, Goddijn M, Nelen WL. Overtreatment in couples with unexplained infertility. *Hum Reprod* 2015;**30**:71–80.

Lukassen HG, Schonbeck Y, Adang EM, Braat DD, Zielhuis GA, Kremer JA. Cost analysis of singleton versus twin pregnancies after in vitro fertilization. *Fertil Steril* 2004;**81**:1240–1246.

McLernon DJ, Steyerberg EW, Te Velde ER, Lee AJ, Bhattacharya S. Predicting the chances of a live birth after one or more complete cycles of in vitro fertilisation: population based study of linked cycle data from 113 873 women. *BMJ* 2016;**355**:i5735.

NICE. National Institute for Health and Care Excellence. *Guideline on: Fertility Problems: Assessment and Treatment*. https://www.nice.org.uk/guidance/cg156 (5 February 2017, date last accessed).

NVOG, Dutch Society for Obstetrics and Gynaecology. *Guideline on: Subfertility*. http://bit.ly/1UhuYMV (5 February 2017, date last accessed).

NVOG, Dutch Society for Obstetrics and Gynaecology. *National IVF Statistics*. 2018. https://www.degynaecoloog.nl/wp-content/uploads/2018/11/IVFlandelijk2017.pdf (7 November 2019, date last accessed).

OECD. *Health at a Glance*. 2013. http://dx.doi.org/10.1787/health_glance-2013-en (12 June 2019, date last accessed).

van den Boogaard NM, van den Boogaard E, Bokslag A, van Zwieten MC, Hompes PG, Bhattacharya S, Nelen W, van der Veen F, Mol BW. Patients' and professionals' barriers and facilitators of tailored expectant management in subfertile couples with a good prognosis of a natural conception. *Hum Reprod* 2011;**26**:2122–2128.

van der Steeg JW, Steures P, Eijkemans MJ, Habbema JD, Hompes PG, Broekmans FJ, van Dessel HJ, Bossuyt PM, van der Veen F, Mol BW. Pregnancy is predictable: a large-scale prospective external validation of the prediction of spontaneous pregnancy in subfertile couples. *Hum Reprod* 2007;**22**:536–542.

van Eekelen R, Scholten I, Tjon-Kon-Fat RI, van der Steeg JW, Steures P, Hompes P, van Wely M, van der Veen F, Mol BW, Eijkemans MJ *et al*. Natural conception: repeated predictions over time. *Hum Reprod* 2017a;**32**:346–353.

van Eekelen R, van Geloven N, van Wely M, McLernon DJ, Eijkemans MJ, Repping S, Steyerberg EW, Mol BW, Bhattacharya S, van der Veen F. Constructing the crystal ball: how to get reliable prognostic information for the management of subfertile couples. *Hum Reprod* 2017b;**32**:2153–2158.

van Eekelen R, McLernon DJ, van Wely M, Eijkemans MJ, Bhattacharya S, van der Veen F, van Geloven N. External validation of a dynamic prediction model for repeated predictions of natural conception over time. *Hum Reprod* 2018;**33**:2268–2275.

van Eekelen R, van Geloven N, van Wely M, McLernon DJ, Mol F, Custers IM, Steures P, Bhattacharya S, Mol BW, van der Veen F *et al*. Is IUI with ovarian stimulation effective in couples with unexplained subfertility? *Hum Reprod* 2019a;**34**:84–91.

van Eekelen R, van Geloven N, van Wely M, Bhattacharya S, van der Veen F, Eijkemans MJ, McLernon DJ. IVF for unexplained subfertility; whom should we treat? *Hum Reprod* 2019b;**34**: 1249–1259.

Wang R, Danhof NA, Tjon-Kon-Fat RI, Eijkemans MJ, Bossuyt PM, Mochtar MH, van der Veen F, Bhattacharya S, Mol BWJ, van Wely M. Interventions for unexplained infertility: a systematic review and network meta-analysis. *Cochrane Database Syst Rev* 2019;**9**:CD012692.

Zorginstituut Nederland. Richtlijn voor het uitvoeren van economische evaluaties in de gezondheidszorg. Diemen, Zorginstuut Nederland, 2016.