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Journal of Clinical Research and Reports

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Review Article

Will non-Ultrasound Monitoring Ovarian Stimulation (NUMOS) Make Freeze all for all? - cost-Effectiveness Analysis

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Received date: March 20, 2024; Accepted date: March 25, 2025; Published date: April 03, 2025

Citation: Iavor K. Vladimirov, Desislava Tacheva, Evan Gatev and Martin Vladimirov, (2025), Will non-Ultrasound Monitoring Ovarian Stimulation (NUMOS) Make Freeze all for all? - cost-Effectiveness Analysis, *J Clinical Research and Reports*, 19(3); **DOI:10.31579/2690-1919/519**

Abstract

Assisted reproductive technologies are one of the most rapidly developing fields in medicine. In recent decades, new technologies and methods have been introduced that have made it possible to increase the success rate of infertility treatment and reduce its costs. Using the vitrification method, it has become feasible to successfully freeze oocytes and embryos, with the freeze-all embryos strategy becoming increasingly popular, as it presents a high success rate, various clinical advantages, and reduced patient risk, especially for patients with a high ovarian response. A major challenge with this strategy, compared to the generally accepted classic approach for the so-called fresh embryo transfer, is the additional costs resulting from freezing/thawing the embryos and the additional visits related to preparation for embryo transfer. A solution to this problem would be to use the non-ultrasound monitoring of ovarian stimulation (NUMOS) approach, allowing to significantly reduce the costs of infertility treatment through IVF procedure, the direct medical and non-medical costs, as well as the indirect costs. NUMOS in combination with progestin (PPOS) is an appropriate protocol when applying the freeze-all strategy. This method also enables the active entry of artificial intelligence (AI) into the treatment process. It is anticipated to usher a shift in the established paradigm in medicine, which should not be seen as a revolution, but rather as part of an evolutionary process.

Keywords: ovarian stimulation monitoring; in vitro fertilization; fet; numos; cost effectiveness

Introduction

Every innovation in assisted reproduction aims to increase the success rate and reduce the risk to the patient and the cost of the service. It is in the interest of both the patient and society to reduce the direct and indirect costs of treating infertility through in vitro procedures. For this reason, with the use of telemedicine and various technologies, different methods and approaches are being used to reduce these treatment costs. A successful example of this strategy is the method, developed by Gerris et al. [1], of self-operated endovaginal telemonitoring (SOET), which enables patients to perform vaginal sonographies from their own homes. This innovation gives the patient the option not to come to the clinic as often. Applying telemedicine elements through SOET in COS monitoring during IVF treatment saves the patients and their partners time and money. Structured communication via email or other means allows the patient to be treated in a clinic of their choice, due to the remote nature of the procedure. This approach increases patient autonomy. Another approach that aims to reduce costs in ovarian stimulation, is measuring E2 saliva levels. A number of studies have shown that a substantial correlation coefficient ranging from 0.68 to 0.91 was discovered between serum and salivary E2 concentrations [2,3]. This patient-friendly non-invasive method could allow frequent hormone monitoring without the need for appointments at the clinic and for phlebotomy, thus resulting in more convenience for both the clinics and the patients [4]. Other studies found that estrone-3-glucuronide (E1-3G) urinary levels are a function of increasing estradiol levels during ovarian stimulation [5,6,7,8]. An advantage of the method is that E1-3G in urine can be determined with a small portable analyzer by patients at home. The established correlation of E2 and E1-3G in this method is in the range of 0.76-0.81 [9,10]. Based on these results, a new approach for OS monitoring was developed, called Controlled Ovarian Stimulation by Self-Determination of Estrone-3-Glucuronide and Single Ultrasound (COSSESU). The growth dynamics of E1-3G during stimulation are used as a marker for follicle growth, accompanied at the end of stimulation with a single ultrasound examination and determination of serum hormone levels. As a result of our extensive analysis and research and our experience with COSSESU,

we have developed a new method of ovarian stimulation monitoring without the use of ultrasound and studying the dynamics of changes in hormones in the blood, the so-called Non-Ultrasound Monitoring of Ovarian Stimulation (NUMOS). In this way, direct medical and nonmedical costs, as well as indirect costs, can be significantly reduced [11]. In this article, the implementation of NUMOS combining with progestin priming ovarian stimulation (PPOS) protocol to freeze embryos will be examined, as well as a comparative analysis of freeze-all and fresh ET strategies will be provided, and the extent to which NUMOS can reduce the cost of infertility treatment by IVF procedure will be determined.

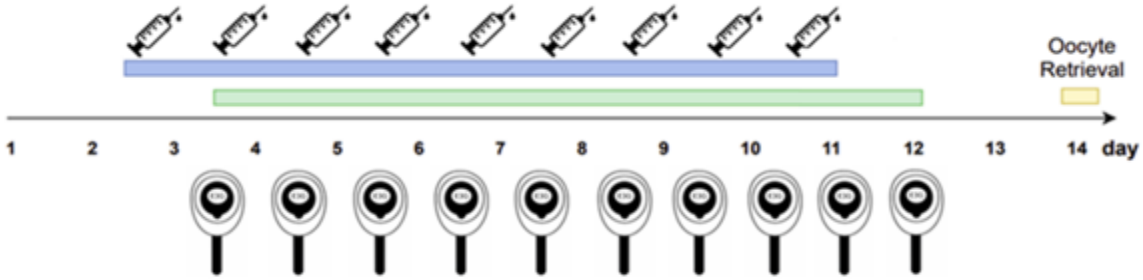

Figure 1: Non-Ultrasound Monitoring of Ovarian Stimulation.

Non-Ultrasound Monitoring of Ovarian Stimulation (Global Reproductive Health 09(04):1-7).

The method includes several key components:

-Choice of stimulation protocol. PPOS is a suitable protocol, because it is equally successful compared to others, easy to apply, and more patient-friendly. Use of GnRH agonist as an ovulation trigger and mandatory embryo freezing, significantly reduce the risk of OHSS [12].

-Starting doses – determined on the basis of a preliminary assessment of the ovarian reserve, carried out in the previous 3 months. Based on the patient's age, BMI, AFC, AMH, FSH, and smoking [13], the starting dose of gonadotropins can be determined, which further reduces the risk of OHSS and cancellation of stimulation due to unsatisfactory response. - Stimulation with fixed doses – this makes the procedure easier for patients and does not reduce the effectiveness of the treatment, compared to adjusting the doses depending on the ovarian response [14,15].

-Control of the adequacy of the ovarian response - based on monitoring the stimulation and the dynamics of E1-3G in urine, by regular determination of E1-3G in urine independently by the patients at home. This is done with the help of a small portable analyzer, which is easy to use and takes a short time to read E1-3G in the sample. [16,17]

-Determining the day for follicular puncture – based on the length of the menstrual cycle [11]. This gives us the opportunity to optimize the work in the clinic, as well as pre-calculate the stimulation doses that must be provided.

Cost-effectiveness in freeze-all and fresh ET strategies using NUMOS with PPOS protocol.

The policy of freezing all embryos requires additional costs to freeze and thaw the embryos, as well as a new FET cycle, which, in turn, means additional clinic visits. Therefore, the cost of the all-embryo freezing strategy is expected to be higher than the conventional strategy and its adoption would only be justified if there is cost-effectiveness. A proper cost-effectiveness analysis should take into account other important parameters, such as the cost of potential complications for the mother and baby (such as OHSS, obstetric and neonatal complications). The profitability aspects of the freeze-all policy are still under debate. Some authors maintain that the freeze-all strategy is cost-effective based on a higher success rate [18,19], while others disagree [20,21]. Research and discussion continue, and most authors are of the opinion that the success rate of base CLBR when applying the freeze-all policy is comparable to that when fresh ET is implemented. If we assume that the success rate of both approaches is approximately equal [22,23,24], then the sole factor that remains is the cost of the treatment. The main advantage of the fresh ET policy is the lower price compared to Freeze all, due to the additional costs for freezing, storing and thawing of the embryos, as well as the preparation of the patient cycle for thawed ET. Comparative studies between the two approaches found significantly fewer costs for IVF treatment using the Fresh ET policy with GnRH agonist and GnRH antagonist protocols. With the introduction of PPOS, which requires freezing of embryos, the cost of medication is significantly reduced. Although the cost of treatment using the PPOS protocol is higher compared to a short GnRH agonist, it is still lower compared to the application of GnRH antagonist protocols [25]. All these comparatives analyze are made on the basis of market-determined prices, as well as the price that the patient pays for the service. However, there is an alternative perspective – pricing based on the real value (what it costs the clinic) of the freezing and thawing procedure. Using these criteria, Papaleo et al. [26], found that the additional costs of FET for drugs were 34 euros and for freezing/thawing each blastocyst were within 57 euros. Another study [27], providing detailed estimates of costs for the different stages of infertility treatment through IVF technologies, found that the costs (including costs of the fertility department and laboratory costs) for carrying out FET were 202 euros more compared to fresh ET. The authors report that 18.9% of IVF procedures resulted in cryopreservation of residual embryos, with the cost of cryopreservation of residual embryos being 141-173 euros. This increases the cost of infertility treatment by 29 euro per oocyte aspirated. Additional costs that would be involved after a cryopreserved embryo transfer leading to a positive pregnancy outcome totaled 111 euro. This is due to the prolonged administration of progesterone in artificially regulated cryopreserved cycles. The price of IVF treatment is partly determined by direct and indirect costs. Direct costs are known and can be easily ascertained. These include the costs of doctor consultations, medication, ultrasound scans, laboratory tests, ART procedures (follicular puncture, anesthesia, laboratory costs of sperm processing, IVF/ICSI fertilization, embryo culture, freezing and embryo transfer), hospital fees, and administrative fees. From an analysis by Collins [28], it is evident that the cost of the IVF procedure varies widely,

from US$ 1,272 in Iran and Pakistan to US$ 6,361 to US$ 9,547 in the United States, respectively. Similar disproportions in the price of the IVF procedure were also reported by other authors, who established an average price for the USA for 2006 of $12,513, while in Japan the average price was $3,956. Medication costs represent a significant part of the total cost of treatment in all countries. The proportion was highest in Canada, where drug costs were 41.5% of total treatment costs, and lowest in Japan, where they totaled 13% of treatment costs. These differences in drug costs partly stem from the different market prices of commonly used drugs, partly from differences in prescribing patterns, i.e. fewer gonadotropins per stimulated cycle used in one country versus another, etc. [29]. The direct non medical and indirect costs related to the IVF procedure mainly include costs related to loss of working time and travel to the treatment center, food, and hotel accommodation. According to some authors, indirect costs are much lower than direct costs and are therefore considered negligible [30]. However, according to other authors, direct non-medical costs and indirect costs of IVF treatment account for 45%-52% of total costs [20]. A study by Wu et al. [31] showed that in a period of 18 months, the patient devoted 162 hours to the treatment of infertility by IVF method, which is equal to 20.25 days, with an 8-hour working day. A study by Bouwmans et al. [32] shows that the patient is absent from work for the realization of the IVF/ICSI procedure an average of 23 hours, which, calculated on a salary basis, is a loss of productivity within 596 euro. Another study [33] showed that depending on the distance to the clinic, patients could spend between 15 and 75 hours on travel, with the main costs being food and accommodation, ranging from 104 – 703 euro. Additional costs are consistently cited as a reason why patients choose not to seek infertility counseling and treatment or discontinue treatment before pregnancy is achieved [34,35], this is also found in countries where infertility treatment services are subsidized by health insurance systems [36,37]. One of the main reasons for these decisions is the high indirect and time costs that patients have to take into account during the treatment. A study by Le et al. [22] is one of the few studies in which indirect costs were included and analyzed alongside direct medical costs. This is a randomized controlled trial (RCT) that included 782 non-PCOS patients with the aim that the strategy be more cost-effective from a patient perspective than fresh embryo transfer (ET). The analysis found that the mean total costs per couple did not differ significantly when comparing the freeze-all policy groups compared to the fresh ET group. However, there is an difference of 393.6 euro less, when applying fresh ET. The study did not specify how many visits per procedure, on average, patients made. But this can be established on the basis of the presented direct costs for examinations in both groups, the price list from the appendix, information on the type of protocol, and the number and type of examined hormones in the serum [38], namely antagonist protocol and determination of hormones (E2 and P) at each ultrasound examination. From the analysis, it can be determined that patients had 6-8 visits per procedure, and FET patients had to make 1 visit more. Respectively, approximately 2/3 of the visits (4-6 visits) were related to OS monitoring. This corresponds to established practice for the number of visits when using an antagonist protocol, including visits for follicular puncture and ET. Along with its scientific advantages, this study provides specific information about direct non-medical and indirect costs: 1,767.3 euros for freeze-all and 1,827.9 euros for fresh ET, which amounts to 45-52% of the total costs of the IVF treatment. The question arises, whether the application of NUMOS can reduce and by how much the cost of treating infertility through an IVF procedure? The answer to the question should take into account the market prices of services and medication, in this case in Vietnam, as well as the fact that using NUMOS is related to the freeze-all policy. The authors of the above study found that patients spent 3,905.8 euros when applying the classic method of OS monitoring, embryo freezing, and FET implementation. When applying NUMOS for monitored stimulation, visits for the entire IVF procedure would be reduced approximately three times, respectively patients would save 1000-1200 euros from direct non-medical and indirect costs. To these, we can add saved costs from ultrasound examinations and hormonal tests within 100-120 euros. Cost savings for the medications used in the antagonist protocol, when replaced with the PPOS protocol, would amount to 180-220 euros. From the calculation, it is clear that the application of the NUMOS method can reduce the cost of IVF treatment by 25-30%. Expressed in concrete terms based on the economic analysis of Le et al. [22], patients would save a minimum of 1,000 euros. This means that the costs of the whole procedure would fall within 2,900 euros when freezing all embryos, while with a fresh ET policy, the costs would be within 3,500 euros. This means that the Freeze all policy becomes financially more sound compared to the fresh ET policy. Another study by Maheshwari et al. [23] also found that a policy of freezing all embryos compared to fresh embryo transfer did not increase the delivery rate. The elective freeze (E-Freeze) trial was a pragmatic, multicentre, two-arm, parallel-group, non-blinded, randomized controlled trial, carried out in eighteen different clinics in the UK and included 619 couples that were randomized in fresh-embryo transfer arm and freeze-all arm groups. The authors conclude that, when efficacy, safety, and costs are considered, freeze-all policy is not better than fresh-embryo transfer. Looking closely at the information presented in the study, it can be found that treatment costs under the freeze-all policy are indeed higher on average by £322 compared to fresh ET – respectively £1538 and £1216. However, fresh ET cases included significantly more cases of OHSS and had more outpatient visits and longer inpatient stays than participants in the freeze-all group. The average additional cost required to treat OHSS in the allocation was £17 for frozen embryo transfer and £201 for fresh embryo transfer. Moreover, when costs were recalculated according to NHS prices, the results were similar, respectively £3431 for the group with freezing all embryos and £3574 for the group with fresh embryo transfer. Compared to the study by Lee et al. [22], the direct medical costs of ovarian stimulation (OS) monitoring were significantly higher than the indirect costs. Respectively, the cost of a visit with an ultrasound examination is £160-220 and £40-60 for the examination of each hormone during stimulation monitoring. The information received from patients about total travel costs and time costs per visit averaged £58. Total time costs are based on (ASHE) calculations. If NUMOS is applied to monitor stimulation, the reduction in visits will significantly reduce direct medical costs. By reducing visits to 3-5 during OS, the costs will be reduced by a minimum of 800-1000 pounds, and this will be mainly coming out of direct medical costs. Therefore, in this case, applying a NUMOS approach for monitored stimulation using the Freeze all strategy also will be cost-effective, compared to a fresh ET policy. From the presented facts and results, it is clear that applying the NUMOS method for monitoring ovarian stimulation can significantly reduce the costs of infertility treatment through the IVF method. They would be further reduced if the NUMOS method were combined with home-based monitoring of ovulation to time frozen embryo transfer (HOMET), the efficacy of which was established by Zaat et al [39]. I would refer to this strategy as Two Visits IVF (TV/IVF): first visit for follicular puncture and second visit for ET. Some colleagues may view this new approach with scepticism. Nevertheless, thanks to new technologies, telemedicine, and the active

entry of artificial intelligence (AI) into assisted reproduction (ART), the TV/IVF approach is a reality. This will make infertility treatment more accessible and optimize the work of ART clinics.

Ethics Statement- NA

Author Contributions

IKV: Design, conception, analysis and interpretation of data, drafting of article, writing - review & editing, supervision. DT: Design, drafting of article, funding acquisition. IG: Analysis and interpretation of data, writing - review & editing, visualization. MV: Conception, writing - review & editing, visualization. All authors approved the final manuscript. All authors contributed to the article and approved the submitted version.

Funding -Non

Conflict of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Acknowledgments:

The authors would like to thank all the medical staff in the SBALAGRM-SOFIA for their assistance in data collection.

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DOI:10.31579/2690-1919/519