
ASSISTED REPRODUCTIVE TECHNOLOGIES IN CENTERS FOR BIOMEDICAL ASSISTED FERTILIZATION WITHIN AND OUTSIDE THE NETWORK PLANS IN THE REPUBLIC OF SERBIA AND THEIR FINANCING

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ABSTRACT: INTRODUCTION: Assisted reproduction technologies (ART) are technologies that are used today, in the treatment of infertility, on human germ cells (oocytes and sperm) and embryos. Currently in the Republic of Serbia, there are various procedures of assisted reproduction technologies that are used to treat infertility in patients depending on medical indications. The availability of assisted reproduction technologies has been evolving over the years, and their application differs in biomedically assisted fertilization centers that are in the Network Plan (state institutions) and outside the Network Plan (private institutions). The aim of this article is to analyze available ART methods in Fertility centers within and outside the Network plan regulated by the Law on the Treatment of Infertility Procedures of Biomedical Assisted Fertilization (Official Gazette of the Republic of Serbia”, No. 72/2009), their financing and availability to patients in the Republic of Serbia. **METHOD:** This article is assembled upon seeking documents using the Internet and based on analyzed literature available on the Internet. **RESULTS:** The results were gathered by analyzing official ART centers’ websites and analyzing available external secondary data from the National health insurance fund and the Institute for public health “Dr Milan Jovanovic Batut”. Fertility clinics in the Republic of Serbia have access to all the important technologies for ART. ART technologies funded by National health insurance fund include in vitro fertilization, intracytoplasmic sperm injection and frozen embryo transfer. Patients whose medical indications require for some other technology may approach Fertility Centers outside the Network plan on their own budget. **CONCLUSION:** Based on the available and updated data we can conclude that Fertility centers in the Republic of Serbia have access to all the important technologies for ART. Fertility centers within the Network plan can implement only the technologies financed and invoiced by the Fund. **KEY WORDS:** infertility, biomedical assisted fertilization centers/Srbija, Assisted reproduction technologies, Fertilization in vitro, frozen embryo transfer, preimplantation genetic diagnosis.

INTRODUCTION

Assisted reproduction technologies are technologies that are applied today, in the treatment of infertility, on human germ cells and embryos. Currently in the Republic of Serbia, there are various procedures of assisted reproduction technologies that are used to treat infertility in patients depending on medical indications. The availability of assisted reproduction technologies has evolved over the years, and their application differs in biomedically assisted fertilization centers that are in the Network Plan (state institutions) and outside the Network Plan (private institutions). Assisted reproductive technology (ART) is a group of state-of-the-art therapeutic procedures for the treatment of infertility [1].

Assisted reproductive technologies

ART refers to all technologies used to manipulate gametes outside of the human body. Those most commonly used are in vitro fertilization (IVF) and intracytoplasmic sperm injection (ICSI). They do not include technologies such as intrauterine insemination (IUI) that manipulates only male gametes [2]. Innovative technologies that increase the success rate have also been developed. Some of them are in vitro maturation (IVM), preimplantation genetic diagnosis (PGD), sperm and oocyte donation (SD, OD) [3], frozen embryo transfer (FET) procedure and assisted hatching (AH).

Medical indications for different assisted reproductive technologies

In vitro fertilization (IVF) is an assisted reproductive technology that may be applied only to patients whose spermogramme shows normospermia. Cultivated sample is then laid among the egg cells and fertilization occurs alone. Medical indications for IVF require for the male patient’s sample to show

normospermia [4], and indications for the female patient require blocked Fallopian tubes, ovulation problems, endometriosis [5] and genetic diseases that result in miscarriage [2].

Intracytoplasmic sperm injection –ICSI is a technology of micromanipulation where one sperm is injected in the egg cell cytoplasm, thus fertilizing it. Medical indications for ICSI are mostly connected to male infertility, as well as patients who haven't achieved fertilization through IVF [5]. Male infertility comprises oligospermia, asthenospermia, teratospermia, obstructive and non-obstructive azoospermia, when sperms are collected surgically (PESA – percutaneous epididymal sperm aspiration, TESA / TESE – testicular sperm aspiration / extraction). In the case of the presence of antispermatozoal antibodies in both partners, the ICSI method is performed, and after thawing frozen seed samples, the microfertilization method is also applied [2].

Frozen embryo transfer (FET) is an embryo transfer obtained in one of the previous procedures by the classical IVF or ICSI method, followed by frozen vitrification processes. In the FET process, the embryos are thawed and returned to the previously prepared substance. Advantages of FET procedure lie in the fact that the excess embryos from IVF procedures is frozen and then transferred in successive cycles, which enables high cumulative rate of in vitro fertilization [6].

In vitro maturation – IVM is a cycle in which egg cells are gathered from antral follicles of unstimulated or mildly stimulated ovaries. Immature ova are gathered, and the last phase of their maturation is done under laboratory conditions. Medical indications for IVM cycles include patients with polycystic ovary syndromes (PCOS) so as to decrease the risk of ovarian hyperstimulation [7]. In patients with estrogen-dependent cancers (oncology patients), stimulated cycles with standard ovulation stimulation protocols are avoided because they stimulate follicle growth and stimulate estrogen production, so eggs are collected from antral follicles of unstimulated ovaries.

Preimplantation genetic diagnosis – PGD is a micromanipulation technology done by biopsying several embryo cells 5-6 days old, followed by analyzing genetic material of biopsied cells. Medical indication for PGD includes patients with high risk of passing down hereditary diseases to child, patients with repeated miscarriages and patients above 38 years of age with risk of aneuploidy.

Assisted hatching – AH is a micromanipulation technology by which zona pellucida on embryo is pierced so as to facilitate its release, which increases implantation, as well as pregnancy rates. Medical indications include multiple failed in vitro procedures, as well as multiple failed transfers of frozen embryos.

Frozen oocyte replacement – FORs [8] are cycles which use frozen ova (Oocyte cryopreservation – OoC) [9].

Oocyte donation (OD) represents inseminating ova of the female donor with sperms taken from a male partner. The child's genetics comes from the male partner. Medical indications for oocyte donation include premature ovarian failure (POF), poor quality of ova and oncologically treated patients.

Sperm donation (SD) represents inseminating ova from a female partner with sperms coming from a donor. Medical indications for sperm donation are azoospermia, or other sperm abnormalities.

ART financing

Public financing among countries is available for an entire series of reproductive technologies, including IVM, PGD, AH, OD, SD. Seven countries (Denmark, France, Slovenia, Sweden and the UK (England, Scotland, Wales) fully or partially finance IVM through national health programs. Twenty-two countries (Australia, Austria, Belgium, Bulgaria, the Czech Republic, Denmark, Finland, France, Greece, Hungary, Israel, Italy, Latvia, New Zealand, Norway, Russia, Spain, Sweden, the UK (England, Scotland, Wales) fully or partially finance PGD through their national health programs. There is no documented evidence that the AH expenses are paid through public financing, and there is no documented evidence that the expenses sperm or ovum donation for in vitro are paid through national financing program [3].

ART financed by the National health insurance fund is done in Fertility centers from the Network plan and there are no other options for technologies that cannot be invoiced through National health insurance fund's forms [10]. Technologies such as IVF and ICSI were funded until 2017, and ever since then the National health insurance fund has financed new technologies, such as FER procedure, as well [11,12]. Fertility centers outside the Network plan offer some other mentioned ART technologies apart from IVF and ICSI that are financed by patients themselves.

According to Article 23 of the Law on the Treatment of Infertility Procedures of Biomedical Assisted Fertilization, ("Official Gazette of the Republic of Serbia", No. 40/2017 and 113/2017, etc.), a Fertility Center must keep medical records sent to the biomedicine Board. Those records delivered to the

Board for biomedicine include data on all ART technologies. Those forms are delivered to the Board for biomedicine, stating which technologies have been used in ART procedures and this is recorded in the state register.

The aim of this article is to analyze available ART methods in Fertility Centers within and outside the Network plan regulated by the Law on the Treatment of Infertility Procedures of Biomedical Assisted Fertilization (Official Gazette of the Republic of Serbia", No. 72/2009), their financing and availability to patients in the Republic of Serbia.

MATERIAL AND METHODS

This article is assembled upon seeking documents using the Internet and based on analyzed literature available on the Internet. The results were gathered by analyzing official ART centers' websites and analyzing available external secondary data from the National health insurance fund and the Institute for public health "Dr Milan Jovanovic Batut".

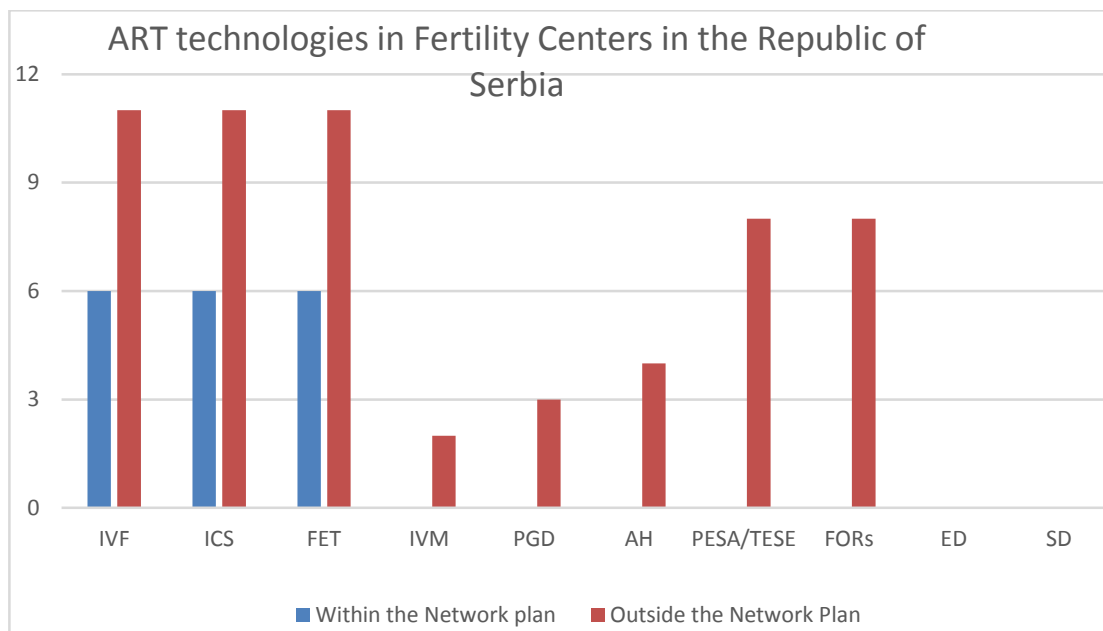
RESULTS

Fertility Centers with whom the National health insurance fund has concluded the contract on providing infertility treatments are:

- Fertility Centers within the Network plan:
 1. Clinic for Gynecology and Obstetrics, Clinical Centre of Serbia, Belgrade
 2. Gynecology and Obstetrics Clinic, Clinical Centre of Vojvodina, Novi Sad
 3. Obstetrics and Gynecology Clinic, Clinical Centre of Nis, Nis
 4. Obstetrics and Gynecology Clinic "Narodni Front", Belgrade
 5. Gynecology and Obstetrics Center, General Hospital of Valjevo, Valjevo
 6. Clinic of Gynecology and Obstetrics, Clinical Center of Kragujevac, Kragujevac
- Fertility Centers outside the Network plan:
 1. Special Gynecological Hospital for Treatment of Infertility "Nikolov", Kragujevac
 2. Special Hospital for Infertility Treatment "Spebo Medical", Leskovac
 3. Special Hospital for Gynecology "Perinatal", Novi Sad
 4. "Feron" IVF Clinic, Novi Sad
 5. Special Hospital for Gynecology "GINS", Novi Sad
 6. Special Gynecological Hospital "Genesis", Novi Sad
 7. Special Gynecological Hospital "Teofanović", Belgrade
 8. Special Gynecological Hospital "Beograd", Belgrade
 9. Special Gynecology Hospital with Maternity Ward "Jevremova", Belgrade
 10. General Hospital "Analife", Belgrade
 11. Special Hospital for Infertility Treatment "Intermedicus Bis", Belgrade

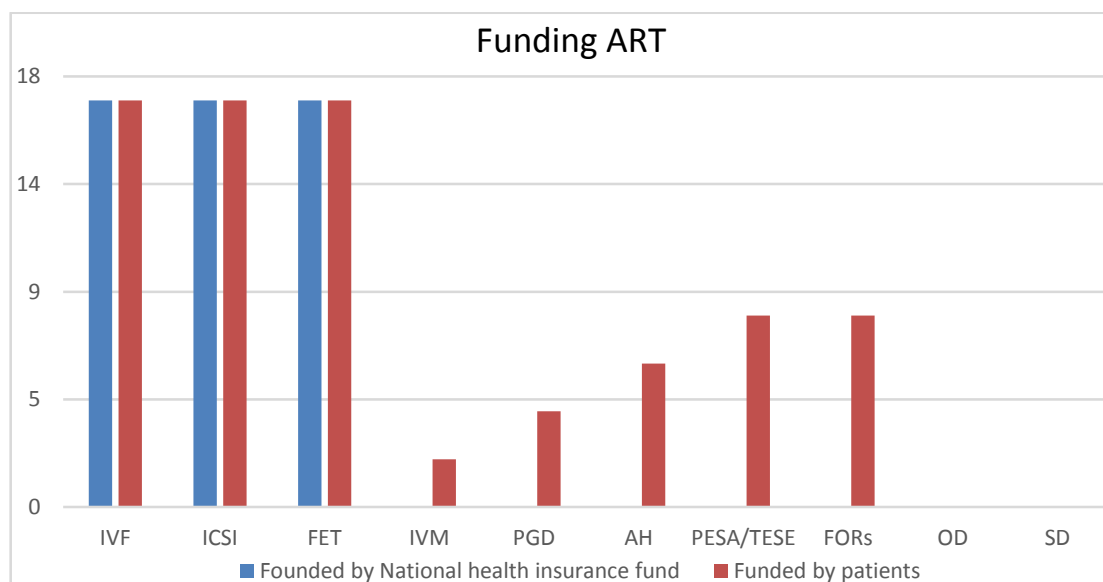
Fertility Centers in the Republic of Serbia have access to all the important technologies for ART. ART technologies available in Fertility Centers within and outside the Network plan are displayed on Chart 1.

Chart 1. ART technologies available in Fertility Centers within and outside the Network plan in the Republic of Serbia



ART technologies funded by National health insurance fund include in vitro fertilisation, intracytoplasmic sperm injection and frozen embryo transfer. Patients whose medical indications require for some other technology may approach Fertility Centers outside the Network plan on their own budget (Chart 2).

Chart 2. ART technologies funded by National health insurance fund and funded by patients



DISCUSSION

Additional challenges for couples in our country are weakness of the so-called National System for the implementation of ART procedures. Such problems are relatively numerous. They concern the assembling necessary diagnostic analyses and documentation for eligibility and criteria needed for the

onset of the procedure. Frequent inadequate equipment of institutions and expertise of staff that provide services during the BMPO procedure, lack of application of the most modern methods and procedures of reproductive medical science, as well as the existence of a relatively long waiting period for the procedure itself. The time dimension is extremely important here, taking into account that the patient's age is extremely important for the success of fertilization [13].

Earliest found data in the Republic of Serbia date from 2004, where eight private clinics are mentioned and their internal documentation could not be obtained. In Serbia, ART was only done on Clinic for Gynecology and Obstetrics of the Clinical Centre of Serbia. Summary annual reports show that the number of treatments varied and it probable depends on the (under)development of technology, but also on the social and economic factors. These data show that the number of ART in public institutions, compared to the number of started cycles in Serbia for the year of 2000, amounted to 178 started cycles; 296 started cycles for the year of 2001; 174 started cycles for the year 2002; and 149 started cycles for the year of 2003. A very expensive ART procedure in Serbia was financed by couples themselves [1].

National health insurance fund has financed infertility treatments by Biomedical Assisted Fertilization procedures since 2006, according to indications prescribed by National Expert Commission of the Ministry of Health of the Republic of Serbia. Between 2009 and 2013, The Ministry of Health has passed the Law on the Treatment of Infertility Procedures of Biomedical Assisted Fertilization (Official Gazette of the Republic of Serbia", No. 72/2009), as well as a series of bylaws that regulate this area. As the existing capacities of medical institutions within the Network plan are not enough to meet the needs of all insured individuals, National health insurance fund has concluded contracts for administering mentioned services with private medical institutions on several occasions [14].

In the year of 2013, there were 634 second phases of assisted IVF fertilizations done in Serbia, accompanied by 1,105 ICSI procedures [15]. Based on the data available from analyzed planned and achieved scope of content rights of insured individuals to stationary medical care in the Republic of Serbia in 2013, the right to infertility treatment financed by the Fund (based on invoiced services of National health insurance fund) was granted to 2055 patients, 1659 of which in Fertility Centers within the Network plan (925 IVF and 734 ICSI) and 396 in private BAF Centers outside the Network plan mreže (25 IVF and 371 ICSI). Frozen embryo transfer was not financed by the Fund, so patients financed the procedure themselves in Fertility Centers outside the Network plan, of which there are no accurate data.

The total of 933 second phases of assisted fertilizations by IVF method were done in 106, followed by 1,474 ICSI methods and 140 frozen embryo transfers [11]. Based on the data available from analyzed planned and achieved scope of content rights of insured individuals to stationary medical care in the Republic of Serbia in 2016, the right to infertility treatment financed by the Fund (based on invoiced services of National health insurance fund) was granted to 2407 patients, 1,529 of which in Fertility Centers within the Network plan (854 IVF and 675 ICSI) and 878 (79 IVF and 799 ICSI) in private Fertility Centers outside the Network plan. Frozen embryo transfer also came to be funded, so there were 140 invoices from patients, 5 of which in Fertility Centers within the Network plan and 135 in private ART centers.

There were 712 second phases of assisted fertilizations by IVF method done in 2017, followed by 2,396 by ICSI method and 445 frozen embryo transfers [12]. Based on the data available from analyzed planned and achieved scope of content rights of insured individuals to stationary medical care in the Republic of Serbia in 2017, the right to infertility treatment financed by the Fund (based on invoiced services of National health insurance fund) was granted to 4064 patients, 956 of which in Fertility Centers within the Network plan (634 IVF and 322 ICSI) and 3,108 (712 IVF and 2,396 ICSI) in private Fertility Centers outside the Network plan. Frozen embryo transfer also came to be funded, so there were 445 patients, 5 of which in Fertility Centers within the Network plan and 440 in private Fertility Centers.

CONCLUSION

Based on the available and updated data we can conclude that Fertility Centers in the Republic of Serbia have access to all the important technologies for ART. Fertility centers within the Network plan can implement only the technologies financed and invoiced by the Fund. Based on the data available from analyzed planned and achieved scope of content rights of insured individuals to stationary medical care in the Republic of Serbia, it is evident that the number of invoiced ICSI cycles is significantly larger in Fertility Centers outside the Network plan, which shows that patients with graver medical indications are

referred to private clinics. Thus for example patients with medical indications for azoospermia do not have possibility of treatment in Fertility centers within the Network plan, only in Fertility centers outside the Network plan that are financed by patients themselves. Moreover, the higher number of available ART technologies may be one of the reasons for the significant growth of services provided in private medical institutions.

P.S. A question arises as to why the lawfully granted oocyte and sperm donation services are not available neither in Fertility Centers within, nor outside the Network plan. If Fertility Centers within the Network plan are not equipped, why aren't these services available in Fertility Centers outside the Network plan?

LITERATURE:

1. Devedžić M. Development of reproductives and its demographic aspects. BIBLID 0038-982X(2004): 1-4 p.45-65. Available from: https://www.researchgate.net/publication/275676887_Development_of_reproductives_and_its_demographic_aspects
2. Begum MR. Assisted Reproductive Technology: Techniques and Limitations. Journal of Bangladesh College of Physicians and Surgeons Vol.26, No.3, September 2008. Available from: https://www.researchgate.net/publication/270114969_Assisted_Reproductive_Technology_Techniques_and_Limitations
3. Keane M, Long J, O'Nolan G, Farraghe L. Assisted reproductive technologies: International approaches to public mechanisms and criteria. An evidence review. Health Research Board: Dublin; 2017. Available from: https://www.researchgate.net/publication/322244930_Assisted_reproductive_technologies_International_approaches_to_public_funding_mechanisms_and_criteria_An_evidence_review
4. WHO laboratory manual for the examination and processing of human semen. 5th ed. Geneva: Switzerland; 2010.
5. In vitro fertilization (IVF) & intra-cytoplasmic sperm injection (ICSI) [homepage on internet]. New Zealand: Merck Serono Australia ; 2011. Available from: <https://fertilityfirst.com.au/wp-content/uploads/2017/02/in-vitro-fertilisation-ivf-intr.pdf>
6. Bjelica A. Komparacija politika vantelesne oplodnje u Srbiji I drugim evropskim zemljama. Timočki medicinski glasnik. 2017; 236-244. Available from: <http://www.tmg.org.rs/v420406.htm>
7. Grynberg M, Hachem HE, de Bantel A, Benard J, Parco S, Fanchin R. In vitro maturation of oocytes: uncommon indications. Fertility and Sterility. 2013; 99(5). Available from: [https://www.fertstert.org/article/S0015-0282\(13\)00133-7/fulltext](https://www.fertstert.org/article/S0015-0282(13)00133-7/fulltext)
8. 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. Human Reproduction 2012; 32(10). Available from: <https://pubmed.ncbi.nlm.nih.gov/29117383/>
9. Shenfield F, De Mouzon J, Scaravelli G, Kupka M, Ferraretti AP, Prados FJ, Goossens V. Oocyte and ovarian tissue cryopreservation in European countries: statutory background, practice, storage and use. Human Reproduction 2017; 1(003). Available from: <https://academic.oup.com/hropen/article/2017/1/hox003/3092404>
10. Republički fond za zdravstveno osiguranje [homepage on internet]: <http://www.rfzo.rs/index.php/osiguranalica/vto>
11. Brcanski J, Ločkić N, Živković Šulović M, Savković S. Analiza planiranog i ostvarenog obima sadržaja prava osiguranih lica na stacionarnu zdravstvenu zaštitu u Republici Srbiji u 2016.godini. Institut za javno zdravlje Srbije“ dr Milan Jovanović Batut“. 2017. Available from: <http://www.batut.org.rs/download/izvestaji/AOIS%202016.pdf>
12. Brcanski J, Ločkić N, Živković Šulović M, Antanasijević D, Savković S. Analiza planiranog i ostvarenog obima sadržaja prava osiguranih lica na stacionarnu zdravstvenu zaštitu u Republici Srbiji u 2017.godini. Institut za javno zdravlje Srbije“ dr Milan Jovanović Batut“. 2018. Available from: <http://www.batut.org.rs/download/izvestaji/AIOS%20prava%20na%20stacionarnu%20zdravstvenu%20zastitu.pdf>
13. Marjanski V. Mogućnost uvođenja privatnog osiguranja troškova sprovođenja postupka biomedicinski potpomognutog oplođenja (BMPO). Zbornik radova Pravnog fakulteta. 2012; 3: 297-308. Available from: <http://scindeks-clanci.ceon.rs/data/pdf/0550-2179/2012/0550-21791203297M.pdf>
14. Republički fond za zdravstveno osiguranje. Lečenje neplodnosti postupcima biomedicinski potpomognutog oplođenja preliminarni izveštaj. Available from: <http://www.rfzo.rs/download/vto/Preliminarni%20Izvestaj%20o%20lecenju%20neplodnosti%20postupcima%20BMPO,010414.pdf>
15. Radović Crnčević Lj, Savković S, Mutavdžić T. Analiza planiranog I ostvarenog obima I sadržaja prava osiguranih lica na stacionarnu zdravstvenu zaštitu u Republici Srbiji u 2013. Godini. Institut za javno zdravlje Srbije“ dr Milan Jovanović Batut“. 2014. Available from: <http://www.batut.org.rs/download/izvestaji/2013AnalizaObimalSadržajaStacionarna.pdf>