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DESCRIPTIVE STUDY OF THE TREATMENT COST OF ASSISTED REPRODUCTIVE TECHNOLOGY IN ESTONIA

Master's Thesis

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KUNSTLIKU VILJASTAMISE PROTSEDUURID EESTIS

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Author’s declaration of originality

I hereby certify that I am the sole author of this thesis and this thesis has not been presented for examination or submitted for defense anywhere else. All used materials, references to the literature and work of others have been cited.

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ABSTRACT

Background: In Estonia, most healthcare services are covered by state funding through Estonian Health Insurance Fund (EHIF) including Assisted Reproductive Technology (ART) services. However, the high cost caused a lot of challenges in achieving the maximum benefits from ART treatments. In addition, due to its complex procedure and structure, most evaluations of ART studies did not make use of full data.

Aim: The purpose of this thesis is to describe and explore the trends of ART services in Estonia from 2004 to 2018. The full description of ART services and reimbursement from EHIF would be presented.

Methods: This study used the descriptive study. The analysis is based on the financial and medical records of EHIF from five clinics in Estonia in 2004-2018.

Results: There are total 28 543 treatment bills with 44 030 procedures. Total of 8 995 women took part in the treatment and performed 24 171 embryo transplantation and 19 499 IVF procedure. The total the reimbursement from EHIF is 23257220.65 €. The cost for each patient is 2586 € annually. The age group of 30-34 contained the highest number of procedures per patient and the amount of change during the study period. The older patients had more times of treatment than the younger. The distribution of treatments bill among centers is significant difference in which 33% of total treatments is performed by East-Tallinn Central Hospital Center for Infertility Treatment. Follitropin Alfa (G03GB05) had the highest number of prescriptions.

*Conclusion: T*he utilization of ART in Estonia and the reimbursement paid by EHIF has increased by year. There is the considerable difference of treatment bills among centers and age group. Age of woman is one of the important factors in the infertility treatment. The further research should be study whether the distribution of health expenditure is effective.

Thesis is written in English is 44 pages long, including 4 chapters 11 figures and 4 tables

Annotatsioon

Enamik tervishoiuteenuseid täielikult Eesti haigekassa kaudu, sealhulgas kunstliku viljastamise. Kuid kõrged kulud põhjustasid suuri raskusi kunstilisest ravist saadava maksimaalse kasu saavutamisel. Lisaks sellele ei kasutanud enamik kunstiuuringute hinnanguid keeruka menetluse ja struktuuri tõttu täielikku teavet.

Töö eesmärk: Magistritöö eesmärk oli kirjeldada ja uurida Eesti ART suundumusi aastatel 2004 – 2018. Esitatakse kunstiteenuste täielik kirjeldus ja hüvitis ehifilt.

Meetod: selles uuringus kasutati kirjeldavat uuringut. Analüüs põhineb EHIFi finants- ja meditsiinilistel andmetel viiest Eesti kliinikust aastatel 2004 – 2018.

Tulemused: kokku on 28 543 raviarvet 44 030 protseduuriga. Ravis osales kokku 8 995 naist ja teostas 24 171 embrüo siirdamist ja 19 499 IVF protseduuri. Naised osalesid ravis ja tegid 24 171 embrüo siirdamist ja 19 499 IVF-i protseduuri. EHIFi hüvitise kogusumma on 23257220.65 €. Iga patsiendi hind on 2586 eurot aastas. 30-34-aastases vanuserühmas oli uuringuperioodi jooksul kõige suurem protseduuride arv patsiendi kohta ja muutused. Eakatel patsientidel oli ravi rohkem aega kui noorematel patsientidel. Raviarve jaotamine keskuste vahel on oluline erinevus. 33% ravi teostab Ida - Tallinna Keskhaigla Naistekliinik. Alfafollitropiin (G03GB05) oli suurim retseptide arv

Kokkuvõte: Kunsti Eestis ART ja EHIFi makstud hüvitis on aastaga kasvanud. Keskuste ja vanuserühmade raviarvete vahel on märkimisväärne erinevus. Naiste vanus on üks viljatusravi tähtsamaid tegureid. Edasised uuringud peaksid uurima, kas tervishoiukulude jaotamine on tõhus.

Lõputöö on kirjutatud inglise keeles ja on 45 leheküljel, sisaldades 4 peatükki, 11 joonist ja 4 tabelit

ABBREVIATIONS

ART	Assisted Reproductive Technology
ESHRE	European Society of Human Reproduction and Embryology
EHIF	Estonian Health Insurance Fund
IVF	in vitro fertilization
WHO	World Health Organization
ICSI	Intracytoplasmic sperm injection
GIFT	Gamete intrafallopian transfer
ROSNI	Round nuclei injection
ZIFT	Zygote intrafallopian transfer

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Introduction

Fertility rates differ significantly from country to country in the world, in which Europe is among the lowest. It is below the 2.1 babies per woman that is required for population replacement. Infertility, a medical condition preventing people from becoming parents, is experienced by at least 50 million couples worldwide (Mascarenhas M, Flaxman S, Boerma T., & Vanderpoel S, 2012), causing extremely adverse social and psychological implications (Suneeta M, et al., 2011). It is increasingly recognized as a serious, worldwide public health concern. In the European Union (EU) alone, approximately 25 million citizens are affected by infertility (A policy audit on fertility analysis of 9 EU countries, March 2017). According to the annual European Society of Human Reproduction and Embryology (ESHRE) Assisted Reproductive Technology (ART) report, the demand for infertility treatment has been increasing in EU due to the ageing populations (Kupka MS, et al., 2014). Since 1978, the world's first test tube baby born via in vitro fertilization, a revolution in infertility treatments has started. Although the ethical and philosophical issues remain complex and controversial, millions of people who have experienced childlessness have received benefits from this innovation technique. It is estimated that more than 8 million babies around the world have been conceived through in vitro fertilization (IVF) (European Society of Human Reproduction and Embryology, 2018).

The prominent development of IVF and other type of ART is leading to an increasing number of research studies in this field. The fertility treatment techniques are suggested as a complex study area involving various dimensions of treatments (Audibert C & Glass D, 2015). It has become one of the most challenging topics both from technical but also from the medical point of view. Several research studies have aimed at identifying and assessing factors that could maximize a woman's chances of becoming pregnant. On the other hand, recent targets of interest have been changing. The research studies with the aim of identifying and measuring the total cost of IVF treatments also have been increasing. In fact, infertility services are very expensive everywhere in the world. The high cost is contributed by the complex procedures including investigations, hormone therapy, tubal surgery, laboratory equipment and treating the complications (Teoh P & Maheshwari A, 2014). The high cost is recognized as one of the main

barriers in accessing infertility services. Previous research also suggests that the cost per live birth for older women is high and increases due to additional IVF program attempts (Griffiths A, et al., 2010).

Infertility treatment costs and reimbursement systems vary worldwide and across Europe, resulting in the various levels of accessibility to these services (Berg Brigham K, Cadier B, & Chevreul B, March 2013; Teoh P & Maheshwari A, 2014). Critical questions have been raised about how much reimbursement should be paid for that kind of treatment (Klitzman, 2017). In Estonia, healthcare is largely publicly financed, and health services are primarily funded by the Estonian Health Insurance Fund (EHIF). According to Estonian law, infertility treatment related to embryo transplantation and artificial insemination is covered from the EHIF budget for patients to up to 40 years of age (Artificial Insemination and Embryo Protection Act, 2013). As a consequence, women's socioeconomic status does not influence access to these services. However, health care resources are limited and the questions what would be the best way for allocation of health care resources to achieve the maximum benefit for public health is discussed (Klemetti R, Gissler M, Sevón T, & Hemminki E, 2007). Therefore, ART treatment cost in the context of all state medical and social welfare budget has received considerable critical attention.

Although there are studies on the infertility topic and ART, not many studies have focused on resource utilization and the cost in detail in Estonia. Tonsiver T, et al., (2014) performed the study with the objective to describe the effectiveness and costs of IVF in Estonia. The study provided the total costs related to the IVF during 2005–2011 including procedures, medication and cost per child.

This thesis includes three parts. The first part focuses on the background information related to the research topic. The second part defines the objectives, questions and research methodology. The final part provides results of the study, discussion and conclusions.

I. Background information

1. Infertility

1.1. Definition and classification

There are multiple criteria used to define infertility. There are also differences between demographic and epidemiological definitions. According to demographers, infertility is defined as childlessness in a population of women of reproductive age, while the epidemiological definition is based on ‘trying for’ or ‘time to’ the pregnancy, generally in a population of women exposed to the risk of conception (Gurunath S, Pandian Z, Anderson RA, & Bhattacharya S, 2011). The World Health Organization (WHO) defined that "infertility is a disease of the reproductive system defined by the failure to achieve a clinical pregnancy after 12 months or more of regular unprotected sexual intercourse".

There are two types of infertility. Primary infertility refers to the couples who have never had a pregnancy. Secondary infertility is a failure to conceive after a previous pregnancy. The causes of infertility are various. It can be caused by genetic factors, congenital factors, acquired diseases or lifestyle and environmental factors (Tarín JJ, 2015). Through blood tests, sperm tests, imaging studies, many of these causes can be identified and may guide treatment. In some cases, there is more than one cause contributing to the problem. Also, in some other cases, unexplained infertility occurs. However, higher maternal age is considered as an important factor for infertility (Masoumi SZ, et al., 2015).

1.2. Infertility treatment - ART

ART is the medical treatment for treating infertility. ART includes all fertility treatments in which human gametes (either eggs or embryos) are handled outside the body to achieve a pregnancy. In general, its procedures involve surgically removing eggs from a woman’s ovaries, combining them with sperm in the laboratory and returning them to the woman’s body or donating them to another woman. They do not include treatments in which only sperm is handled (i.e., intrauterine—or artificial—insemination) or procedures in which a woman takes medication only to stimulate egg production without the intention of having eggs retrieved. The first and the

most common procedure is (IVF), however, there are various other procedures used widely today. They include: intracytoplasmic sperm injection (ICSI), gamete intrafallopian transfer (GIFT), zygote intrafallopian transfer (ZIFT), round nuclei injection (ROSNI) (Nardelli A, Stafinski T, Motan T, Klein T, & Menon D, 2014)

a. IVF and embryo transplantation

IVF involves a process of fertilization where an egg is combined with sperm outside the body in an artificial environment. The term includes the use of Latin words "in vitro" which literally means "in glass". IVF is used in order to overcome problems with tubal damage or block. Also, the problems concerning the sperms when there are too few or too poor quality to fertilize an egg under normal conditions (Djahanbahkch O, Ezzati M, & Saridogan E, 2010). This procedure was first used for infertility in humans in 1977 at Bourne Hall in Cambridge, England (Cohen J, et al., 2005).

IVF process includes several formalized procedures. The first step is stimulation, also called super ovulation, in which egg production stimulated by hormone therapy. In the next step, eggs are retrieved from the ovary by minor surgery called follicular aspiration. If a woman does not or cannot produce any eggs, donated eggs may be used. At the same time, the sperm is provided and placed together with the best quality eggs and stored in an environmentally controlled chamber. When the fertilized egg divides, it becomes an embryo. Laboratory staff will regularly check the embryo to make sure it is growing properly. Within about 5 days, a normal embryo has several cells that are actively dividing. Finally, embryos are placed into the woman's uterus 3 - 5 days after egg retrieval and fertilization. It is called embryo transplantation. If an embryo sticks to (implants) in the lining of the uterus and starts to grow, pregnancy results (DeCherney A.H, 1986).

b. Other treatments

ICSI is an IVF procedure in which a single sperm is injected directly into an egg. It is used in the situation where the sperm count, or motility is very low, or due to high numbers of abnormal sperm, IVF failed to produce fertilization. Many fertility programs routinely do ICSI

on some of the eggs. It has revolutionized the treatment of male factor causing infertility and results in an excellent number of pregnancies. After the direct injection of the single sperm into each egg to achieve fertilization, the following process is exactly the same as described for IVF (Merchant R, Gandhi G, & Allahbadia GN, 2011).

GIFT is similar to IVF that fertilization occurs in the laboratory, however, the very young embryo is transferred to the fallopian tube instead of the uterus (Romito K, & Husney A, 2018)

ZIFT involves transferring eggs and sperm into the woman's fallopian tube. Fertilization occurs in the woman's body (Romito K, & Husney A, 2018)

ROSNI uses testicular spermatozoa (immature sperm) which is directly injected into an oocyte. Because the round spermatids in ROSI are immature haploid cells and they have little or no capacity to activate oocyte, so the oocyte needs to be pre-activated and follow quite different protocol than in standard method using epididymal spermatozoa (mature sperm) (Birmingham A, 2008).

1.3. Medications used in ART

The aim of the most common medications used to treat female infertility is to help stimulation of ovulation by impacting the hormones. Clomiphene or clomiphene citrate is an oral medication that increases the level of hormones in the blood that induce the maturation of eggs in the ovaries. The maximum number of times that this type of stimulation is used is six menstrual cycles (Medications for inducing ovulation: A guide for patients, 2014). Letrozole, an oral pill, decreases the amount of estrogen. This medication stimulates ovaries to release eggs. Bromocriptine and cabergoline are pills taken orally to treat abnormally high levels of the hormone prolactin, which can interfere with ovulation. Gonadotropins such as follicle-stimulating hormone (FSH) are hormones that are injected in a woman to directly stimulate eggs to grow in the ovaries, leading to ovulation (Diamond PM, et al., 2015)

1.4. Success rates of ART

Success rates of ART treatments depend on many factors. One of the general factors is the age of the woman that also influences the success of treatments. The chances of having a

baby decrease rapidly every year after the age of 30 (Dunson DB, Colombo B, & Baird DD, 2002). For example, the success rate is 37% in women younger than 35 years of age, it decreases to 30% in women aged 35 to 37 years and 20% in women aged 38 to 40 years. It is estimated that women older than 44 years of age have 1% chance to achieve pregnancy after ART procedures (2016 Assisted Reproductive Technology, 2018).

1.5. The public funding of ART

Although the fertility/infertility has remained as an important health care issue, it is regularly questioned how the distribution of national health budgets would be fair and/or equal. The pressure of the limited budget is an important reason why policy makers limit access to fertility treatments. The different eligibility criteria are mainly determined by women's age, marital status, having children already, type of service provider (public or private clinic) and number of treatment cycles or embryo transplantations allowed (Mladovsky P, & Sorenson C, 2010). The most common age limit is 40 years for the female partner (The funding of IVF treatment, 2017). Krol M, Nap A, Michels R, Veraart C, & Goossens L (2019) performed the study in health care resources utilization for infertility in the Netherlands. In the Netherlands, the couple can get a maximum of three IVF procedures reimbursed through the basic benefit package of the mandatory health insurance. The result of the analysis indicated that the majority of the general population is in favor of the current law and only over a quarter of the population suggested that the fertility treatments should be reimbursed without limits (IVF en cry embryo's (uitleg regelgeving), 2015). The statistical summary on the financing of ART treatments in (Ory S J, et al., 2014) study indicated that most of the countries in Europe provide coverage via national health budget, some with the complete plan and some with a partial plan.

2. Situation in Estonia

2.1. Estonian statistics

Estonia has a small population, 1 324 820 citizens (Jan 2019), with the low fertility rate around 1.67 children per woman (2018) (Tammur, 2019). The population of Estonia is ageing. According to Estonian Women's Health Questionnaire Survey, 15.8% of women in the age range from 18 to 44 years of age had experienced infertility (Lippus H, et al., 2015). In September

1994, the first IVF laboratory was established at Tartu University Women´s Clinic. The first IVF child was born in Estonia in 1995. It was also the first IVF-baby in the Baltic countries (Sõritsa A, 2018).

According to Estonian Women's Health Questionnaire Survey in 2018 13.4% of women with infertility had applied IVF technique to have a child (Lippus H, et al., 2015). The demand on using the infertility treatment is increasing (Health data , 2018).

2.2. The law for ART

In Estonia, applying for ART is legal for unmarried couples and single women. They need to sign a consent form for being parents. The costs of treatments are funded from the EHIF budget for patients up to 35 (2004), now to 40 years of age (2018) who are insured under the Health Insurance Act (Artificial Insemination and Embryo Protection Act, 2013).

Regarding the Artificial Insemination and Embryo Protection Act, women with active legal capacity up to 50-year-old are permitted to undergo artificial insemination. Up to three embryos per cycle can be transferred. Women aged 41–50 years must pay for the IVF treatment themselves (Artificial Insemination and Embryo Protection Act, 2013)

Until 2017 all ART related medications were reimbursed 50% by EHIF, since 2018 all ART related medications are also reimbursed 100% for eligible patients (Kunstliku viljastamisega seotud ravimite hüvitamine).

2.3. The centers for the ART treatment

There are six medical facilities which provide ART services, including 3 public clinics and 3 private clinics. EHIF has a contract and is covering the ART services according to pre-planned budgets in five clinics (Artificial insemination and filiation, 2018).

Three centers in Tallinn with 2 belong to Tallinn city and 1 private clinic:

- East-Tallinn Central Hospital Center for Infertility Treatment (Ida-Tallinna Keskhaigla Naistekliinik) (city-owned clinic)
- West-Tallinn Central Hospital Women's Clinic (Lääne-Tallinna Keskhaigla Naistekliiniku reproduktiivmeditsiini keskus) (city owned clinic)

- AS Nova Vita Clinic (the private clinic)

Two centers in Tartu with one belong to state foundation and one private clinic:

- University of Tartu Women's Clinic (Tartu Ülikooli kliinikumi naistekliinik) (state fund owned clinic)
- Elite Private Clinic (Elite Erakliinik) (private clinic)

2.4. EHIF

In Estonia, health insurance is solidarity-based and administrated by EHIF. Founded in 2001, the EHIF is made up from pooled funds transferred from the Estonian Tax and Customs Board, that covers the cost of health care services. The insured persons joining the national compulsory health insurance system, constitute 95% of the Estonian population and 100% of retired persons. EHIF covers partially or completely all healthcare services in Estonia including emergency care, primary health care, specialized healthcare. EHIF also covers the costs related to medicine according to pre-agreed list of services (Estonian health care system).

Since 2004, the EHIF has maintained a complete electronic health record of healthcare services. It contains personal information of patients, date of services, diagnoses, treatment type and the date of death (Jürisson M, Raag M, & Kallikorm R, 2017).

EHIF is one of the main stakeholders also covering costs for medications. EHIF has open commitment for prescription medications. The reimbursement of medications has different levels: 0%, 50%, 75% and 100% of reimbursement to ensure the accessibility of medicinal products (Ferrario, Reinap, Pederse, & Kanavos , 2016). EHIF is also responsible for the reimbursement of pharmaceuticals in the hospital setting but these budgets are pre-planned and negotiated with health care providers (Mägi K, Lepaste M, & Szkultecka-Dębek M, 2018).

2.5. The medications of ART treatment

From 2004 to 2017 patients had 50% reimbursement in ART medications. Since 2018, the women up to 40 years old (included) get 100% reimbursement at the pharmacy immediately when dispensing the medication with prescription with the exeption of clomifence. (Kunstliku viljastamisega seotud ravimite hüvitamine).

2.6. The previous study related to cost of ART

The analysis of ART has been done in 2014 covering data from 2005 to 2011. According to this analysis 4445 women had received these procedures and the number of procedures both for IVF and embryo transplantation had tripled. They also demonstrated that both IVF and embryo transplantation costs were 8 790 951 EUR and the costs of medications covered directly by EHIF were 558 213 EUR, additional compensation cost 5 993 668 EUR. So, total direct costs for ART procedures and medication was 15 342832 EUR for this seven-year period (Tonsiver T, et al., 2014)).

3. The importance of study

There are probably over 10 thousand married couples in Estonia, who are unable to achieve pregnancy (Infertility treatment, n.d.). According to the National Institute for Health Development, there is an increase in the demand for infertility treatment (Health data , 2018). The patients and infertility treatments over the years are changing and therefore close follow-up and annual analysis is important to be aware of the changing scene in the ART.

Also, the costs for services related to ART are high causing a lot of challenges in ensuring the optimal benefits from ART treatments. In Estonia, overall trend is towards increased access to services, but this approach also needs careful cost surveillance and analysis.

4. The aim of the study

The aim of this study is to describe and explore the trends of ART services in Estonia from 2004 to 2018. This period was chosen as a period where data collection methods and quality are comparable. Also, the aim of the study was to evaluate only the costs covered by EHIF and to leave out the services not covered by EHIF.

The objectives include:

1. Determine the change in number of services used during the study period
2. Determine the total reimbursement paid by EHIF
3. Determine the difference in infertility treatments in age groups
4. Determine the differences providing ART services among centers in Estonia

5. Determine the number of treatments per patient and the cost per patient
6. Describe the difference in drug usage

II. Research methodology

1. Research objective

The purpose of this study is to explore the trends of ART services in the term of the utilization and the cost in Estonia during 2004 and 2018 for EHIF.

The total annual budget of ART treatments is determined with estimation of costs per procedure, including costs for medications. Also, analysis of cost per person is analyzed. Additionally, the changes in the number of ART treatments provided and the procedures performed and repeated is analyzed. In addition, the cost of medications is analyzed.

The current study seeks to answer the following questions:

1. How is the trend of ART services in Estonia during the study period?
2. How much reimbursement is paid by EHIF?
3. How are the differences cost among centers in Estonia?
4. How many treatments annually per patient and how much cost for each patient?
5. Which is the most common age group in Estonia
6. Which medications are used/reimbursed for ART services?

The hypothesis:

1. The cost/reimbursement by EHIF for infertility treatment has increased during the study period.
2. The higher cost may be attributed to higher number of provided services and increased cost per service.
3. The EHIF compensation for services is distributed unequally among the centers.
4. The cost per patient increases with patients´ age.
5. The higher costs are related to changes in reimbursement rules

2. Research method and databases

2.1. Research method

This thesis performed a descriptive study to provide a full picture of ART services provided and reimbursed by EHIF. The financial and medical records of EHIF in ART services have been collected since 2004, therefore, the analysis is provided for the period from 2004 to 2018.

The study population are the insured women in the range from 20 to 40 (42) years old who have received ART between 2004 and 2018 in Estonia. The study only focused on the direct medical costs during treatment.

2.2. Database

EHIF database collect the treatment invoices that are submitted by healthcare providers. Those invoices are used to identify the number of treatment bills as well the cost paid by EHIF (Rüütel K , Lemsalu L, & Lätt S, 2018). The electronic invoicing system used ensures that all invoices contain appropriate patient information, diagnoses and other relevant information related to the services provided. The national health care database has been collecting data on a single population for long, extended period using generally similar methodology.

The EHIF reimbursement database has recorded detailed information of the ART procedures. EHIF database provided the information since 2004 two complex services codes: 2208K (IVF) and 2281K (embryo transplantation), including the use of medical services over the years and the use of medical services in different age groups and centers.

. Not all collected health care data in general at the EHIF database is the same quality. However, data concerning ART services are provided by very few competence centers under permanent and regular data monitoring from EHIF specialists and other Estonian ART specialists (Dr Veerus, personal communication) and therefore is considered to be high quality data.

The medications with ATC codes: G03GB02, G03GA05, G03GA07, G03GB08 (table 1) are prescribed for ART procedures (Health care service – Eesti haigekassa). Also, medications

that are reimbursed for ART treatments are described and analyzed. Statistical analysis was done using MS Excel program. Results are presented as average annual change over period. The calculation ratio of a number of treatments and patients is performed.

ATC code	Active substances	Medicine brand names
G03GB02	Clomifence	Serophene
		Clostilbegy
		Clomiphene citrate
G03GA05	Follitropin Alfa	Gonal F
		Ovaleap
		Bemfola
G03GA07	Lutropin alfa	Luveris
G03GA08	Choriogonadotropin Alfa	Ovitrelle

Table 1: List of medications used in ART treatment

III. Results

1. The change of infertility treatment bills in the period 2004-2018

Since 2004 two different codes (unchanged until 2018) have been used: 2281K for IVF and 2208K for embryo transplantation.

During the period 2004 – 2018, 28780 treatment bills with 44 348 procedures (coded either as 2208K (IVF) or 2281K (embryo transplantation)) were collected. There are total 17966 patients received treatment, in which half of them are repeated the treatment in following years.

The change in infertility treatment services in 15 years is presented in Figure 1. The number of treatment bills have increased. In the first 5 years, there is a sharp rise in both the number of treatment bills (procedures) and patients. After the plunge in 2009, the number of treatment bills continued to increase while number of patients has started to remain constant per year. In average, every patient produced 1.6 treatment bills with 2.6 procedures per year.

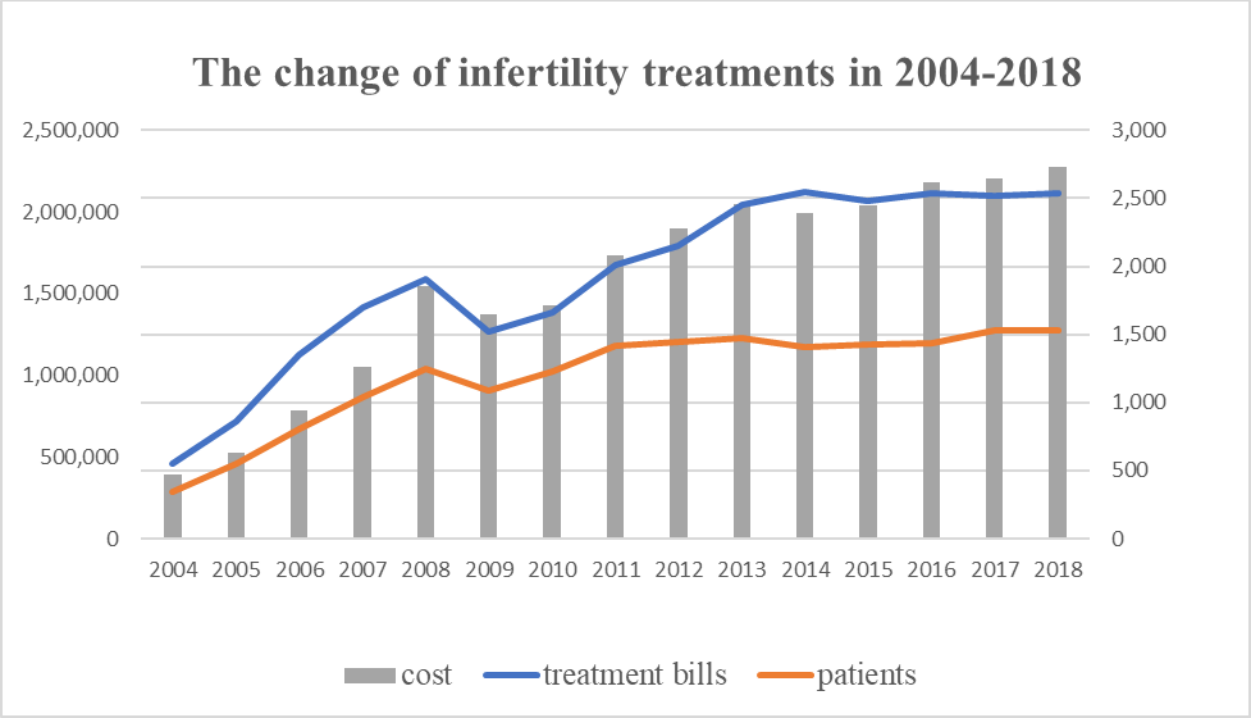

Figure 1: The change of infertility treatments in 2004-2018

During the studied period 24 370 embryo transplantation and 19 655 IVF procedures were performed. The division of ART treatments between IVF and embryo transplantation is presented in the figure 2

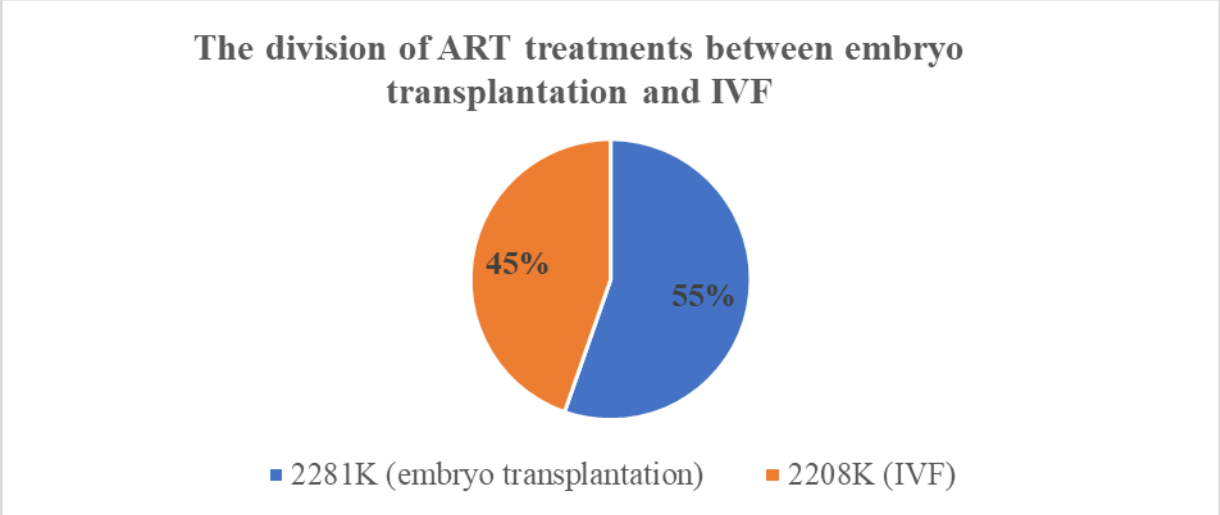

Figure 2: The division of ART treatments between IVF and embryo transplantation

The change in procedures for IVF and embryo transplantation has been increasing mirroring the trend of treatment bills. The number of IVF procedures per patient has been very stable but the number of embryo transplantations per patient has increased slightly (figure 3).

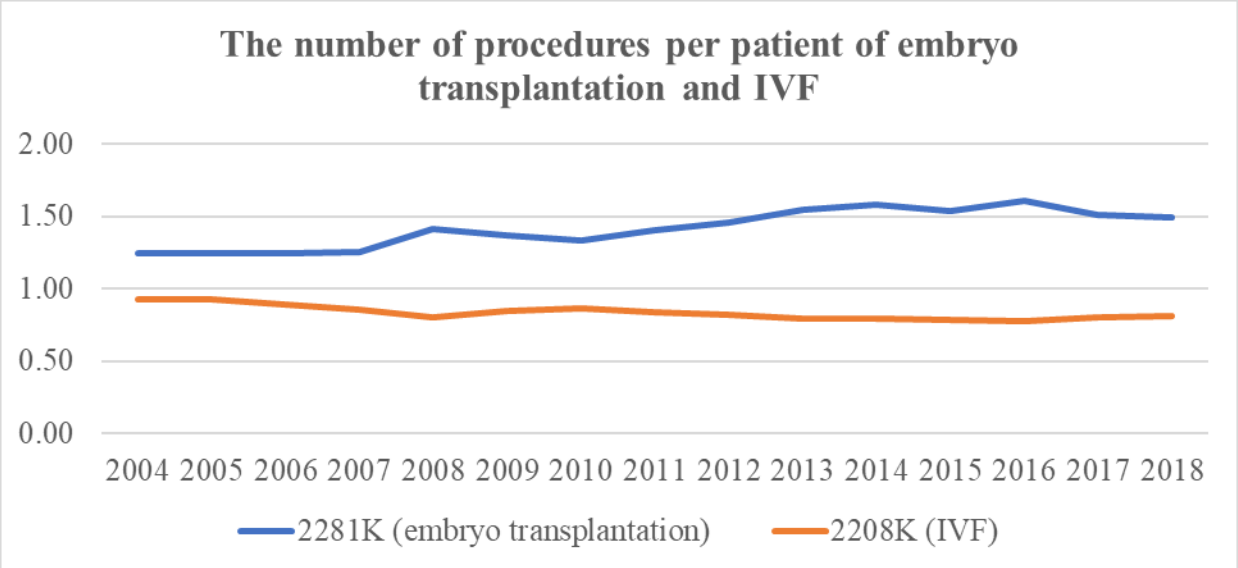

Figure 3: The number of procedures per patient of IVF and embryo transplantation.

2. Cost of treatments

Along with the increase of number of treatment bills, the cost for treatment also increased by year (figure 1). The total cost for EHIF in 15 years of the study period is 23 467256.30 €. The cost of treatment per patient is 1300 €. In addition, the cost per treatment bills has increased from 715.23 € (2004) to 897.22 € (2018).

During the studied period, 12757755 € and 10709501 € was paid for embryo transplantation and IVF procedure. The division of ART treatments between IVF and embryo transplantation is presented in the figure 4.

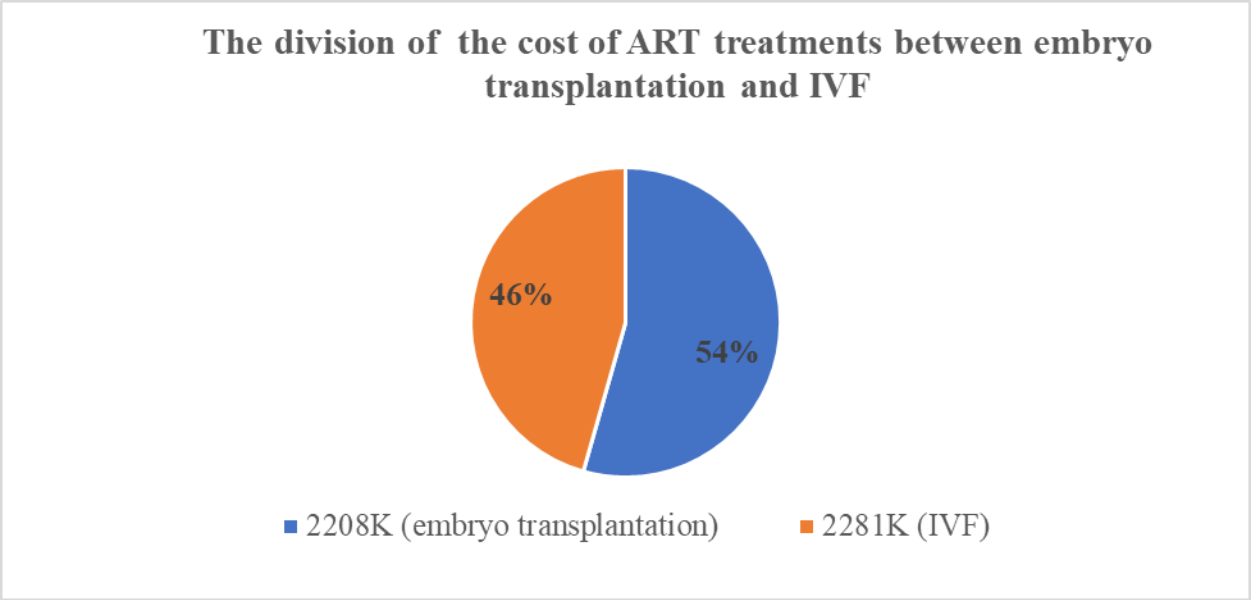

Figure 4: The cost for ART treatment including embryo transplantation and IVF.

The cost for both IVF and embryo transplantation has been increasing mirroring the trend of the cost. The cost of embryo transplantations and IVF procedures per patient has increased significantly (Figure 5). The cost of IVF procedures per patient has increased 40.64 % while the cost of embryo transplantations per patient has increased only 14% since 2004.

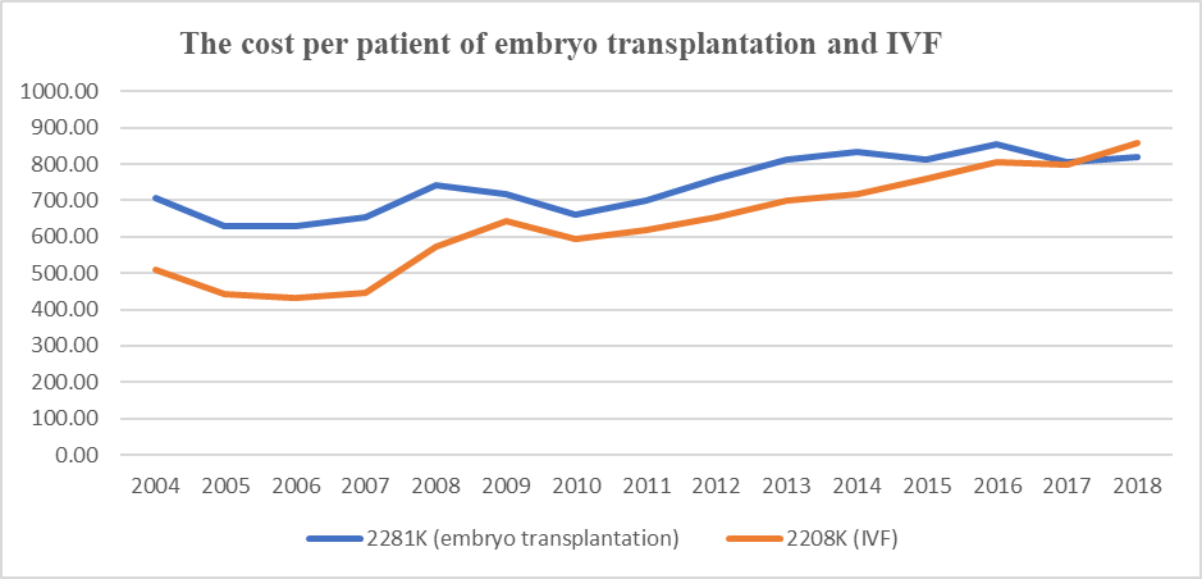

Figure 5: The cost per patient of embryo transplantation and IVF

The increase of costs for embryo transplantation is 12% and one procedure for IVF is 28% during the study period since 2004. One procedure of IVF costs 686,96 € in 2018. There has been no change since 2008- 2018 in the cost for embryo transplantation. One procedure of embryo transplantation costs 525.42 €. Also, (figure 5).

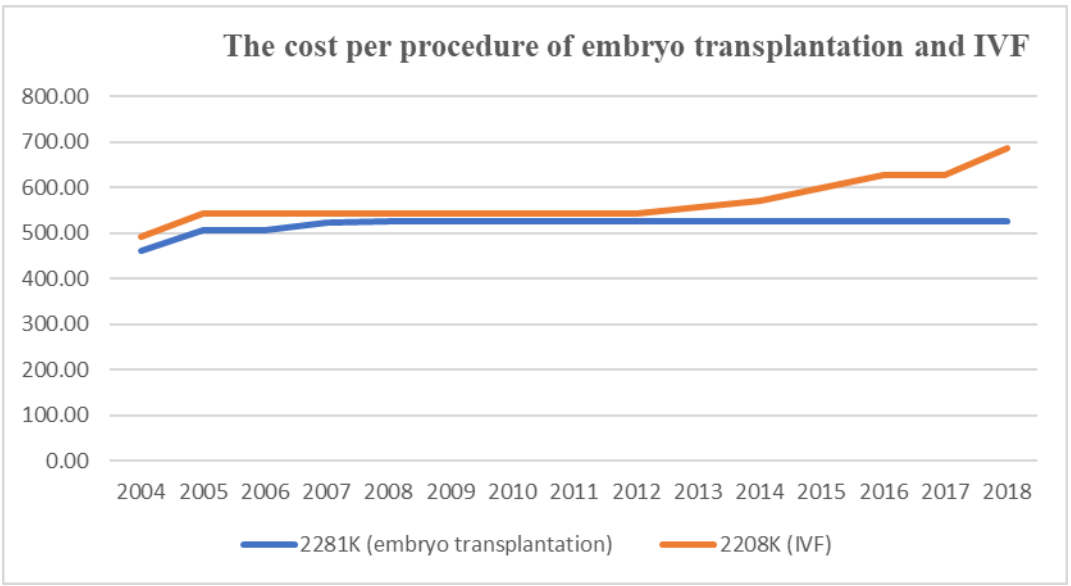

Figure 6: The cost per procedure of embryo transplantation and IVF

3. The differences in usage of infertility treatment in age groups

The infertility patients are divided into 5 age groups: 20-24, 25-29, 30-34, 35-39, 40-42. The age group of 30-34 presents the highest number of treatment bills/procedures (10024 bills) and also the number of patients (4034 patients) is the highest. The second place for treatment numbers is the age group of 35-39 with 9941 bills and 3795 patients. Each patient in the age group of 35-39 performed more than 4 procedures (table 2).

Age groups	20-24	25-29	30-34	35-39	40-44
Treatment bills	568	5272	10042	9941	2706
Procedures	845	8004	15413	15441	4307.51
Patients	297	2261	4034	3795	1412
Bills per patient	1.91	2.33	2.49	2.62	1.92
Procedures per patient	2.85	3.54	3.82	4.07	3.05

Table 2: The use of infertility service in age groups

During the study period, the use of services has increased in all 6 age groups. The change in the first haft period comparing to the latter half is illustrated in figure 2. According to it, the number of treatment bills in the age group 35-34, 3530-34, 35-39, and 40-44 had remarkedly increased 1 578, 2 365 and 1 180 respectively compared to the first haft period. The age group of 35-39 had the biggest change among six age groups (figure 7).

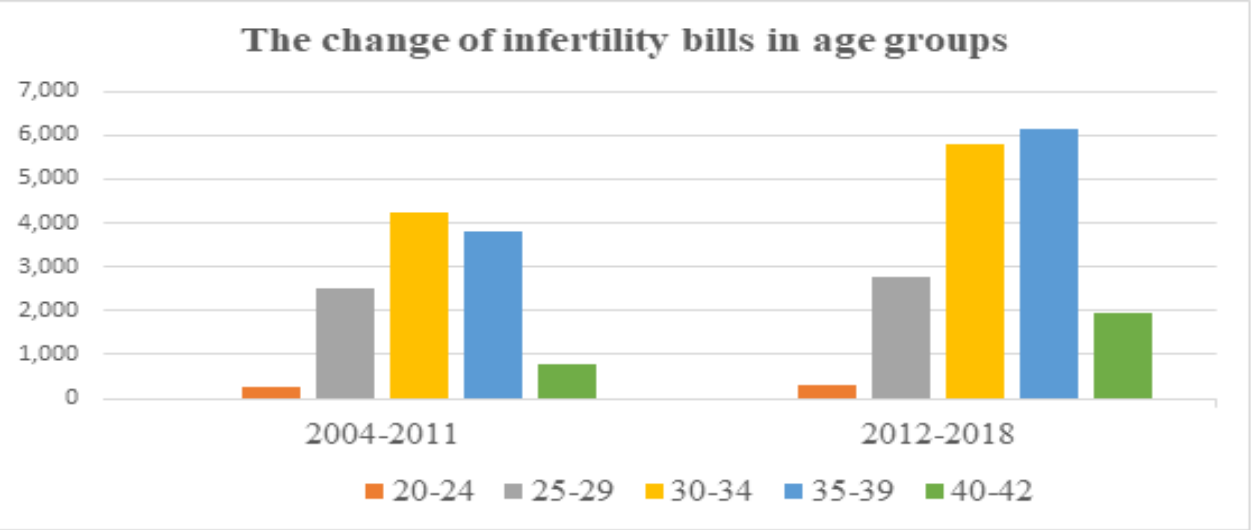

Figure 7: The change of ART treatment bills in different patient in age groups during 2004-2011 and 2012-2018

The number of treatments increases from the age of 25 to 39 and decreases after the 40. With a higher age, the higher number of treatments is performed. In particular, the number of patients in the age of 40 are 1 325 that obtained 2400 treatment bills (figure 8). The ratio of treatment per patient is highest at 1.83 annually.

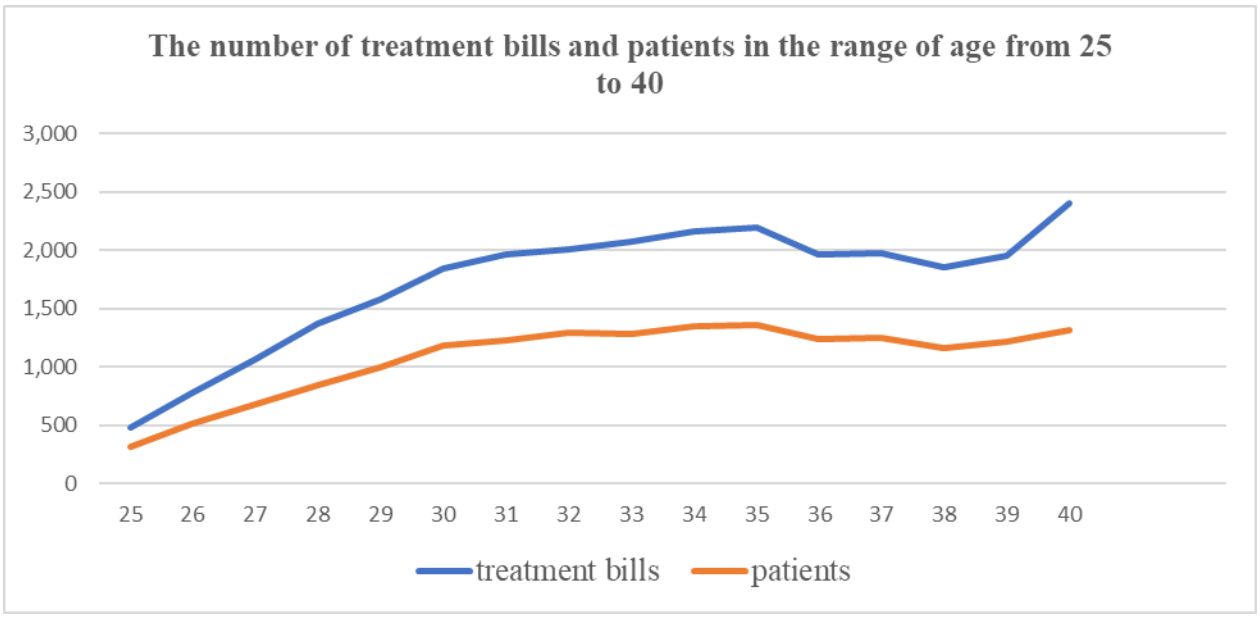

Figure 8: The number of treatment bills and patients in the range of age from 25 to 40.

4. The comparison among centers

East-Tallinn Central Hospital Center for Infertility Treatment provides 33% of total treatments during the study period. Following respectively is University of Tartu Women's Clinic (24%), AS Nova Vita Clinic (19%), Elite Private Clinic (12%) and West Tallinn Central Hospital Women's Clinic (10%) (figure 8).

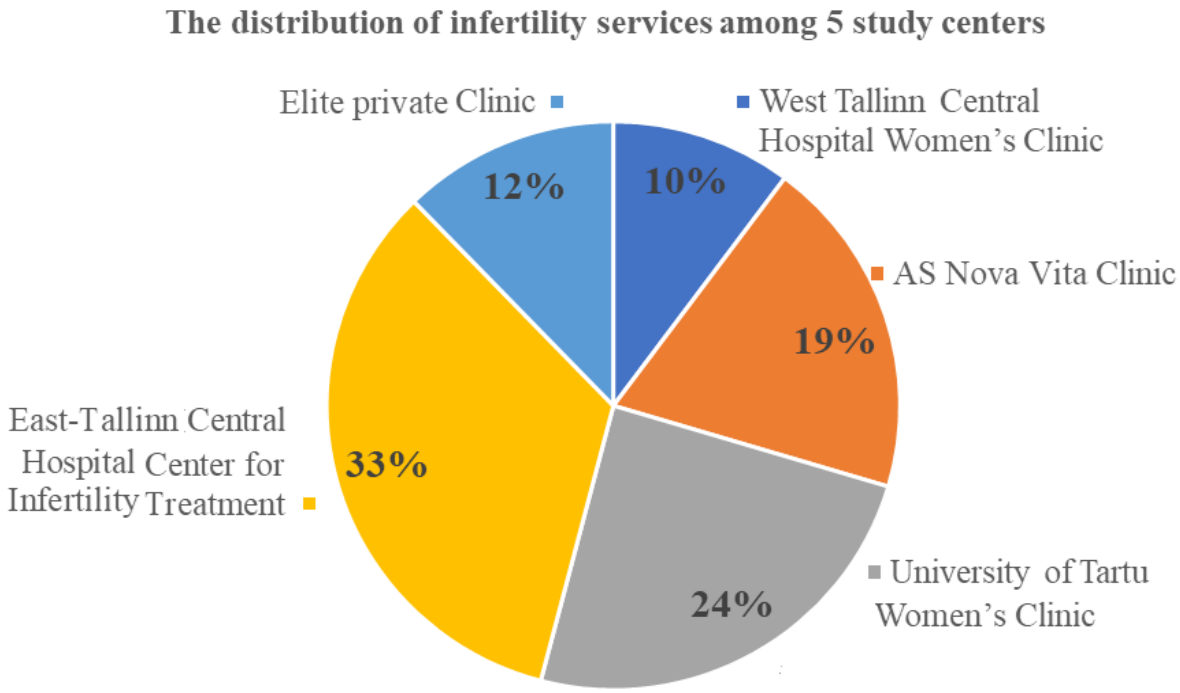

Figure 9: The distribution of infertility services among 5 study centres

In the area of Tallinn, East-Tallinn Central Hospital Center for Infertility Treatment had the highest number of treatments, 9530 treatment bills in 15 years for total of 3500 patients. In the area of Tartu, University of Tartu Women's Clinic has highest number of 6936 treatment bills for 2354 patients.

	Treatment bills	Patients	Treatments/patient
West Tallinn Central Hospital Women's Clinic	2968	1013	2.93
AS Nova Vita clinic	5551	2093	2.65
University of Tartu women's clinic	6936	2354	2.95
East-Tallinn Central Hospital Center for	9530	3500	2.72
Elite private clinic	3556	1546	2.3

Table 3: The statistic of 5 studied infertility centers in Estonia

The number of per patient is presented in the table 3. It indicated that the number of treatment bills per patient is highest in University of Tartu Women's Clinic and West Tallinn Central Hospital Women's Clinic. It is nearly 3 treatment bills for a patient. These centers have higher percentage of patients who belong to the higher age group of 33-39 and 40-42 (figure 9).

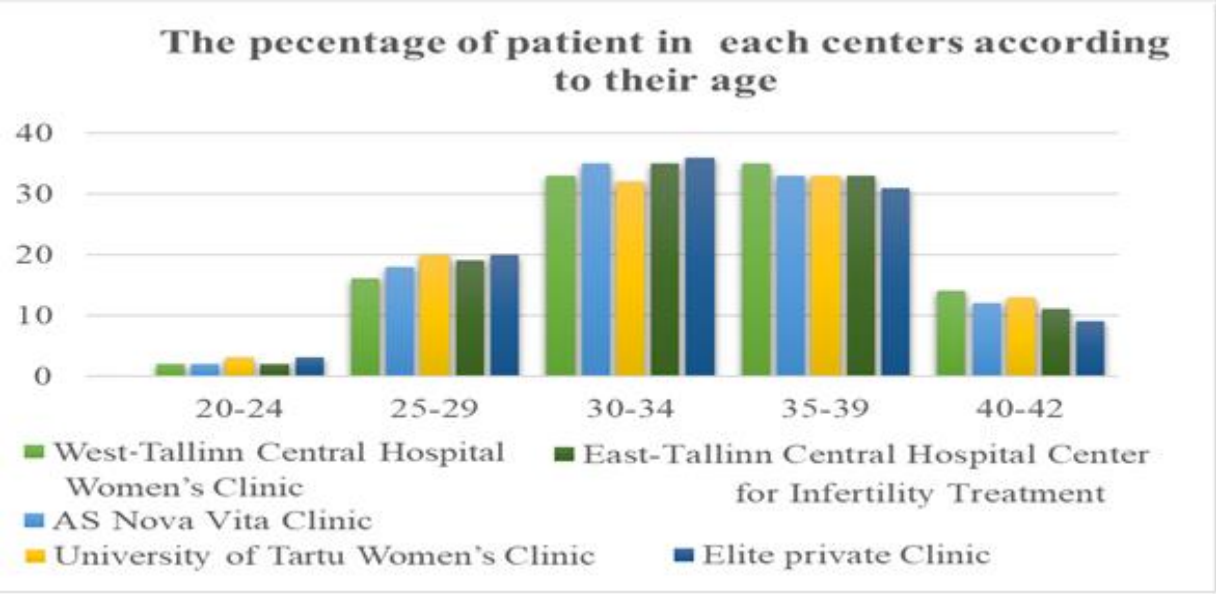

Figure 10. The percentage of the patient in each centre according to their age.

5. The analysis of medication usage

The common medication used for ART in Estonia belongs to 4 groups: Clomifence (G03GB02), Follitropin Alfa (G03GB05), Lutropin Alfa (G03GB07), Choriogonadotropin Alfa (G03GB08) (table 1).

The highest number of patients have prescriptions for Choriogonadotropin Alfa (G03GB08) with 7569 patients but the highest number of prescriptions is for Follitropin Alfa (G03GB05) with 38896 prescriptions for 7068 patients (figure 8). The statistic presented the highest use of Follitropin Alfa (G03GB05) for one patient, which is 5.5 prescriptions. The use of Lutropin Alfa (G03GB07), Choriogonadotropin Alfa (G03GB08) and Clomifence (G03GB02) for one patient is 4, 2.9 and 1.7 prescriptions respectively. Clomifence is not reimbursed by EHIF but the pharmacy price is only 12.77 EUR for 24 tablets.

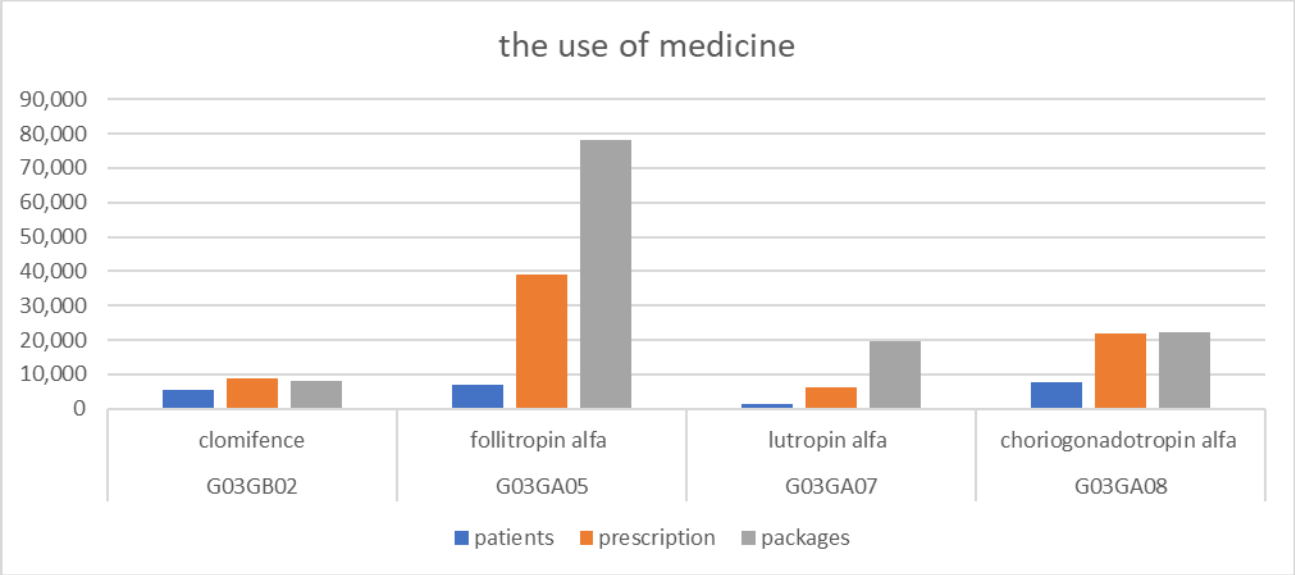

Figure 11: The use of medications for ART procedures

Contributing in high use of Follitropin Alfa (G03GB05), 80% prescriptions is Gonal-F, 19% prescriptions is Bemfola and only 1% is Overlap. The use and the cost for Gonal-F is highest not only in the Follitropin Alfa but also among the ART medicines. The cost of Follitropin Alfa (G03GB05) is also expensive. Its price is in the range from 27 € to 277 € per prescription (2018)

Since 2018, patients have 100% reimbursement. There are a lot of change in 2018 comapred to 2017 (table 4) .

		Total cost of the prescription	Paid By EHIF	Total cost of the prescription	Paid by EHIF
ATC code	**Active substances**	**2017**	**2017**	**2018**	**2018**
G03GA05	Follitropin Alfa	907460.35	421185.48	894799.81	883025.25
G03GA07	Lutropin alfa	134924.41	65687.95	120769.05	118706.55
G03GA08	Choriogonadotropin Alfa	42426.04	15152.43	30054.19	24884.19
Total ART medications		1,084,810.8	502025.86		1026615.99
Other diagnosis related medications				457166.39	448231.88
Total diagnosis related medications				1505453.54	1476733.47

Table 4: The change in ART medication costs** after establishing reimbursement rate of 100%

** unit cost: Euro (€)

In 2018, the total cost of prescription of studied medications is 1500109.43 € (including Clomifence) while the cost in 2017 is 1129540.0 €. The total cost that needs to pay for

prescription in 2018 is higher than 25% in 2017. In the other hand, reimbursement from EHIF in 2018 increased 66% compared to 2017.

6. The total cost for ART in 2018

In 2018, the total cost for ART procedures is 2 273 652.7 € and the total cost for ART medications is 1 026 615.99 €. Thus, EHIF paid for ART treatments is 3 300 268.69 € with 69% contributing to total costs by medications.

In 2018, the healthcare budget from EHIF is € 1.28 billion. ART contained 0.26% of the total budget from EHIF.

IV. Discussion

Infertility has been recognized as a considerable global public health and policy issue which is experienced by approximately one-quarter of all couples (Mascarenhas M, Flaxman S, Boerma T., & Vanderpoel S, 2012). In the current situation European countries have experienced the long-term low birth rate, resulting in ageing of the populations (Population structure and ageing, 2018). ART has become a successful treatment, providing the highest chance of success for infertile couples. So, not surprisingly, Europe has a considerable number of infertility treatment cases (Ch De Geyter, et al., 2018). Therefore, developing ART not only relieve the suffering of individuals with the problem but also a potential solution for raising birth rates in Europe (Präg P, & Mills MC, 2017). The 18th annual report of ART in Europe presented that not only the numbers of reporting clinics have increased but also the overall number of reported treatments (Ch De Geyter, et al., 2018). This thesis analyzed EHIF data on infertility treatments from years 2004 to 2018. The aim of the study is to describe the use and cost of ART services in Estonia.

Our analysis demonstrates that the utilization of ART is growing. The total of treatment bills increased from 549 in 2004 to 2537 in 2018. The number of embryo transplantation and IVF procedures increase from 407 and 340 in 2004 to 2139 and 1674 in 2018. The most interesting finding was that the number of treatment bills continues to increase although the number of patients has become stable since 2010. The number of patients fluctuated narrowly

around 1450 in recent years. The statistics also indicate that during last years each patient needed more than one treatment for the successful pregnancy. There is definitely an increase in the number of treatment bills per patient by year.

In spite of the high demand for ART, the remaining high-cost of the treatments cause the significant barriers to achieve benefits from this technology. The study conducted by Teoh P & Maheshwari A (2014) analyzed the high cost of ART treatments. The statistical evidence from this study indicated that the difference in the provision of ART treatments via public funding is often limited for each person due to the cost involved. The proportion of ART used is more dominant in the countries where these treatments are provided free of charge for patients and by easy accessibility at public clinics (Kocourkova J , Burcin B, & Kucera T, 2014). For instance, Denmark and Belgium demonstrate stable increase in the rate of ART use due to the positive impact of reimbursement policy (Andersen, 2008). Chambers GM, et al., (2014) also conclude that greater affordability of ART is associated with greater ART utilization.

Our analysis also confirms that each treatment bill has become more and more expensive. The cost per treatment bills has increased from 715.23€ (2004) to 897.22 € (2018). Consequently, reimbursement paid from EHIF has increased significantly which is putting the pressure on the national healthcare budget in Estonia. The reimbursement was 392660.17 € in 2004 whereas, it reached 2273652.7€ in 2018. The total cost for the whole studied period was 23 467256.30 €. The high cost is a known barrier to ART procedures. The total cost for embryo transplantation procedure is 12757755 € and for IVF procedures was 10709501 €. The number of patient and procedure of embryo transplantation is always higher than IVF, however the cost to perform an IVF is much more expensive than embryo transplantation. It has been increasing significantly by year. The high of cost mainly due to the complex process is performed in IVF such as investigations, use of medications and laboratorial equipment (Teoh P & Maheshwari A, 2014). In Estonia, the cost of one procedure of embryo transplantation is 525.42 € (2018). It has been no change for 10 years. In the other hand, the cost of one procedure of IVF in 2018 is 686.96 €. There is the growth of the IVF cost, from 492.89 € (2004) to 686.96 € (2018).

The main effort of Estonia health care organizations is to provide high quality, accessible, and affordable health services (Thomson S, Habicht T, Rooväli L, Evetovits T., & Habicht J,

2011). On the other hand, with the high-cost treatments, the regulation in health insurance coverage directly influences the ability to access the treatment services and positive trends in Estonia demonstrate good accessibility to ART treatments in Estonia. The distribution of treatments bill among centers is a significantly different. Most patients prefer to choose the state clinics, especially the East-Tallinn Central Hospital Center for Infertility Treatment and University of Tartu women's clinic. They provide 33% and 24% of total treatments respectively. The analysis why the procedures are divided so unequally between specialist centers was out of the scope of the thesis.

One of the factors influencing the need for ART is the childbearing age of women. The phenomenon of delayed childbearing is still remarkedly common among European countries, including Estonia. The average age for childbirth is around 30 years of age (Population structure and ageing, 2018). Mirroring the statistical data, we were able to demonstrate that the increase for ART treatments starts to increase after 30 years of age and stabilizes at the age of 36.

On the other hand, the age group from 35-39 also needed the highest number of procedures per patient. That group contained the second highest number of treatments and patients. Also, the higher the age of women the higher is the number of treatment procedures.

The analysis of the data shows that University of Tartu Women's Clinic and West Tallinn Central Hospital Women's Clinic have the highest percentage of patients in the group of 33-39 and 40-42, resulting in the highest of the number of treatment bills per patient (table 3.) It indicates that one of the factors leading to the need of multiple procedures is the age of woman.

In other words, the women of 40 need to perform more treatment cycles than the younger. There is confirming the previous studies demonstrating the relationship between the number of treatments and the age of women. All the reviewed papers support the higher maternal age often taken as synonymous with a lower chance of success and higher cost (Ch De Geyter, et al., 2018). This contributes to the reasons for the increased use of ART and the cost of having a child among other known factors like genetic factors, maternal general health and problems of infertility (Tarín JJ, García-Pérez MA, Hamatani T, & Cano A, 2015). Although the state support for ART if needed, likely is an efficient option still to parent a child, it may raise the false

perception that childbearing could be postponed until later in life and still may be successful. Kocourkova J , Burcin B, & Kucera T (2014) suggested that ART reimbursement policy should put the effort in promoting socially acceptable early childbearing as an option to enhance that negative situation.

In order increase the chances of achieving a pregnancy is related to the number of oocytes available for ART (Hughes EG, et al., 1992). Therefore, there are a number of medications (table 1) used as the hormonal stimulation to super ovulate the ovaries in order to produce higher numerous of eggs (IVF Protocols, n.d.). In current study, among main ART medications in Estonia (table 4), the use and the cost of Follitropin Alfa is the highest. Follitropin Alfa is a recombinant human follicle stimulating hormone (rFSH). Two common medications of rFSH are used Gonal-F – one and Bemfola. Wolzt M, et al., 2016 analyzed these two medications and concluded that Bemfola and Gonal-F are equal from the point of view of efficacy and safety. Our study indicates that Bemfola is prescribed less frequently than Gonal-F. The high cost of ART is usually associated not only for cost of procedures but also with medication cost for controlled ovarian stimulation (Lorente M.R, Hernández J, & Antoñanzas F, 2013). So, partly the high costs of treatments are due to expensive medications and are additional barrier to high-quality biological medicines (Schellekens H, et al., 2011). The difference in Estonian prescribing practices may be influenced by the higher cost of Bemfola resulting in significantly reduced number of prescriptions compared to Gonal-F.

Up to 2017 all women had to pay 50% for medications used for ART. Since 2018 the new reimbursement rules are in practice. Since 2018 also the medications used for ART are reimbursed with 100% rate. The aim is to decrease the proportion that is paid out of pocket of the patients. This on one hand decreased the influence of the socioeconomic status to access the quality of medicine and treatment but increased the costs for ART in Estonia.

So, the overall costs including ART procedures and 100% reimbursed medications increased to 3300268.69 € in 2018. EHIF paid 0.26% of total health budget for ART.

The strength of this study is that using the registered - database from EHIF. This database contains all the data related to reimbursement system in Estonia. After doing review on previous

studies and qualitative input from professionals (dr. Veerus), this database ensures the quality for ART treatment analysis (Appendix).

The thesis contains certain limitations. Firstly, the code 2208K presented all type of ART including IVF, ICSI. Currently, there is no comparison between the number of IVF and ICSI. According to the 18th annual report of ART in Europe, although clinical pregnancy rates per aspiration were similar in both IVF and ICSI, the prevalence of ICSI has become superior to IVF (Ch De Geyter, et al., 2018). Moreover, the cost per procedure of ICSI is higher than IVF (Bouwmans C, et al., 2008). It could cause the increase of high cost in recent years. Secondly, around 5% of the population is not under the cover of EHIF, thereby, is not included in the calculation. Also, the age group of 40+ is by definition incomplete as EHIF is not covering procedures for women over 40. According to the National Institute for health Development, the infertility treatments in general have increased most in the age group of 41 and older (Health data , 2018).

Conclusions

The purpose of the current study was to describe and explore the trends of ART services in Estonia from 2004 to 2018 by using the financial and medical records of EHIF. The main findings of this master's thesis are:

- Although while the number of patients has become stable recently, the utilization and the reimbursement of ART has increased annually; the total cost for treatment bills is 23 467256.30 €. €.
- Each patient has performed more than 2 procedures. The cost for each treatment bill has increased.
- The most common age group in ART treatments is 30-34. The number of procedures per patient increases with the age of women, leading the increase in the cost per patient.
- East-Tallinn Central Hospital Center for Infertility Treatment had highest number of treatments with 33% of the total treatments
- Follitropin Alfa is used most in ART medicine. After the new rules, comparing to 2017, the medication reimbursement increased 66% in 2018
- The general cost for ART has increased from 2004 to 2017, in 2018 with adding the costs for ART medications the annual cost was 3300268.69 €

There is only one study in the cost of ART services in Estonia covering 2005 to 2011. The findings of this study can provide the full and latest information in ART and EHIF budget. It can be the prevalent evidence for the further study in effectiveness of budget distribution. The number of procedures of ART is continuing to increase. Thereby, it is needed to assess the economic impact of the available treatments and find effective ways of minimizing the cost (Audibert C & Glass D, 2015).

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Appendix

The literature review in checking the quality of EHIF database

The literature review from the PubMed database with free full text in latest 10 years. There is 9 research papers using the EHIF as the secondary data.

Name	year
Use of evidence-based pharmacotherapy after myocardial infarction in Estonia	2010
Sex-specific outcomes of diabetic patients with acute myocardial infarction who have undergone percutaneous coronary intervention: a register linkage study.	2012
The effect of continuous monitoring of hypertension and type 2 diabetes mellitus on the number of visits to medical specialists and hospitalization: a retrospective study	2013
Antibiotic prescription preferences in paediatric outpatient setting in Estonia and Sweden	2013
Non-cancer morbidity among Estonian Chernobyl cleanup workers: a register-based cohort study	2014
Potential drug interactions with statins: Estonian register-based study	2015
Pay for performance of Estonian family doctors and impact of different practice- and patient-related characteristics on a good outcome: A quantitative assessment.	2016
Quality of IVF status registration in the Estonian Medical Birth Registry: a national record linkage study	2018
Missed opportunities for HIV testing in people diagnosed with HIV, Estonia, 2014 to 2015.	2019