Assisted reproduction in Greece: Sociodemographic aspects and health behavior analysis

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ABSTRACT

INTRODUCTION The National Organization for HealthCare Services Provision (EOPYY) is the largest Greek insurance company (governmental). Four IVF attempts are reimbursed by EOPYY to women until the 50th year of their age. The aim of this study was to outline the sociodemographic characteristics of infertile patients in Greece and find their association with diagnoses/applied methods in cases of public funded assisted reproduction attempts.

METHODS Data concerned 9648 infertile patients who obtained approval from *In Vitro* Fertilization Committees (IVF Committees) of EOPYY during the period 2013–2015 were collected. Data were not collected directly from patients but from EOPYY's dataset.

RESULTS A total of 10889 IVF cycles were covered during 2013–2015. Mean age of women who underwent IVF was 36.9 years and the most common diagnoses were abnormal semen parameters, male factor and increased sperm adhesion (39.9%) with 11.1% of cases having more than one cause of infertility. The most common method was IVF (86.1%) and 88.6% of women did mostly one to two attempts of IVF whereas the 45.7% of cases were related to female reproductive system problems. Inexplicable infertility was reflected in 11% of cases and 2% of infertile couples used donor sperm. Women were mostly residing in large urban centers (64.7%).

CONCLUSIONS An annual average of 3629 IVF cycles was reimbursed by EOPYY. There was a wide range of infertility causes. Most women were aged 30–39 years and were living in large cities. Couples preferred to use their own sperm/ovaries, did mainly IVF while they were careful regarding the number of attempts.

INTRODUCTION

Nowadays there is a change in lifestyle which translates into a shift in the age of childbearing. Delayed childbearing results in fewer children being born[1] while, at the same time, advanced age affects fertility[2]. Hyperprolactinemia, ovulation disorders, thyroid dysfunction, polycystic ovaries, endometriosis, fallopian tube and uterine abnormalities, infections, autoimmune diseases, neoplasms are causes of infertility[3-7]. Furthermore, alcohol consumption, caffeine, smoking, obesity, and profession, are among the factors that should be taken into consideration[8-10]. In the Western world, infertility results in the increasing use of assisted reproduction methods and their further rapid development[11]. So, infertility has become a social problem with a variety of parameters that need further investigation.

One in six couples worldwide experience some form of infertility problem at least once during their reproductive lifetime[12]. Infertility lasting for at least 12 months is estimated to affect between 8–18% worldwide of women aged 20–39 years[13]. In European countries, infertility affects 14% of the population, which means that about one in seven couples is experiencing difficulties.

In Greece, the assisted reproduction field is rapidly evolving and is characterized by parameters that have not been estimated for the majority of the population[14]. Male infertility was studied during 1992–2008, showing that the male fertility level is declining, the fertility pattern is moving into higher ages, and the reproduction period for men is getting shorter[15]. Another study focused on fertility variations in the recession context showing that fertility rates

in Greece have declined since 2010[16]. No data on infertility of the whole population have been collected up to date and there are no statistical epidemiological data on age, cause of infertility, number of attempts until pregnancy, or even the general profile/background of infertile couples in Greece. The information that can be derived from the largest National Organization for HealthCare Services Provision EOPYY's data concern almost all Greek insured persons. The present study focused on the general background of infertile people in Greece, as it is the first Social Security registry of infertile people of the country.

METHODS

Study design and participants

Epidemiological data for 9648 patients who applied for assisted reproduction techniques to eight IVF Committees of EOPYY during 2013–2015 were collected. Available data were: committee city, social security ID number, approval date, age of spouses, diagnosis, place of residence, reason for rejection, and center where the attempt would take place. For each approved attempt per unique patient (as determined by its social security ID number) all electronic prescriptions that included medicinal products necessary for the attempt were retrieved by the Department of Prescription Monitoring of EOPYY which has prescription data of the country. Data of these prescriptions were linked to the data of the approvals that EOPYY granted in order to outline the profile of the infertile people covered. This was a secondary dataset analysis since data were obtained from the Committees and Department of Prescription Monitoring of EOPYY.

Further data concerning the outcome of the attempts are under the responsibility of the Greek National Authority of Medically Assisted Reproduction (NAMAR), and EOPYY has no access due to restrictions set by local legislation. NAMAR is responsible for all scientific issues concerning assisted reproduction (licensing, collecting outcome data, reporting) and gave its first report in 2018 which concerned the data of 2014 and 2015. Therefore, the social security data of this study are the first (and latest so far) that are available at national level and can be cross-checked with the respective National Authority's data. EOPYY's CEO gave the license for taking and collecting the respective data on 12 March 2013.

Variables

Continuous variables (age, number of cases, number of attempts) are presented as mean and standard deviation, median and range, while nominal variables (residence, method, diagnosis, assisted reproduction center) are presented as frequencies (n) and percentages (%).

Statistical analysis

Relationships between variables were assessed with chi-squared test and analysis of variance. Bonferroni *post hoc* analysis was applied in case of variance analysis. P-values <0.05 were considered as statistically significant. Statistical analysis was performed with the Statistical Package for Social Sciences software (IBM Corp. Released 2012. IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp.).

RESULTS

The sample of the study consisted of 11470 patients. During 2013, 3088 patients applied for an assisted reproduction method approval. During 2014 and 2015 the patients were 3710 and 4672, respectively.

Sociodemographic characteristics and diagnoses of participants

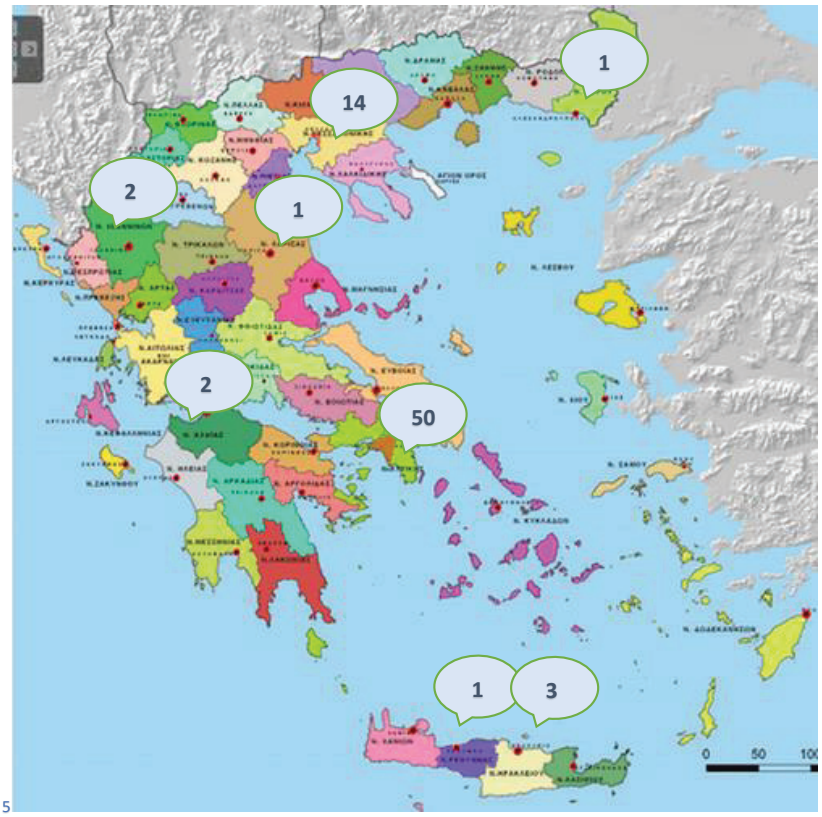
The mean age of women was 36.6 years (SD: 4.8) and the median was 37 years (range: 20–50). The mean age of men was 39.5 years (SD: 5.7) and the median was 39 years (range: 16–74). Women living in five large Greek cities represented

Table 1. Distribution of the prefecture of the IVF center in relation to the prefecture of residence, 2013–2015 (N=11470)

Prefecture of residence		Prefecture of the IVF center			Total
		Attica	Outside Attica/ Thessaloniki	Thessaloniki	
Attica	n	3362	27	14	3403
	%	98.8	0.8	0.4	100
Outside Attica/Thessaloniki	n	2016	1480	1342	4838
	%	41.7	30.6	27.7	100
Thessaloniki	n	153	31	1527	1711
	%	8.9	1.8	89.2	100
Total	n	5531	1538	2883	9952
	%	55.6	15.5	29.0	100

Data from patients that obtained approval from EOPYY's IVF Committees. Retrieval from EOPYY's dataset.

Figure 1. Number and the location of IVF centers in Greece, 2013–2015 (N=74)



IVF centers are located in: Athens, Thessaloniki, Alexandroupolis, Ioannina, Larisa, Patra, Chania, and Heraklion. Retrieval from EOPYY's dataset.

64.7% of those applied for approval.

Regarding the number of attempts, 47.1% (n=3527) of women made two attempts, 41.5% (n=3105) made one attempt, 9.1% (681) made four attempts, and 2.3% (n=173) made three attempts.

In all, 41.7% of women residing permanently outside Attica/Thessaloniki and 8.9% of women living in Thessaloniki went to an Attica IVF center with this relationship being statistically significant (χ^2=6484, p<0.001) (Table 1). In Attica were based 50 of 74 IVF centers (Figure 1).

The most common method was IVF (86.1%) followed by ovulation induction (10.5%), sperm injection (2%) and administration of hormones (gonadotropins) to men (1.3%).

It was found that 45.7% of cases (i.e. 5249 cases) were related to female reproductive system problems, 41% of cases (4713 cases) were related to male factors, while 13% (1509 cases) were related to problems encountered by both prospective parents.

The most common diagnoses (Table 2) were abnormal semen parameters, male factor and increased sperm adhesion (39.9%). In a total of 11470 cases, 1275 had two diagnoses (11.1% of the cases). The most common second diagnoses were failed sperm inseminations and ovulation inductions (n=481) and abnormal sperm parameters, male factor, increased sperm adhesion (n=396).

Table 2. Most common diagnoses, 2013–2015 (N =11470)

Diagnosis	n	%
Abnormal sperm parameters, male factor, increased sperm adhesion	4581	39.9
Fallopian tube obstruction, tubal factor, tubal symphysis	1924	16.8
Anovulation, low AMH	1468	12.8
Infertility	1341	11.7
Azoospermia	481	4.2
Various	405	3.5
Endometriosis-endometrial adhesions	336	2.9
Failed sperm inseminations and ovulation inductions	326	2.8
Pre-implantation genetic diagnosis	172	1.5
Hypogonadotrophic hypogonadism	160	1.4
Salpingectomy	118	1.0
PCOS	106	0.9
Anatomical and functional problems of the uterus	34	0.3
Testicular or prostate cancer, orchiectomy, sperm cryopreservation	18	0.2

Diagnosis/cause of infertility of patients that obtained approval from EOPYY's IVF Committees. Retrieval from EOPYY's dataset. AMH: Anti-Müllerian hormone. PCOS: polycystic ovary syndrome.

Table 3. Distribution of diagnosis according to age, 2013–2015 (N=11470)

Method	Mean age (years)	SD
Various	39.83	5.23
Failed sperm insemination and ovulation inductions	38.34	4.09
Fallopian tube obstruction, tubal factor, tubal symphysis	37.19	4.72
Infertility	37.13	4.62
Anovulation and low AMH	37.04	4.66
Testicular Ca, prostate Ca, orchiectomy, sperm cryopreservation	36.39	6.23
Anatomical and functional problems of the uterus	36.33	5.39
Abnormal sperm parameters, male factor, increased sperm adhesion	36.19	4.74
Endometriosis-endometrial adhesions	36.17	3.82
Salpingectomy	35.94	4.49
Pre-implantation genetic diagnosis	35.63	4.15
Azoospermia	34.85	4.61
Hypogonadotrophic hypogonadism	34.57	5.33
PCOS	31.92	4.73

SD: standard deviation. Diagnosis/cause of infertility of patients that obtained approval from EOPYY's IVF Committees. Retrieval from EOPYY's dataset. AMH: Anti-Müllerian hormone. PCOS: polycystic ovary syndrome.

Association between sociodemographic characteristics and diagnoses/assisted reproduction method

Statistically significant relationships were found between age and other diagnoses ($p<0.001$) as shown in Table 3. In azoospermia, mean age was lower than abnormal semen parameters, male factor, increased sperm adhesion, anovulation, low AMH, infertility, failed sperm inseminations and ovulation inductions, fallopian tube obstruction, tubal factor, and tubal symphysis ($p<0.001$). In abnormal semen parameters, male factor and increased sperm adhesion, the mean age was lower than anovulation, low AMH, infertility, failed sperm inseminations and ovulation inductions, fallopian tube obstruction, tubal factor, and tubal symphysis ($p<0.001$). In pre-implantation diagnosis, mean age was lower than anovulation, low AMH, infertility, failed sperm inseminations and ovulation inductions, fallopian tube obstruction, tubal factor, and tubal symphysis ($p<0.001$). In anovulation and low AMH, the mean age was higher than hypogonadotropic hypogonadism and PCOS. In sperm inseminations and ovulation inductions, the mean age was higher than hypogonadotropic hypogonadism, fallopian tube obstruction, tubal factor, tubal symphysis, salpingectomy, and PCOS and endometriosis. In PCOS, the mean age was lower than in all other cases ($p<0.001$).

IVF was statistically significantly more common in all diagnoses except in the case of hypogonadotropic hypogonadism where hormone administration was more commonly used in men ($p<0.001$) (Table 4). Apart from diagnoses where IVF was one way solution (i.e. cancer or pre-implantation genetic diagnosis), it seems that it was also the

Table 4. Distribution of methods applied according to the diagnosis, 2013–2015 (N=11470)

Diagnosis		*In vitro* fertilization	Ovulation induction	Sperm injection	Hormone administration to men	Total
Azoospermia	n	463	8	2	8	481
	%	96.3	1.7	0.4	1.7	100
Testicular cancer, prostate cancer, orchiectomy, sperm cryopreservation	n	18	0	0	0	18
	%	100	0.0	0.0	0.0	100
Abnormal sperm parameters, male factor, increased sperm adhesion	n	4303	202	71	5	4581
	%	93.9	4.4	1.5	0.1	100
Pre-implantation genetic diagnosis	n	171	0	0	1	172
	%	99.4	0.0	0.0	0.6	100
Anovulation, low AMH	n	779	636	53	0	1468
	%	53.1	43.3	3.6	0.0	100
Infertility	n	1060	222	56	3	1341
	%	79.0	16.6	4.2	0.2	100
Hypogonadotrophic hypogonadism	n	24	7	2	127	160
	%	15.0	4.4	1.3	79.4	100

Continued

Table 4. Continued

Diagnosis		*In vitro* fertilization	Ovulation induction	Sperm injection	Hormone administration to men	Total
Failed sperm inseminations and ovulation inductions	n	285	32	9	0	326
	%	87.4	9.8	2.8	0.0	100
Fallopian tube obstruction, tubal factor, tubal symphysis	n	1900	16	8	0	1924
	%	98.8	0.8	0.4	0.0	100
Salpingectomy	n	117	1	0	0	118
	%	99,2	0.8	0.0	0.0	100
PCOS	n	48	42	16	0	106
	%	45.3	39.6	15.1	0.0	100
Endometriosis-endometrial adhesions	n	318	15	3	0	336
	%	94.6	4.5	0.9	0.0	100
Anatomical and functional problems of the uterus	n	33	0	1	0	34
	%	97.1	0.0	2.9	0.0	100
Various	n	360	28	10	7	405
	%	88.9	6.9	2.5	1.7	100
Total	n	9879	1209	231	151	11470
	%	86.1	10.5	2.0	1.3	100

Diagnosis/cause of infertility of patients that obtained approval from EOPYY's IVF Committees. Retrieval from EOPYY's dataset. AMH: Anti-Müllerian hormone. PCOS: polycystic ovary syndrome.

Table 5. Number of patients per method and age group, 2013–2015 (N=11470)

Method	Age (years)	Number of patients
IVF	*	353
	<25	43
	>45	263
	25–35	3635
	36–37	1448
	38–40	2103
	41–45	2034
Ovulation induction	*	42
	<25	11
	>45	1
	25–35	619
	36–37	192
	38–40	221
	41–45	123

Continued

Table 5. Continued

Method	Age (years)	Number of patients
Sperm injection	<25	5
	>45	3
	25–35	133
	36–37	36
	38–40	34
	41–45	20
Hormone administration to men	*	88
	<25	4
	25–35	32
	36–37	14
	38–40	12
	41–45	1

*The age of the patients was not confirmed in the dataset.

prevalent method in cases of abnormal semen parameters (93.9 %) and infertility which could not be attributed to other causes (79.0%).

Women who performed IVF had a statistically significantly higher mean age than those using the other methods ($p<0.001$) since the mean age for IVF was 36.9 years, whereas the mean age for ovulation induction was 35.1 years and for sperm insemination it was 34.7 years.

Most women of those that did an assisted reproduction method were aged 25–35 years while there was a clear preference for IVF in women over 35 years (Table 5).

DISCUSSION

In European countries infertility affects 14% of the population[13]. In 2016, Spain was the most active IVF country in Europe followed by Russia, France, Germany, Italy, and UK[12]. In Greece, no data on infertility have been collected up to date on behalf of Social Security Institutions. Data of this study relate to the part of the population that decided to use an assisted reproduction method covered by its Social Insurance. It is understood that infertility affects a larger proportion of the population and in many cases it has not yet been diagnosed, and many couples do not wish to use assisted reproduction methods or they prefer to cover all the costs on their own. Data collection and monitoring is performed both by EOPYY and NAMAR. EOPYY has real-world data while NAMAR has a time lag of about 3 years (first report of NAMAR so far was on 2018 regarding data of 2014 and 2015). According to legal framework, only NAMAR is informed by the assisted reproduction units of the outcome of the efforts.

EOPYY has strict guidelines and a maximum of 4 efforts per woman is approved and reimbursed. In the period 2013–2015, EOPYY granted approvals for the performance of 10889 cycles. A total of 3285 approvals were for one cycle, while 3802 approvals were for two cycles. This means that in Greece there is an average of 3629 IVF cycles each year covered by EOPYY. According to NAMAR, 28361 cycles were recorded on 2014 and 30728 cycles for 2015, resulting in 5854 and 7036 newborns, respectively[17], showing that many efforts are carried out privately.

According to this study, the mean age of women was 36.6 years, while that of men was 39.5 years. The majority of women were aged 35–39 years (37%, 4173), while the proportion of women over 40 was 29% (3207). According to the European Society of Human Reproduction and Embryology (ESHRE) 2016 ART fact sheet, most treatments were performed on women aged 30–39 years, whereas 2017 fertility success rates data of CDC show that over 80% of women that have undergone ART procedures were up to 40 years of age[12]. Only 2% of women examined by assisted reproductive committees were over 45 years old (267 persons) given the low probability of these methods being successful in this age group. This is in line with the literature as the observed decrease in fertility is greater between 40 and 44 years, and after 45 years only a fraction of 2–5% of women are able to have successful pregnancies[18].

The method of choice was *in vitro* fertilization at 86.1%. It should be noted that this figure includes Intra-cytoplasmic Sperm Injection (ICSI) cases as it was not feasible to separate these cases in data we received from EOPYY. These data are consistent with the statistics data on medically assisted reproduction units presented by the NAMAR at the ESHRE conference in Barcelona in 2018[17]. According to the Authority, in the year 2015, 14% proceeded with sperm insemination, while the rest (86%) used *in vitro* fertilization (IVF or ICSI). Given the normal decline in fertility over age, it is logical for health professionals to focus more on active methods of assisted reproduction to deal with fertility problems. Women who performed IVF had a statistically significantly higher mean age (36.9 years) than those using other methods. A new study that took place in Southern Brazil also showed that most cases of assisted reproductive technology were by *in vitro* fertilization (70.6%) and ART-mothers were in general older than mothers who had spontaneous pregnancies[19].

In 50% of cases, infertility is attributed to female reproductive system problems, while 30% is attributed to male factors. Finally, in 20% of cases, infertility is thought to be due to problems of both sexes[20]. According to other research, there is a male factor in 25–40% of infertile couples, whereas the ovarian factor is responsible for female infertility in 30–40% of cases[21]. According to this study, problems are found to a similar degree in both sexes (45.7% female and 41% male reproductive system problems). Unexplained infertility was reported in 11% of the cases studied (1208 cases), consistent with what ESHRE reports, i.e. in 10–20% of cases there is no apparent cause of infertility[12]. Additionally, this finding is in agreement with 2017 fertility success rates data of CDC which reported 11% for unexplained infertility[22].

In the present study, the necessity of using IVF is also indicated by the most common diagnoses which are abnormal sperm parameters, male factor, increased sperm adhesion, fallopian tube obstruction, tubal factor, tubal symphysis, anovulation and low AMH, infertility, and azoospermia. Infertility includes diagnosis of primary and secondary fertility, miscarriages, failed IVF, and early menopause. In addition, IVF appears to be the only choice as, among the 11470 cases, in 1275 (11.1%) there were more diagnoses, the most common of which were failed sperm insemination and ovulation inductions (n=481); abnormal sperm parameters, male factor, increased sperm adhesion (n=396), fallopian tube obstruction, tubal factor, tubal symphysis (n=195), i.e. problems that can only be resolved with *in vitro* fertilization. Regarding the contribution of male factor, these findings were slightly different from those presented by ESHRE 2016 ART fact sheet according to which 20–30% of infertility cases are explained by physiological causes in men[12]. Furthermore, 2017 fertility success rates

data of CDC reported that the reason for an attempt was the male factor in the 28% of cases[22]. According to our data, the contribution of male factor seemed to be even higher in cases where there was a relative second diagnosis.

The 88.6% of women with infertility problems are doing one or two assisted reproductive efforts at most (*in vitro* fertilization, ovulation induction, sperm insemination), avoiding being approved for two additional attempts by EOPYY. In cases of ovulation induction and sperm insemination, this is a signal for their turn to IVF, whereas in cases of IVF this is a signal for demonstrating skepticism of patients and their physicians against two additional efforts that require additional thousands of units of gonadotropins as medication. These data correspond to data mentioned in a relevant guideline given by the National Health System of the United Kingdom. According to a study conducted on the number of previous failed IVF cycles during the period 1991–1994, the probability of success decreases in each cycle from 14% in the first attempt to 13% in the second, 11.4% in the third[23] and 9.3% in the fourth attempt. Additionally, data collected by the Human Fertilization and Embryology Authority (HFEA) showed that the percentage of IVF cycles that resulted in births decreases from 20% when the mother is aged 38–39 years, to 12.3% at age 40–42 years, and to just 4.9% when she is over 42 years[24].

During the study period, there were 158 cases of women who stated that they would use donor semen. Of these, 149 requested approval for IVF, 8 to induce ovulation, and one for sperm insemination. In addition, there were 4 cases of surrogate mothers and no cases of female HIV carriers wishing to conceive using assisted reproduction methods. This fact characterizes Greek society's view of the family and the triptych 'father-mother-child'. Women in today's Greece will find it difficult to turn to the sperm donor or surrogate mother as they want to exhaust all available (medical and non-medical) childbirth opportunities in a way that meets the standards set by the society in which they live[25,26].

The majority of women who came to EOPYY IVF Committees were living in large urban centers. This finding agrees with previous research showing that the majority of women dealing with infertility live in cities[27,28]. Maybe the higher educational level combined with better career possibilities in cities could drive women to postpone motherhood[27,29]. Furthermore, general lifestyle conditions in cities (smoking, alcohol, caffeine, occupation or lack of exercise) may contribute to the observed fertility decline.

Limitations

The main limitation of this study was that it was not possible to know the outcome of each effort funded by EOPYY, since these data are reported only to NAMAR by IVF units. Furthermore, it was not possible for EOPYY to detect which IVF cases are referring to the classic IVF method and which to an ICSI method performed. Finally, it was not feasible to collect data for those women who used IVF services at their own expense.

CONCLUSIONS

During 2013–2015, there was an annual average of 3629 IVF cycles performed in the country (mainly in the capital, Athens) and reimbursed by EOPYY. Infertility was mainly attributed to abnormal sperm parameters, increased sperm adhesion, fallopian tube obstruction, tubal factor, and tubal symphysis. Problems of the female reproductive system are found in a similar percentage to problems of male etiology. Greece follows the European pattern since most patients were aged 30–39 years, did mostly *In Vitro* Fertilization/ICSI and received approval for one to two attempts at most, mainly with their own sperm. Inexplicable infertility was reflected in 11% of cases in this study, whereas a very small percentage of women over 45 years had undergone some method.

Women and men should be informed at a young age about factors affecting fertility. Specialized training programs could be developed for this purpose. Specific and targeted actions should be designed to ensure full information and awareness of young ages in order to prevent situations that can lead to fertility disorders. Since EOPYY's guidelines set a strict administration framework, many efforts were made at the expenses of the patients. EOPYY-NAMAR co-operation is considered absolutely necessary in order the risk/benefit ratio to be assessed. Sharing data regarding outcomes will give Social Insurance the ability to re-evaluate reimbursement procedures and lead to evidence-based legislation updates.

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DATA AVAILABILITY
Data supporting this research are available from the authors on reasonable request.

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