ENVIRONMENTAL FACTORS AND INFERTILITY-PARTICULAR ASPECTS IN ROMANIA'S POPULATION

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Keywords: causes of infertility, male factor, tubal factor, lifestyle and fertility Abstract: Objective: to examine the distribution of causes of infertility in Romania's population compared with other studied populations. Identifying the differences may suggest exposure to some environmental factors and lifestyle in Romania's population that can affect natural fertility. Material and methods: data collected from couples attending one of the larger private fertility clinics in Romania-Gynera Fertility Centre. All patients underwent the same diagnostic protocol. The data were compared with similar studies reviewed from electronic libraries (PubMed or Medline) using appropriate key words (causes of infertility, tubal factor, male factor). Results: The study population consisted of 1006 couples who attended the fertility clinic for a 7 year period. Male factor was the most common cause 46,95%, followed by tubal factor 40,44% and oligo/anovulation disorders 21,88%. The man alone was responsible for infertility in 255 couples (35,31%). Combined infertility factors were found in 136 couples (18,83%). The rate of unexplained infertility was of 23,77%. Published literature reported also that the male factor was the most common diagnosis in most of the studies conducted in fertility care centres. The second common cause varies among population: ovulation disorders versus tubal factor. The incidence of unexplained infertility varies between 4,7% and 23,27% mainly dependent on the protocol used to diagnose infertility. Conclusions: The major causes of infertility are population dependent. Most of the study reported that male factor accounts for almost half of the causes of infertility in couples. Our study revealed that in Romania, tubal factor is a very common cause of infertility. This could be explained by the growing numbers of induced abortion as a contraceptive method instead of using other methods to prevent unwanted pregnancies and due to increased incidence of sexually transmitted disease. National health programmes about contraception and sexually transmitted disease could reduce the numbers of infertile couples.

Cuvinte cheie: cauze ale infertilității, factor masculin, factor tubar, stil de viață și fertilitate Rezumat: Obiectiv: examinarea distribuției cauzelor infertilității în populația română comparativ cu alte populații studiate. Identificarea unor diferențe ar putea sugera influența unor factori de mediu și stil de viață caracteristic populației române ce ar putea afecta fertilitatea. Material și metodă: date culese de la pacienții ce s-au adresat unei clinici private de fertilitate din România – Gynera Fertility Center. Toți pacienții au parcurs același protocol de diagnostic. Datele culese au fost comparate cu studii similare publicate în librării electronice (PubMed, Medline) folosind cuvinte cheie adecvate: cauzele fertilității, factor masculin, factor feminin. Rezultate: lotul de studiu a fost alcătuit din 1006 cupluri ce s-au adresat clinicii pe o perioadă de 7 ani. Cea mai frecventă cauză a infertilității a fost reprezentată de factorul masculin (46,9%), urmată de factorul tubar (40,44%) și de oligo/anovulație (21,88%). Factorul masculin a fost identificat ca și diagnostic unic de infertilitate în cadrul a 255 cupluri (35,31%). Factori combinați de infertilitate au fost diagnosticați în cadrul a 136 cupluri (18,83%). Rata de infertilitate de cauză idiopatică a fost de 23,77 %. Datele obținute sunt concordante cu datele publicate în literatura de specialitate, factorul masculin fiind cea mai frecventă cauză de infertilitate în marea majoritate a studiilor conduse în centrele de fertilitate. Diferențele apar în cazul factorului tubar versus oligo/anovulație ce variază ca și pondere în funcție de populația de referință. Infertilitatea de cauză idiopatică variază între 4,7% și 23,27% în special în funcție de protocolul folosit pentru diagnosticul infertilității. Concluzii: Cauzele infertilității sunt dependente de populația studiată. Marea majoritate a studiilor raportează factorul masculin ca fiind responsabil de aproape jumătate din cauzele infertilității în cuplu. Studiul prezent indică prezența crescută a factorului tubar în populația română. Explicația ar putea fi dată prin numărul mare de avorturi la cerere folosite ca și metodă de prevenire a unei sarcini și de ponderea crescută a bolilor cu transmitere sexuală, în absența unui program educațional. Dezvoltarea unor programe naționale de contracepție și educație sexuală ar putea reduce numărul cuplurilor infertile.

INTRODUCTION

Infertility is defined as 1 year of unprotected intercourse without conception. Approximately 85-90% of

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Article received on 28.01.2014 and accepted for publication on 10.04.2014

ACTA MEDICA TRANSILVANICA June 2014;2(2):161-164

healthy young couples will conceive within 1 year. The rest of 10-15 % couples will be infertile. Nowadays, infertility is considered the most prevalent disease among young couples.

- The explanation for this fact can be:
- advance maternal age: women have grater interest in education and career delaying pregnancy when they are less biologically fertile;
- sexually transmitted infections such as Chlamydia infection will increase risk for subsequent infertility;
- lifestyle and environmental factors: obesity, smoking, substance abuse (marijuana, cocaine), heavy alcohol consumption will reduce fertility and raise the risk of malformation and spontaneous abortion.

Diagnostic assessment of infertility is recommended when a pregnancy has not occurred within 1 year of regular (twice a week) unprotected intercourse among healthy couples. Earlier assessment (only 6 month of unprotected intercourse) is indicated when: 1. women is older than 35 years, 2. women had previous ovarian surgery 3. woman is diagnosed with endometriosis, 4. exposure to chemotherapy, 5. man is older than 40 years.

Causes of infertility: there are three major causes for infertility: 1. male factors, 2. ovulatory dysfunctions and 3. mechanical factors - most frequent, tubal factors and less frequent uterine factors. There are couples diagnosed with only one infertility factor and others that have a combination of these factors. In others, the test results are normal leading to unexplained infertility. The prevalence of each factor can varies with age and is population-dependent.

Male factors - abnormalities of semen quality- semen analysis is the initial step to diagnose an infertile couple; this is a routine test, non-invasive and cost effective and can be easily done in any laboratory. Male factors are diagnosed in approximately 35% of infertile couples. There are three major causes of impaired sperm count: abnormalities of sperm production, abnormalities of the ductal system and abnormalities of sperm function. Abnormalities of sperm production can be primary (genetic syndromes, testicular failure) or secondary to a trauma, varicocele, infections (urlian virus) and toxic exposure. Abnormalities of the ductal system can be congenital (cystic fibrosis) or acquired (surgery, trauma). Abnormalities of sperm functions can be due to infections, varicocele, drugs abuse and smoking. Unfortunately, most of the causes of an impaired sperm count remain unexplained.

Women factors: Oligo/anovulation - is present in polycystic ovary syndrome (high ovarian reserve) and in ovarian dystrophies (low ovarian reserve). PCOS is an endocrinological disorder that associates oligomenorrhea with obesity, hirsutism, hyperandrogenism and insulin resistance. PCOS is not considered to be a disease but a cumulus of disturbances in the mechanism of ovulation. There was a workshop in Rotterdam in 2003 to establish a consensus for the diagnostic of PCOS.

Low ovarian reserve can be primary (hypergonadotropic hypogonadism) or secondary associated with advanced maternal age, ovarian surgery, single ovary, infections (urlian virus), drug abuse.

 $\label{eq:mechanical factors} Mechanical factors - includes tubal factors and uterine factors.$

Tubal factors are the most common causes for infertility among women. They represent 30-35 % of the causes of infertile couples. There are divided in tubal occlusion and tubal adhesion. Tubal factor can be suspected in cases of pelvic inflammatory disease (gonorrhea, Chlamydia), pelvic surgery for peritonitis, endometriosis, previous ectopic pregnancy.

Uterine factors are less common causes for infertility. They include congenital malformation, leiomyomas, endometrial polyps and uterine adhesions (Asherman Syndrome).

Endometriosis represents a genital pathology that associates tubal adhesions with uterine factors and ovulation disorders. Endometriosis affects 8-10% of women of reproductive age; it is represented by the presence of endometrial heterotopic islets who are responding to hormonal stimuli. Endometriosis has no pathognomonic signs or symptoms and therefore, it is difficult to diagnose. It is associated with primary or secondary infertility.

METHODS

The study population was represented by 1006 couples who attended Gynera Fertility Clinic in Bucharest for a 7 year period. All the couples underwent the same protocol for infertility diagnostic:

- Sperm count conditions: 2-5 days of abstinence; 1 sperm probe was collected at the centre or at home and brought to the centre at body temperature in maximum 30 minutes. The sperm probe was evaluated using WHO criteria: low sperm count < 15 mil/ml sperm cells (oligozoospermia), low motility < 32%(asthenozoospermia), abnormal morphology < 4%(teratozoospermia). In cases of severe impaired sperm count (<5 mil/ml sperm cells) there where indicated additional tests: hormonal status, urological Y chromosome examination, cariotype, microdeletions and CFTR mutation.
- 2. Women's hormonal profile (day 1-5 of menstrual cycle): FSH, LH, Estradiol, TSH, Prolactin, AMH when suspected low ovarian reserve (late 30s, ovarian surgery, low response to previous ovarian stimulations).
- 3. Women's general blood test: hemoleucogram, coagulation test, Rubella antibodies, urinary probe.
- 4. Tubal permeability and uterine cavity were evaluated by hysterosalpingography, sonohysterography, laparoscopy, hysteroscopy when needed (uterine adhesions, endometrial polyps, endocavitary leiomyomas).
- 5. Transvaginal ultrasound to evaluate ovarian reserve, ovarian abnormalities (tumours), uterus and fallopian tubes pathology (hydrosalpynx).

Male factors were defined in case of an abnormal sperm count. Tubal factor was defined in case of tubal obstruction as no passage of the contrast substance in the abdominal cavity. It can be divided in unilateral or bilateral obstruction, proximal or distal occlusion (hydrosalpinx).

Uterine factor was define in case of space occupancy lesions, irregular contour of uterine cavity or a malformation indicating a congenital anomaly (arcuate, septate, bicornuate or unicornuate uterus).

Oligo / Anovulation were defined by irregular menstrual cycle and ultrasound findings. Endometriosis was defined due to abnormal findings on laparoscopy and a positive histopathological exam.

RESULTS

1006 couples referred to the fertility clinic during the period of study (2007-2013). 941 couples (93,53%) had a definitive diagnosis after complete workup and they formed the study group. Primary infertility was found in 605 couples (60,14%).

Table no. 1 presents the distribution of the causes of infertility: male factor was the most common cause 46,95%, followed by tubal factor (mechanical obstruction) 40,44% and

oligo / anovulation disorders 21,88%. The man alone was responsible for infertility in 255 couples (35,31%). Combined infertility factors were found in 136 couples (18,83%). The rate of unexplained infertility was of 23,27%.

Table no. 1. Distribution of patients according to the causes of infertility

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No of couples	% of diagnosis						
339	46,95 %						
292	40,44 %						
158	21,88 %						
61	8,44 %						
8	1,10 %						
	No of couples 339 292 158 61 8						

DISCUSSIONS

Male factor was the most common cause of infertility. There are previous studies on the distribution of the causes of infertility in different populations, conducted in fertility clinics. As in the present survey, male factor was the most prevalent factor for infertility. Some studies have noted a decline in sperm quality over the last few decades in general population. Most of them have attributed the decline to lifestyle factors: smoking, substance abuse (marijuana, cocaine), heavy alcohol consumption, obesity. Other studies have linked advanced paternal age (over 40s) with infertility and neurocognitive disorders such as autism and schizophrenia in the offspring due to DNA damage. In Romania, increased prevalence of sexually transmitted disease could explain the high numbers of infertile man. Tubal factor - mechanical obstruction incidence ranged between 18% and 40, 44%

The large variation was associated with the developmental status of the population and the increase of sexually transmitted infections (such as Chlamydial infection in our country). Tubal factor was the second common cause for infertility in our survey 40,44%. This could be explained by the growing numbers of induced abortion as a contraceptive method instead of using other methods to prevent unwanted pregnancies, leading to obstruction of the internal ostium of the fallopian tubes. This is due to the lack of family planning and sexual education programmes supported by the government.

Ovulation disorders vary between 21,88 and 37%. The highest rate was reported in Israel. Here, women are postponing motherhood beyond age of 35 and even over 40 or 45 years of age when pregnancies are possible only with the use of IVF. Israeli society has often been described as particularly favourable to technology at large and to ART in particular, with the state being exceptionally generous in its funding of such procedures.

Table no. 2. Distributions of causes of infertility in different countries conducted in primary infertility clinics

Authors	Country	Date	Male factor	Oligo/ Anovulation	Tubal factor	Unexplained infertility	Combined factors
Present study	Romania	2013	46,95%	21,88%	40,44%	23,27%	18,83%
Jacob Farhi et all	Israel	2010	45%	37%	18%	20,7%	18%
Elussein et all	Sudan	2008	36,2%	29,7	19,5%	13%	-
Chiamchanya & Su- angkawatin	Thailand	2008	74%	20,8%	21,5%	4,7	-
Thonneau & Spira	France	1992	57%	32%	26%	-	39%

Combined causes of infertility were found in 18, 83% in our study. The rate of unexplained infertility was of 23,27%. The difference in rates among studies is probably a consequence of the variable diagnostic protocols used and the differences in study populations. Laparoscopy is not routinely performed or indicated in our clinic. This could explain the low rate of diagnosed endometriosis - 8,44% and the high rate of unexplained infertility - 23,27%.

We prefer a treatment approach (for example ovulation induction with clomifene citrate / FSH in PCOS rather then ovarian drilling).

CONCLUSIONS

Distribution of causes of infertility is population dependent. The developmental status of the country and the degree of higher education will determine different attitudes in achieving pregnancy.

Studies from the USA, Europe and Israel have shown that better-educated women tend to embark on motherhood later in life than do women who are less well-educated. In this population, oligo/anovulatory factor will have a higher incidence.

Countries that are less economic developed will have a higher incidence of pelvic inflammatory disease (due to increased sexually transmitted disease such as gonorrhea, Chlamydia and the reduced level of primary care). In this population tubal factor will be more prevalent.

Induced abortion has become legal since early 90s in Romania. Due to the lack of family planning programs, induced abortion was highly used as a contraceptive method. The result was the increased incidence in tubal factors leading to infertility. National health programmes about contraception and sexually transmitted disease as well as educational programmes about decrease of natural fertility with advance maternal age will reduce the incidence of infertility factors.

The most prevalent cause of infertility during the last years in all the studied populations was male factor. It has a wide variation ranging between 36-74% due to environmental factors exposure. This fact destroys the myth that women pathology is the main cause for infertility in a couple.

Acknowledgement:

This paper is supported by the Sectoral Operational Programme Human Resources Development (SOP HRD) 2007-2013, financed from the European Social Fund and by the Romanian Government under the contract number POSDRU/107/1.5/S/82839.

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