FAMILY HEALTH AND NATALITY AT THE BEGINNING OF XXI CENTURY FROM A ENDOCRINOLOGICAL PERSPECTIVE

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The deterioration of the demographic potential of a nation induces a lot of negative consequences in different domains (labour system, health, education and social protection system). In Romania, the demographic dynamics is characterized by an important decline of population size (since 1990-1991) with changes of age structure. Natality, affected by different factors (age-sex structure, age of marriage, social and religious beliefs availability of family planning services, female employment, economic prosperity, poverty levels, infant morbidity rate and conflicts) decreased. Fertility is one of the three principal components of population dynamics, the other being mortality and migration. In Romania, the rate of total fertility decreased after 1990. After1990, Romania registered a decreasing of total fertility rate from 1.83 children per woman to 1.64 children per woman (2016). Demographic decrease is also related to infertility. Endocrine infertility has complex causes in females and males. This review discusses the most essential endocrinopathies associated with infertility.

Keywords: endocrinopathies, female infertility, male infertility, hyperprolactinemia, hypothyroidism, polycystic ovary syndrome, endocrine disruptors.

INTRODUCTION

The development of a nation is dependent on its demographic potential. Demographic changes affect all countries and have crucial influences on economic and social development, higher nowadays than in the past[1].

In Romania, the demographic dynamics is characterized by an important decline of population size and a change of age structure. An accurate demographic analysis reveals that our country is losing population since 1990–1991, because of the birth decreasing and migrations. After 1991, Romania had a negative natural growth, a decrease of births and an increase of deaths. The deterioration of the demographic potential induced a lot of negative consequences in different domains (labour system, health, education and social protection system)[1].

NATALITY IN ROMANIA AT THE BEGINNING OF XXI CENTURY

Natality or birth rate is defined as the number of births per unit time and unit area, per

1000 individuals of a population. Natality is calculated by means of number of births per year divided by number of population per year x 1000. The birth rate is used to calculate the dynamics of population. A birth rate over 30 is considered high, a value between 20 and 30 is a moderate one and a value under 20 is interpreted as low. Natality may be affected by different factors like age-sex structure, age of marriage, social and religious beliefs (mainly related to abortion and contraception), availability of family planning services, female employment, economic prosperity, poverty levels, infant morbidity rate and conflicts.

The current population of Romania is of 19,030,833 (2022) inhabitants, based on the latest United Nations (UN) data. Romania 2020 population is estimated at 19,237,691 people at midyear, according to UN data. This population is equivalent to 0,25% of the total world population. The country ranks number 61 in the list of countries by population. The population density in Romania is 84 per km². The total land area is 230,170 km² (88,869 sq. miles). 54,6% of the population is urban (10,507,365 people in 2020). The median age in Romania is 43,2 years. Birth rate comprises 8.7 births/1,000 population (2018). Romania's population has decreased over recent

decades and is projected to shrink further. It dropped by 3.8 million since 1990 and is projected to fall to 15 million by 2070 (Fig. 1) from the current level, driven by demographic change, including emigration.

FERTILITY AND INFERTILITY

Fertility is one of the three principal components of population dynamics, the other being mortality and migration**.** Fertility rates appreciate the level of childbearing in a population, evaluating both the growth rate of a population and its age structure. From a demographical perspective, the birth rate represents a measure that allows to quantify fertility levels. Fertility rate represents the average number of children born by women during their reproductive period.

The best parameters to define fertility rates within a population are represented by two statistical tools: the general fertility rate and the total fertility rate (TFR). The general fertility rate is the number of live births per 1,000 females of childbearing age, between the ages of 15–44 years. TFR represents the sum of the age-specific birth rates multiplied by five. TFR estimates the fertility growth factor in a population.

It is important to differentiate between birth rates and fertility rates. The single most important factor for populational growth is TFR. When TFR is greater than 2.1, the population in a given area will increase and when it is less than 2.1, the population will eventually decrease. If there are numerous women of childbearing age and a relatively small number of older individuals in a society, the death rate will be low, so even though TFR is below the replacement rate, the population remains stable or increases slightly. Global TFR has declined significatively since 1970 in many parts of the world, despite fertility rates above the replacement rate. If TFR was at that time 4.5 and by 2015 it decreased to 2.5. In the 21st century, developed countries had lower fertility rates than developing countries, because of lower childhood mortality rates and better access to birth control.

In Romania, the rate of total fertility decreased after 1990, as in other countries. After 1990, Romania registered a decreasing of total fertility rate from 1.83 children per woman to 1.64 children per woman (2016).
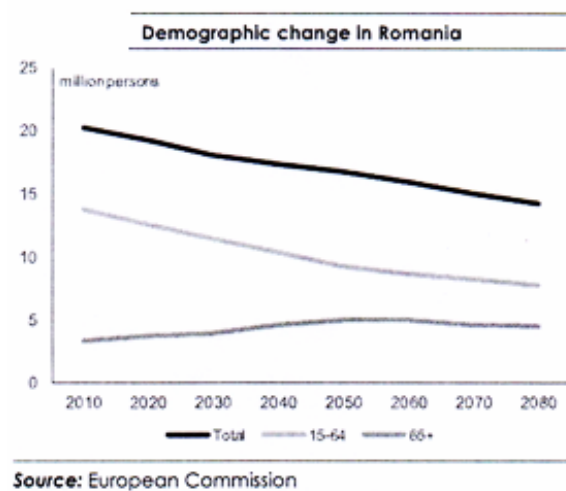

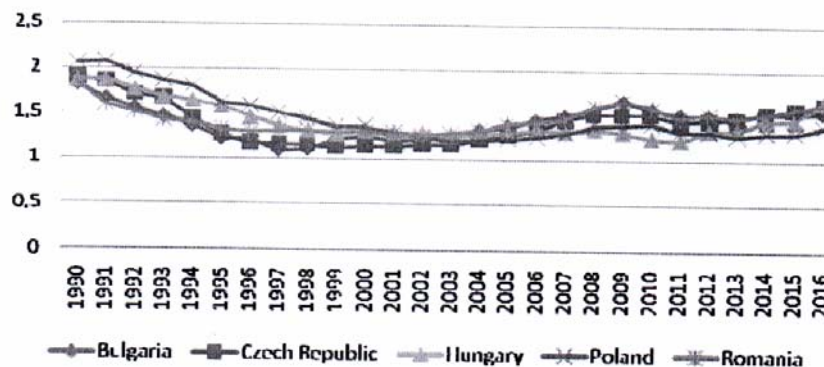Figure 1. The demographic change in Romania, in the last decades (EC Commission Staff Working Document, 2020).

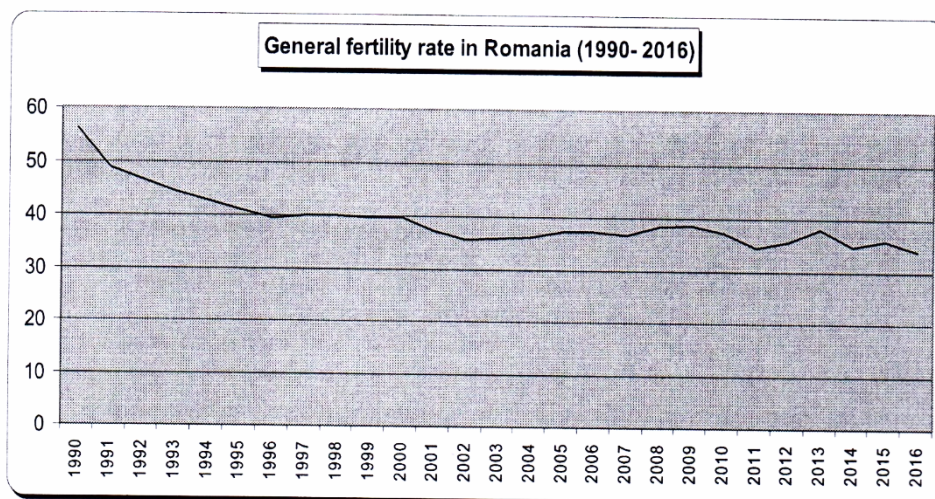Figure 2. Total Rate of Fertility (V. Dumitraşcu *et al.*, 2018).

Figure 3. General Fertility Rate in Romania (V. Dumitrașcu *et al.*, 2018).

Eurostat studies showed that although Romanian women are the youngest in Europe at the time of first child (having theoretically more time to procreate), the population is gradually declining. The Romanian demographic decline began about 30 years ago. Between the years 1995–2004, the fertility rate was around 1.3, with the lowest value in 2001 and 2002 – about 1.27. After Romania joined the European Union, fertility rate showed a slowly but not sufficient increase. Nowadays, the fertility rate is currently around 1.56[2]. The decline in fertility after 1990 is correlated with women's increased interest in tertiary education, an increased access to and use of modern means of birth control, a limited availability of childcare units (and a low socio-economic status[3–6].

FAMILY HEALTH

Family is a primary unit in all societies. It is represented by a group of individuals, related by blood, adoption or marriage, living together and sharing a common physical and social environment. Every family is unique and is affected by different aspects of community life. There are more types of family: a traditional nuclear family with children, a married couple without children, a single parent family and a non-traditional family.

Family health is defined as a state of positive interaction between family members, which allows each component of the family to enjoy optimum physical, mental, social and spiritual wellbeing. The family is a unit of health care. The health service providers are interested to understand family organization, customs, traditions and beliefs.

Family health is a part of the community health, representing more than the sum of personal health of individuals. The determinants of family health are represented by living and working conditions, physical environment, psycho-social environment, education, economic factors, health practices, cultural factors and others[7].

The last four decades are characterized by important changes of European family, including also Romanian family. Economic, social and demographic changes modified the family structure. Increasing divorce rates, declining fertility and increasing female role in the labour field, modified the traditional family image. The new social ambient had important and sometimes unexpected influences on family structure and life[8]. Decreased fertility associated with an increased lifespan led to an important proportion of older generations. The new family model is defined by a low frequency of marriages, an increased prevalence of celibacy, an advanced average age at the first marriage, fewer children, etc.

Every family recognises a cycle, where its various functions develop at different rhythms. WHO identifies six phases of the family life cycle: formation, extension, completed extension, contraction, completed contraction and dissolution. The passage through each phase of the family life cycle induces major family events and even disturbances (marriage, birth of the first child, retirement, diseases, etc.), that could affect the health of one or more family members.

Over the time, reproduction has been a main objective of couples. The demographic revolution, a consequence of an epidemiological transition has drastically changed the pattern of human reproduction.

Family planning, (which allows people to obtain the desired number of children and determine the spacing of pregnancies) has a lot of benefices on health, social and economic condition. It is achieved through use of contraceptive methods and the treatment of infertility[9]. The improved health of mothers and children has been the rationale to support family planning projects. It was shown that investments in family planning are highly cost effective.

The major changes in the family altered its roles and functions. Even so, the family remains the stimulus of the socio-economic development. The role of the family increased after its impact with different kind of troubles (economical, socio-political, etc.)

INFERTILITY OF ENDOCRINE ORIGIN

INTRODUCTION

Infertility, a global public health problem, is usually defined as inability of a couple to conceive after one year of unprotected intercourse. From an epidemiological point of view, 10%–15% of couples will experience difficulties to conceive (primary infertility) or to conceive the number of wanted children (secondary infertility). Both female and male factors can lead to infertility. WHO estimates that female infertility in developed countries accounts for 37% of causes in infertile couples, male infertility for 8% and both for 35%.

FEMALE INFERTILITY

Female infertility recognises the following main causes: ovulatory disorders (25%), endometriosis (15%), pelvic adhesion (11%), tubal blockage (11%), other tubal abnormalities (11%) and hyperprolactinemia (7%). Anovulation accounts for 25% to 50% of the causes of female infertility[10].

OVULATORY DYSFUNCTION

Ovarian factors comprise anovulation, ovulation with luteal insufficiency (low progesterone secretion) and luteinized non-ruptured follicle syndrome (the developed follicle remains in the ovary, undergoing here a luteinization process). Ovulatory dysfunctions recognise genetic and modifiable factors. Genetic factors include age at menarche and menopause, endometriosis and uterine fibroids (leiomyomas)[11]. Modifiable factors that may affect fertility are represented by obesity, smoking and time of intercourse.

Female fertility starts to decline before the age of 35 years. The factors that modify the risk of infertility (obesity, smoking, etc.) can be prevented. Regarding obesity, it was observed a strong association between increased mass index, lower pregnancy rates and increased rate of miscarriage. Associated factors (age, polycystic ovary syndrome) have also a role. Obesity is characterized by an unproper ovarian stimulation and a lower percentage of retrieved oocytes. Active smoking is associated with reduced ovarian reserve, low serum Anti-Müllerian Hormone (AMH) levels, etc.

Many endocrine disorders (hypothalamic amenorrhea, functioning pituitary adenomas, thyroid diseases) may induce ovulatory dysfunctions and infertility.

HYPOTHALAMIC CAUSES

Hypothalamic amenorrhea (HA) is the consequence of a change in the episodic pattern of Gonadotrophin Releasing Hormone (GnRH) secretion, with secondary ovulation failure and amenorrhea[12]. It can be functional or induced (by congenital deficiency, hypothalamic lesions and other rare causes). Functional hypothalamic amenorrhea (representing an exclusion diagnosis) represents the absence of menstrual cycles for more than 6 months and recognises three types (induced by stress, weight loss and exercise).

The diagnosis of HA comprises clinical signs and biochemical findings (low oestradiol levels with normal/low gonadotrophins) and evidence of a causative factor. Other amenorrhea etiologies must be sometimes ruled out (polycystic ovary syndrome, premature ovarian insufficiency, uterine abnormalities, etc.).

Functional hypothalamic amenorrhea (FHA) is generally reversible, with a recovery in time. As FHA is caused by a combination of factors, a multidisciplinary approach is often necessary.

The treatment comprises lifestyle changes, hormone replacement therapy (to replace oestrogen) and sometimes assisted reproduction, to achieve pregnancy. Hypogonadotropic anovulation of hypothalamic origin can be treated with pulsatile GnRH administration. Ovulation stimulation in hypothalamic disorders can be performed with injectable gonadotropins.

FUNCTIONING (SECRETING)
PITUITARY ADENOMAS

Functioning pituitary adenomas are represented by prolactinomas, GH-secreting adenomas and ACTH-secreting adenomas.

Prolactinomas represent the most common pituitary secreting tumours. The clinical picture is characterized by menstrual abnormalities, galactorrhea and infertility. Prolactin (PRL) excess impairs hypothalamic pulsatile secretion of GnRH and thus pulsatile hypophyseal LH and FSH release. The ovarian hormonal secretion (oestradiol, progesterone) is reduced and follicular maturation is inhibited. Gonadotropin receptors are also inhibited[13]. The diagnostic evaluation comprises complex hormonal investigations (PRL, gonadotropins, gonadal hormones) and imagistic methods.

PRL levels increase also after physiological stimuli and drugs (neuroleptics, antidepressants, H_2-blockers, metoclopramide, methyldopa, etc.), a differential diagnosis with hypophyseal tumors being sometimes necessary.

The medical treatment uses dopamine agonists (cabergoline, bromocriptine, etc.), which inhibit prolactin release. A tumor shrinking effect was also noticed. Cabergoline is considered more effective at normalizing PRL levels and regressing tumor mass. Ablative therapy is reserved for selected cases.

Acromegaly induces menstrual disturbances and low fertility in about 50% of affected women. The pathogenic mechanisms may comprise pituitary causes (damage of gonadotrophic cells, associated hypersecretion of GH and PRL in mixed adenomas, pituitary stalk compression). The treatment is a pathogenic one.

Cushing disease has many common features with polycystic ovary syndrome (PCOS), comprising obesity, low SHBG, increased androgens and virilization signs. Infertility has a complex pathogeny (conversion of adrenal androgens into oestrogens, with disturbed feedback to hypothalamic-pituitary axis, inhibition of oestrogen secretion by GnRH release, secondary to cortisol excess, disruption of GnRH and LH secretion by high levels of CRH and ACTH). The first line treatment is a surgical one.

THYROID DISORDERS

Hyperthyroidism

Hyperthyroidism may be involved in primary and secondary sterility in 5.8% women. Thyro-toxicosis induces an increased serum levels of SHBG and oestradiol (E2). High levels of E2 represent a consequence of SHBG increase and raised conversion rate of testosterone and androstenedione (both also increased) into E2. Patients with Graves' disease show at the same time, high levels of LH, normalized after antithyroid drug therapy.

Hypothyroidism

Hypothyroid women present fertility difficulties, along with increased miscarriage rates. The pathogeny of infertility is represented by altered peripheral oestrogen metabolism (decreased clearance of androstendione and estrone, increased aromatization to testosterone and oestradiol, decreased SHBG), hyperprolactinemia, disturbances in GnRH secretion (inducing a disturbed pulsatile release of LH and GnRH)[14].

Adrenal disorders

Adrenal disorders as congenital adrenal hyperplasia and Addison's disease contribute also to infertility.

Congenital adrenal hyperplasia (CAH) due to 21-hydroxilase deficiency, related to a genetic mutation, manifests itself by menstrual disturbances till amenorrhea. In cases with Non-Classical Congenital Adrenal Hyperplasia (NCAH), reduced fertility is associated to a secondary PCOS and hyperandrogenism, inducing anovulation. Progesterone concentrations are increased.

Addison's disease is characterized by a deficiency of adrenal hormones, usually induced by an autoimmune reaction. Androgenic deficiency is involved in infertility occurrence and increased spontaneous abortion rate. Associated autoimmune endocrinopathies (thyroid insufficiency, premature ovarian insufficiency) contribute also to the pathogeny of infertility in selected cases.

Ovarian disorders

Polycystic ovary syndrome (PCOS) is the most common endocrinopathy in female, affecting up to 10% of women of reproductive age. It is characterized by ovulatory dysfunction, androgenic excess, obesity and complex metabolic changes. PCOS cases may develop diabetes type 2, cardiovascular disease and endometrial cancer.

The pathogeny of anovulation is complex, associating a dysregulated gonadotropin secretion with high LH pulsatility and affected LH/FSH ratios. It is believed that increased Anti-Müllerian Hormone (AMH) blocks primordial follicle

recruitment and reduces the responsivity of recruited follicles to FSH, preventing thus the selection of a dominant follicle. Altered production of adipokines participate in the determinism of insulin resistance, near elevated triglycerides and small dense LDL. Increased leptin secretion is probably involved in the overactivity of sympathetic nervous system and hypertension. A large participation of different other adipokines is also implied in the development of atherosclerosis and inflammatory process (essential for the cardiovascular risk). Obesity is associated with disturbed adipokine levels and a high prevalence of the metabolic syndrome. Adipokine dysfunction recognises a peculiar severity in condition of an androgenic excess[15].

The positive diagnosis of PCOS needs at least two of the following three features: oligo-or anovulation, clinical and/or biochemical hyperandrogenism (considered by some the best criterion) and ultrasound examination with specific features (ovarian volume 10 mL and/or 12, follicles less 9 mm in size). In type I PCOS phenotype, the patients present hyperandrogenia, anovulation and polycystic ovaries and in type II PCOS, hyperandrogenia and mild anovulation is associated with normal ovaries. Type I cases have a higher LH/FSH ratio and type II patients show milder clinical pictures. In normoandrogenic phenotype, the cases present a normal body mass index, a normal free androgen index, insulin sensitivity, but the ratio LH/FSH is increased.

The treatment is initially performed with clomiphene citrate in a low dosage. In case of no response, the dosage can be increased. Resistant patients or those who do not conceive after six months, must be treated with gonadotropins. Metformin may be added to clomiphene in insulin-resistant cases. When medical treatment fails, ovarian drilling represents an option[16].

Premature ovarian insufficiency

Premature ovarian insufficiency (POI) is characterized by amenorrhea, low oestrogen levels and increased gonadotropin values, in women under 40 years. The disease represents the result of premature exhaustion of the follicular pool or is secondary to a follicular dysfunction[17,18].

AMH is a marker of ovarian failure with predictive value, strongly correlating with the percentage of growing follicles. Because serum AMH is not dependent on hypothalamic-pituitary-gonadal (HPG) axis functionality, its levels could mirror the progression of ovarian senescence.

The treatment is initiated with oestrogen replacement. Serial AMH measurements are often used before starting in vitro fertilization (IVF) procedures.

ENDOCRINE MALE INFERTILITY

INTRODUCTION

Male infertilities represent about half of global infertilities. In the last years, it showed a trend of increasing prevalence. An identifiable cause cannot be always detected.

Male reproductive functions are dependent on a complex interference of hormones, comprising GnRH, gonadotropins and testicular testosterone. Endocrine causes of male infertility are involved in only 1% to 2% of cases. The responsible endocrine diseases are divided into two categories: those characterized by a hormonal insufficiency lack and those presenting a hormonal excess (Table 1).

Table 1

Different Endocrinopathies and their Impact on Male Reproduction

Endocrinopathy	Changes in Male Reproduction
Hypogonadotropic Hypogonadism (genetic form: Kallmann syndrome)	Delayed puberty and infertility caused by a malfunction of GnRH-secreting neurones, presenting a failure to migrate; cessation of gonadotropin secretion
Hypergonadotropic Hypogonadism	Increased FSH/LH ratio, normal or decreased testicular volume, decreased pubic hair, decreased penis size, infertility
Androgen Excess	Inhibition of GnRH secretion, normal or decreased FSH and LH levels
Oestrogen Excess	Decrease of the ratio T/E2, decrease of semen parameters
Hyperprolactinemia	Normal or decreased ratio FSH/LH, low testosterone levels
Insulin Disorders	Decreased spermatogenesis, low fertility, decreased semen parameters, decreased Leydig cell count, low serum testosterone levels

HYPOGONADOTROPIC HYPOGONADISM (HH)

HH represents a syndrome characterized by a deficiency of pituitary gonadotropins (FSH and LH), leading to secondary testicular failure (low libido, erectile dysfunction, loss of tertiary sexual characteristics, etc.).

HH recognise congenital and acquired causes (most of cases). Kallmann syndrome is secondary to different genetic mutations. This form of hypogonadism presents characteristic phenotypic features (anosmia, neurological abnormalities, renal agenesis, etc.). As a result of the malfunction of GnRH-secreting neurons, GnRH secretion is absent, with impact on gonadotropins secretion[19]. Acquired causes of HH are very complex (tumours, granulomatous or inflammatory diseases, injuries or damages induced by ischemia, chemotherapy or radiotherapy in the hypothalamic or pituitary areas).

The treatment begins with a causal one. If this is impossible, a replacement therapy with testosterone is necessary to achieve normal sexualization. Spermatogenesis can be induced by clomiphene, gonadotropins or pulsatile GnRH administration. Gonadotropin therapy must begin with hCG alone (for 3 to 6 months), before introduction of other hormones. After hCG monotherapy, FSH replacement is necessary. Antioestrogens (clomiphene citrate, raloxifene, tamoxifen), preventing hypothalamic negative feedback of oestradiol, stimulate GnRH upsurge with activation of the entire gonadotropic axis The effectiveness of therapy is determined by testing serum testosterone levels. Spermatogenesis needs appropriate intratesticular testosterone concentrations.

HYPERGONADOTROPIC HYPOGONADISM

The primary disturbance in hypergonadotropic hypogonadism is represented by an insufficient or absent testicular function. The lack of negative feedback of testosterone raises the gonadotropins. Spermatogenesis is obstructed by the androgenic insufficiency. The patients show also testicular shrinkage with fibrosis.

The treatment comprises testosterone, avoided in men, who are attempting to conceive. Infertile patients are treated with medical therapies alone or in combination with assisted reproductive techniques (ARTs). The most available therapeutic options are represented by gonadotropins, selective oestrogen receptor modulators (SERM), aromatase inhibitors and combinations.

ANDROGEN EXCESS

Excess testosterone (after aromatization into oestradiol) supresses hypothalamic GnRH, the entire axis and spermatogenesis process. Excess testosterone is caused by exogenous testosterone administration or endogenous hormone synthesis. The hormonal overproduction may be induced because of therapy or after the illicit use of anabolic steroids. Exogenous administration reduces gonadotropin release, resulting in decreased intratesticular testosterone levels and decreased spermatogenesis. This condition is suspected when normal – to – high testosterone levels are associated with reduced gonadotropins. Endogenous androgen synthesis is observed in congenital adrenal hyperplasia, functional adrenal and testicular tumors and androgen insensitivity disorders (very rare).

The treatment of this condition begins with the identification and exclusion of the exogenous source of androgens. Generally, spermatogenesis returns to normal approximately after some months and exceptionally after three years. If spermatogenesis does not improve as expected, following a trial of gonadotropins, clomiphene citrate may be tried, to reestablish the functionality of HPG axis[20].

ESTROGEN EXCESS

A primary estrogenic excess has an inhibitory effect on the hypothalamic-pituitary-gonadal (HPG) axis, resulting in lower fertility. The testicle secretes testosterone and oestrogens, but the main source of oestrogens in males is represented by peripheral aromatization of testosterone by aromatase, enzyme found in adipose tissue. Many researchers believe that the ratio testosterone/estradiol is the main indicator of an estrogen excess. This category of infertile patients presents a lower ratio T/E2 as fertile patients. Aromatase inhibitors (steroidal, nonsteroidal) are effective in infertile males with low T/E2 ratios, increasing the ratio and enhancing sperm quality.

THYROID DISORDERS

Hypothyroidism

Hypothyroidism is associated with a reduction in SHBG levels and total serum testosterone. Free testosterone levels are also low. Hypothyroid males show an impaired sexual and erectile function, complex disturbances of sperm

parameters, and a decrease of erectile function. The levels of estradiol and gonadotropins are decreased. Hypothyroidism may also result in prolactin excess, secondary to elevated levels of thyrotropin-releasing hormone (TRH)[21]. Aromatase inhibitors (steroidal, nonsteroidal) are effective in the treatment of infertile males with low T/E2 ratios.

Hyperthyroidism

Hyperthyroidism, on the other part, affects sexual and erectile functions, sperm count, testicular germ count and sperm mobility. SHBG and gonadotropin levels (LH) are increased, but free testosterone concentrations are low. Sperm parameters are compromised (see table). After euthyroidism achieving, seminal abnormalities restaurate in most patients.

Hyperprolactinemia

Hyperprolactinemia is a major endocrinopathy involved in the pathogenesis of male infertility. Hyperprolactinemia can arise because of PRL and mixed secreting adenomas, peripheral hypothyroidism, stress, liver insufficiency and different drugs (tricyclic antidepressants, phenothiazines). There are described different clinical situations: asymptomatic patients, with hypoandrogenia, with galactorrhea, with reduced libido and erectile dysfunction.

Male infertility is secondary to the inhibitory effects of PRL excess on hypothalamus. In these conditions, hypothalamus becomes unable to secrete gonadotropins, which in turn affects testosterone production and spermatogenesis. A hyperprolactinemia imposes humoral and imagistic investigations (pituitary MRI). The most important distinction is between microadenomas and macroadenomas.

The medical treatment uses dopamine agonists (cabergoline, bromocriptine, etc.), which inhibit prolactin release. A tumor shrinking effect was also noticed. Cabergoline is considered more effective at normalizing PRL levels and regressing tumor mass. In men who remain hypogonadic after treatment, clomiphene citrate represents an option. Ablative therapy is reserved for selected cases[23].

Insulin Disorders and Diabetes Mellitus

90% of cases with diabetes mellitus are associated with changes in the reproductive functions (diminished libido, subfertility, infertility). In diabetes, insulin insufficiency or insulin insensitivity the negative feedback loop is affected, resulting in reduced reproductive functions. Additional effects include reduced spermatogenesis, reduced vacuolization of Sertoli cells, decreased fertility. The levels of gonadotropins and serum testosterone are low, and the count of germ cells is diminished. The drop in Leydig cells count is associated with a reduced serum LH, which may partially explain its stimulating role on Leydig cells. Insulin insufficiency does not seem to directly affect spermatogenesis, but rather though a change in serum FSH levels[24].

Obesity

Obesity impairs the regulation of HPG axis on testicular functionality. Pituitary gonadotropins are controlled by the pulsatile hypothalamic GnRH release. The process of spermatogenesis relies on the production of LH and FSH in response to hypothalamic GnRH release. At the testicular level, the action of FSH and LH are produced through specific receptors. If LH acts on Leydig cells regulating spermatogenesis, FSH acts on Sertoli cells. Obese men have a higher number of larger adipocytes, which generate more adipokines and metabolic hormones, able to increase the levels of inflammatory mediators in the circulation. Obesity related parameters (body mass index, total body and abdominal fat, etc.) correlate to lower testosterone and increased estrogen levels[25]. The increased activity of aromatase explains the high estrogen levels. Estrogens are involved in the disruption of testicular functions, inhibiting also GnRH release and gonadotropins release. The deficiency of gonadotropins is involved in an insufficient androgen synthesis and spermatogenesis. Inhibin B, elaborated in Sertoli cells functions also as a feedback inhibitor of FSH synthesis and high oestrogen levels reduce inhibin production in obese males[26]. High insulin levels seen in obesity diminish SHBG, resulting in lower testosterone, not sufficient for optimal spermatogenesis.

Impact of the Endocrine Disrupting Chemicals on the Reproductive System

The humans are constantly exposed to complex environmental chemical substances, including endocrine-disruptor compounds (EDC), detected in body fluids and tissues. EDC are chemicals that disrupt the hormonal homeostasis of the body, playing an important role in the functionality of endocrine function, including HPG axis[27].

Table 2

Effects of hypothyroidism and hyperthyroidism on male reproductive functions (Romano *et al.*, 2017)

Pathologic changes	Hypothyroidism	Hyperthyroidism
Prepubertal testicular volume and function	Increased and early onset of spermatogenesis	↓
Sperm count	N, ↓	↓
Testicular germ cell count	↓	↓
Sperm motility	↓	↓
Sexual function	Impaired	Impaired; precocious ejaculation
Erectile function	↓	↓
Free testosterone level	↓	↓
LH and FSH levels	↓	↑
E2	↓	↑

EDC have a broad spectrum of activity on endocrine system, better studied being plasticizers (bisphenol A, phthalates), polychlorinated biphenils, polybrominated diethyl ethers, dioxins, pesticides and phytoestrogens. EDC induce an environmental pollution with impact on more endocrine glands and metabolic homeostasis[27].

The mechanism of action of EDC is not fully understood. They may impair the functioning of the endocrine system, both in females and males. Several studies indicated unpredictable effects in humans even at low doses. The reproductive system represents the most vulnerable endocrine axis to EDCs actions in both genders[28].

In females, EDC act on gonads causing changes in the oestrogen signalling pathways or interact with estrogen receptors (ER). At level of male gonads, EDC may interfere with natural hormones and their receptors. EDCs can act as hormonal agonists or antagonists. EDCs from pesticides reduce the hormonal concentrations, influencing their synthesis, transport, metabolism and elimination.

EDCs are also involved in the pathogeny of uterine and ovarian cancers, premature puberty and fertility disorders. In men, they reduce sperm count (phthalates), testosterone levels (phthalates) and cause benign testicular tumors (phthalates). They also influence the quality of sperm, which can result in the development of a prostate cancer. The timing of EDC exposure is very important in the initial development stages when the organism is extremely sensitive to disturbing agents.

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